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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, cervical spine malformation and/or instability), craniofacial features (widely spaced eyes, 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 individuals based on characteristic clinical findings in the proband and family members and/or by the identification of a heterozygous pathogenic variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*.

Management

Treatment of manifestations: Important considerations when managing cardiovascular features of LDS: 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 amenable to early and aggressive surgical intervention. Surgical fixation of cervical spine instability may be necessary to prevent

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spinal cord damage. Treatment is standard for clubfeet and severe *pes planus*. Management by a craniofacial team is preferred for treatment of cleft palate and craniosynostosis. Standard treatment for allergic complications with consideration of referral to an allergy/immunology specialist in severe cases. Careful and aggressive refraction and visual correction is mandatory in young children at risk for amblyopia. Hernias tend to recur after surgical intervention. A supporting mesh can be used during surgical repair to minimize recurrence risk. Optimal management of pneumothorax to prevent recurrence may require chemical or surgical pleurodesis or surgical removal of pulmonary blebs.

Prevention of secondary complications: Consider subacute bacterial endocarditis (SBE) prophylaxis in those undergoing dental work or other procedures expected to contaminate the bloodstream with bacteria. Because of high risk for cervical spine instability, a flexion/extension x-ray of the cervical spine should be performed prior to intubation or any other procedure involving manipulation of the neck.

Surveillance: All individuals with LDS require echocardiography at frequent intervals to monitor the status of the ascending aorta; the frequency of magnetic resonance angiography (MRA) or computerized tomography angiography (CTA) evaluation to image the entire arterial tree depends on clinical findings. Individuals with cervical spine instability and severe or progressive scoliosis should be followed by an orthopedist.

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: If the pathogenic variant in the proband is known, molecular genetic testing can be used to clarify genetic status of at-risk family members; if the pathogenic variant is not known, relatives at risk should be evaluated for signs of LDS, including echocardiography and extensive vascular imaging if findings suggest LDS or if findings were subtle in the index case.

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.

Therapies under investigation: The safety and efficacy of angiotensin II receptor type 1 blockers (ARBs) has not been addressed for persons with LDS in a clinical trial setting, but ARBs have proven safe and comparable or superior to beta blockers in treating other vascular connective tissue disorders, such as Marfan syndrome.

Genetic counseling

LDS is inherited in an autosomal dominant manner. Approximately 25% of individuals diagnosed with LDS have an affected parent; approximately 75% of probands have LDS as the result of a *de novo* pathogenic variant. Each child of an individual with LDS has a 50% chance of inheriting the pathogenic variant and the disorder. Prenatal testing for a pregnancy at increased risk for LDS is possible if the pathogenic variant in the family is known.

Diagnosis

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) (see Phenotype Correlations by Gene), it is now recognized that LDS caused by a heterozygous pathogenic variant in any of the six known genes (see Table 1) is a continuum in which affected individuals may have various combinations of clinical features.

Suggestive Findings

Loeys-Dietz syndrome (LDS) **should be suspected** in individuals with the following vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, and ocular 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

- Widely spaced eyes
- 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, prominently 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

Establishing the Diagnosis

The diagnosis of Loeys-Dietz syndrome **is established** in a proband (by definition a person without a known family history of LDS) who has a heterozygous pathogenic (or likely pathogenic) variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* (see Table 1) and EITHER of the following [MacCarrick et al 2014]:

- Aortic root enlargement (defined as an aortic root z-score ≥2.0) or type A dissection
- Compatible systemic features including characteristic craniofacial, skeletal, cutaneous, and/or vascular manifestations found in combination. Special emphasis is given to arterial tortuosity, prominently including the head and neck vessels, and to aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree.

Note: (1) In the presence of a family history of documented LDS, the diagnosis can be made in at-risk relatives on the basis of molecular genetic testing even if vascular involvement or other features are not yet apparent (see Evaluation of Relatives at Risk). (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) Identification of a heterozygous variant of uncertain significance in one of the genes included in Table 1 does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (serial single-gene testing or a multigene panel) and **genomic testing** (comprehensive genomic sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because of clinical overlap, it is difficult to predict which of the known LDS-related genes will be causative in any given affected individual. Although individuals with the distinctive findings of LDS described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), those who do not have sufficiently discriminating features to consider the diagnosis of LDS are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical findings suggest the diagnosis of LDS, molecular genetic testing approaches can include **serial single-gene testing** or use of a **multigene panel**.

Serial single-gene testing. Sequence analysis of the genes listed in Table 1 can be performed first, typically in order of descending frequency (i.e., *TGFBR2*, *TGFBR1*, *SMAD3*, *TGFB2*, *SMAD2*, and *TGFB3*). Gene targeted deletion/duplication analysis for *SMAD3*, *TGFB2*, and *TGFB3* should be considered upon strong clinical suspicion and normal sequence analysis.

- Sequencing of *SMAD3* could be considered first if early osteoarthritis is evident in the proband or family.
- *TGFB2* or *TGFB3* can be analyzed first in individuals with milder phenotypes.

A multigene Marfan syndrome / Loeys-Dietz syndrome / familial thoracic aortic aneurysms and dissections panel that includes *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*,*TGFBR1*, and *TGFBR2* as well as a number of other genes associated with disorders that include aortic aneurysms and dissections (see Differential Diagnosis) may be offered by clinical laboratories. 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*; thus, clinicians need to determine which multigene panel is most likely 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. (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 LDS a multigene panel that also includes deletion/duplication analysis may be considered (see Table 1).

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 syndrome, molecular genetic testing approaches can include **comprehensive genomic testing** (exome sequencing and genome sequencing).

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]	Proportion of LDS Attributed to Pathogenic Variants in Gene [2]	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
SMAD2	~1%-5%	90%-95%	Unknown [6]
SMAD3	~5%-10%	90%-95%	Rare [7]
TGFB2	~5%-10%	90%-95%	Rare [8]
TGFB3	~1%-5%	90%-95%	Rare [9]
TGFBR1	~20%-25%	~100%	See footnote 10.
TGFBR2	~55%-60%	~100%	See footnote 10.
Unknown [11]		NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Meester et al [2017b]
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. 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.
6. No data on gene-targeted del/dup analysis are available.
7. Hilhorst-Hofstee et al [2013]
8. Lindsay et al [2012], Gaspar et al [2017]
9. Deletion of *TGFB3* has been observed [Author, personal communication].
10. 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 Loeys-Dietz syndrome. Smaller deletions/duplications that lead to in frame events are likely to cause an LDS phenotype, whereas events leading to out of frame are not.
11. 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 [Authors, personal observation].

Clinical Characteristics

Clinical Description

Loeys-Dietz syndrome 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 a more aggressive vascular course (with routine involvement of vascular segments distant from the aortic root) than that observed in Marfan syndrome. Mean age at death is 26 years [Loeys et al 2006]. 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 death was greater in families with a heterozygous *TGFBR2* pathogenic variant. Similarly, a study of 228 families with a heterozygous pathogenic variant in either *TGFBR1* or *TGFBR2* demonstrated similar aortic risk (dissection or aortic surgery) in both groups [Jondeau et al 2016].

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 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; however, isolated carotid artery dissection in the absence of aortic root involvement has not been observed.

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 of 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 clinico-pathologic 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 more prominently than the long bones.

Arachnodactyly is present in some, but true 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.

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.

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 one third (or more) of affected individuals have structural cervical spine anomalies and at least 50% 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 widely spaced eyes 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 (other than on the lower legs), and slower scar formation and dystrophic scarring.

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 in rare cases. Ectopia lentis is not observed.

Other

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 learning disability is an extremely rare primary manifestation of LDS.

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

Pregnancy. Pregnancy can be dangerous for women with LDS; see Pregnancy Management.

Phenotype Correlations by Gene

Various clinical presentations have in the past been labeled as LDS type I (craniofacial features present), LDS type II (minimal to absent craniofacial features), LDS type III (presence of osteoarthritis), and so on. These subtype designations provide a general indication of the spectrum of disease severity, from most to least severe: LDS1=LDS2>LDS3>LDS4>LDS5. Note: There is not yet enough information on the spectrum of features of LDS caused by heterozygous pathogenic variants in *SMAD2* to place this gene on the continuum or in Table 2.

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

Gene	Subtype of LDS [1]	Comment	Reference
TGFBR1	LDS1 [2]		Loeys et al [2005], Loeys et al [2006]
TGFBR2	LDS2 [2]		
SMAD3	LDS3 [3]	Strong predisposition for osteoarthritis [4]	van de Laar et al [2011]

Table 2. continued from previous page.

Gene	Subtype of LDS [1]	Comment	Reference
TGFB2	LDS4	Systemic findings possibly less severe & more like Marfan syndrome [5]	Lindsay et al [2012], Bertoli-Avella et al [2015]
TGFB3	LDS5		

1. Ordered from most to least severe
2. No differences in phenotype are observed between individuals with a heterozygous pathogenic variant in *TGFBR1* and those with a heterozygous pathogenic variant in *TGFBR2*.
3. The severity of aortic disease in individuals with a heterozygous pathogenic variant in *SMAD3* is similar to that associated with a heterozygous pathogenic variant in *TGFBR1* or *TGFBR2*.
4. Several individuals with a heterozygous pathogenic variant in *SMAD3* who do not have osteoarthritis have been reported [Wischmeijer et al 2013].
5. Boileau et al [2012]

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 phenotypic variability has been documented. 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. These data suggest the strong influence of genetic modifiers of disease that are independent of the pathogenic variant itself.

Penetrance

Intrafamilial clinical variability has been described and rare examples of non-penetrance in LDS have been documented. In one case, this was related to somatic mosaicism; in another, no evidence for mosaicism was observed.

Intrafamilial variability likely relates to genetic modification; genes encoding factors that regulate TGFβ signaling are excellent candidates for sites of modifying variation.

Nomenclature

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.

Prevalence

The prevalence of LDS is unknown.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SMAD3*, *TGFB2*, or *TGFB3*. While pathogenic variants in *TGFB3* have been associated with Rienhof syndrome, this phenotype is clinically related to Loeys-Dietz syndrome.

SMAD2. Two pathogenic variants in *SMAD2* have been reported in a series of 362 individuals with severe congenital heart disease [Zaidi et al 2013]. These two individuals presented with dextrocardia associated with multiple other congenital heart defects.

***TGFBR1* and *TGFBR2*.** A number of disorders have been thought to be caused by a heterozygous pathogenic variant in *TGFBR1* or *TGFBR2* (see Differential Diagnosis).

The only disorder not clinically related to Loeys-Dietz syndrome that is caused by a heterozygous loss-of-function variant in *TGFBR1* is multiple self-healing squamous epithelioma, also known as Ferguson-Smith disease [Goudie et al 2011].

Differential Diagnosis

Syndromic Forms of Thoracic Aortic Aneurysms

Marfan syndrome is a systemic disorder with a high degree of clinical variability. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems [Judge & Dietz 2005]. 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 mutation of *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 LDS, and can be mild. An important feature distinguishing SGS from LDS is the near-uniform incidence of developmental delay in SGS.

Molecular analysis of a series of individuals with typical SGS did not reveal pathogenic variants in *TGFBR1* or *TGFBR2* [Loeys et al 2005]. Affected individuals are usually simplex cases (i.e., no family history of SGS), although rare instances of apparent autosomal dominant inheritance have been described. Most individuals with SGS have a heterozygous *de novo* pathogenic missense variant in *SKI* [Carmignac et al 2012, Doyle et al 2012]. The SKI protein is a known repressor of TGFβ signaling, functionally linking SGS to LDS. Note: An individual reported with SGS by Kosaki et al [2006] was felt to have LDS based on the presence of arterial tortuosity and a bifid uvula [Robinson et al 2006].

Table 3. Clinical Features of Loeys-Dietz Syndrome by Associated Gene Compared to the Clinical Features of Marfan Syndrome and Shprintzen-Goldberg Syndrome

Clinical Feature	Marfan Syndrome	Loeys-Dietz Syndrome					Shprintzen -Goldberg Syndrome
	FBN1	*TGFBR1/ TGFBR2*	*SMAD3*	*TGFB2*	*TGFB3*	SMAD2	*SKI*
Developmental delay	–	–	–	–	–	–	++
Ectopia lentis	+++	–	–	–	–	–	–
Cleft palate / bifid uvula	–	++	+	+	+	+	+
Widely spaced eyes	–	++	+	+	+	+	++
Craniosynostosis	–	++	+	–	–	–	+++
Tall stature	+++	+	+	++	+	+	+
Arachnodactyly	+++	++	+	+	+	+	++
Pectus deformity	++	++	++	++	+	+	++
Clubfoot	–	++	+	++	+	–	+

Table 3. continued from previous page.

Clinical Feature	Marfan Syndrome	Loeys-Dietz Syndrome					Shprintzen -Goldberg Syndrome
	FBN1	*TGFBR1/ TGFBR2*	*SMAD3*	*TGFB2*	*TGFB3*	SMAD2	*SKI*
Osteoarthritis	+	+	+++	+	+	+	–
Aortic root aneurysm	+++	++	++	++	+	+	+
Arterial aneurysm	–	++	+	+	+	+	+
Arterial tortuosity	–	++	++	+	+	+	+
Early dissection	+	+++	++	+	+	+	–
Bicuspid aortic valve	–	++	+	+	+	+	+
Mitral valve insufficiency	++	+	+	++	+	+	+
Striae	++	+	+	+	+	+	+
Dural ectasia	+	+	+	+	–	–	+

+ = feature is present; the presence of more than one "+" indicates that a feature is more common, with "+++" indicating most common.
– = feature is absent.

***BGN*-associated aortic aneurysm syndrome** is an X-linked condition caused by a hemizygous pathogenic variant in *BGN*, coding for biglycan [Meester et al 2017a]. Clinical features significantly overlap with both Marfan syndrome and Loeys-Dietz syndrome, including early-onset aortic root dilatation and dissection, widely spaced eyes, joint hypermobility, contractures, bifid uvula, and pectus deformities. In some families, heterozygous females are also affected. The type of pathogenic variants in *BGN* suggest loss of function as the mechanism of disease.

MASS phenotype (OMIM 604308) is characterized by *m*itral valve prolapse, *m*yopia, borderline and non-progressive *a*ortic enlargement, and nonspecific *s*kin and *s*keletal findings that overlap with those seen in Marfan syndrome. One is most confident in this diagnosis when concordant manifestations are seen in multiple generations in a given family. However, some individuals in such a family could be predisposed to more severe vascular involvement, and thus a regimen of intermittent cardiovascular imaging should be maintained. It is difficult to distinguish MASS phenotype from "emerging" Marfan syndrome when assessing a simplex case (i.e., single occurrence in a family), especially during childhood. Heterozygous variants in *FBN1* can be causative. Inheritance is autosomal dominant.

The Ehlers-Danlos syndromes

Table 4. Selected Ehlers-Danlos Syndrome (EDS) Subtypes

Disease Name	Gene(s)	MOI	Clinical Features/Comments
Classic EDS (cEDS)	*COL5A1* *COL5A2* *COL1A1* [1]	AD	In cEDS & hEDS: • Some individuals have aortic root enlargement, but progression of the dilatation & predisposition for aortic dissection have not been established. [2] • No history of sudden death also argues against progressive aortic root dilatation.
Hypermobile EDS (hEDS)	Unknown/ *TNXB* [3]	AD	

Table 4. continued from previous page.

Disease Name	Gene(s)	MOI	Clinical Features/Comments
Vascular EDS (vEDS)	*COL3A1* *COL1A1* [4]	AD [5]	If vEDS is clinically suspected, collagen biochemistry normal, & no *COL3A1* or *COL1A1* pathogenic variant, consider LDS/ molecular analysis of *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, & *TGFBR2*. [4]
Cardiac-valvular EDS (cvEDS) (OMIM 225320)	*COL1A2*	AR	Features of cvEDS [6]: • Joint hypermobility • Skin hyperextensibility • Severe cardiac valvular defects
Kyphoscoliotic EDS (kEDS)	*PLOD1*	AR	In kEDS: • Risk for rupture of medium-sized arteries & respiratory compromise if kyphoscoliosis is severe • Aortic dilatation & rupture variably seen

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Mutation of *COL1A1* is not a major cause of cEDS [Malfait et al 2005]. See EDS, Classic Type.
2. Wenstrup et al [2002]
3. In most individuals with hEDS, the gene in which mutation is causative is unknown and unmapped. Haploinsufficiency of tenascin-X (encoded by *TNXB*) has been associated with hEDS in a small subset of affected individuals.
4. 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].
5. vEDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported.
6. Schwarze et al [2004]

Congenital contractural arachnodactyly (CCA) is characterized by a Marfan-like appearance (tall, slender habitus in which arm span exceeds height) and long, slender fingers and toes (arachnodactyly). Progressive enlargement of the ascending aorta at the sinuses of Valsalva has been reported, but there is no evidence that the aortic dilatation progresses to dissection or rupture [Gupta et al 2002]. Infants have been observed with a severe/ lethal form characterized by multiple cardiovascular and gastrointestinal anomalies in addition to the typical skeletal findings. CCA is caused by mutation of *FBN2* and is inherited in an autosomal dominant manner.

Arterial tortuosity syndrome (ATS) is a rare autosomal recessive connective tissue disorder, mainly characterized by severe tortuosity, stenosis, and aneurysms of the aorta and middle-sized arteries [Wessels et al 2004]. Skeletal and skin involvement is also common. The underlying genetic defect is homozygosity for loss-of-function variants in *SLC2A10*, the gene encoding solute carrier family 2, facilitated glucose transporter member 10. Although a glucose transporter defect would not be expected to cause abnormal arterial patterning, additional studies indicated upregulation of the TGFβ signaling pathway [Coucke et al 2006], consistent with the pathophysiology in LDS and Marfan syndrome.

Other Syndromes Associated with Ascending Aortic Aneurysms

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 40% 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.

Noonan syndrome is characterized by short stature, congenital heart defect, and developmental delay of variable degree. Congenital heart disease occurs in 50%-80% of affected individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of affected individuals. Hypertrophic cardiomyopathy, found in 20%-30% of affected individuals, may be present at birth or appear in infancy or childhood. Other structural defects frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Rarely, aortic aneurysms have been described. Noonan syndrome is caused by mutation of *BRAF*, *KRAS*, *MAP2K1*, *NRAS*, *PTPN11*, *SOS1*, *RAF1*, or *RIT1*. Inheritance is autosomal dominant.

Cutis laxa. Autosomal dominant cutis laxa (ADCL) was historically considered a strictly cutaneous disorder without systemic involvement, in contrast to autosomal recessive cutis laxa (ARCL), which is associated with high morbidity and mortality resulting from pulmonary emphysema and aortic aneurysms.

Table 5. Cutis Laxa Subtypes to Consider in the Differential Diagnosis of Loeys-Dietz Syndrome

Disease Name	Gene	OMIM	MOI	Clinical Findings				
				Cutis laxa	Emphysema	Aneurysms	ID	GI & GU malformations
FBLN5-related cutis laxa	*FBLN5*	219100	AR	+++	+++	–	–	+
EFEMP2-related cutis laxa	*EFEMP2* (*FBLN4*)	614437	AR	++	++	+++	–	–
ADCL	*ELN* or *FBLN5*	123700 614434	AD	+	+	+	–	–

AD = autosomal dominant; ADCL = autosomal dominant cutis laxa; AR = autosomal recessive; GI = gastrointestinal; GU = genitourinary; ID = intellectual disability; MOI = mode of inheritance

Nonsyndromic Familial Thoracic Aortic Aneurysms and Dissections

Bicuspid aortic valve with thoracic aortic aneurysm (BAV/TAA). Many cases of a dilated ascending aorta are associated with an underlying BAV. A bicuspid aortic valve 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. For a long time, it was believed that the aneurysms were caused by "post-stenotic dilatation" of the ascending aorta. However, 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 and are found in 9% of first-degree relatives of affected individuals. Family members of probands with BAV and aneurysm can show aneurysm and dissection in the absence of the accompanying valve abnormality, suggesting that both BAV and aneurysm represent primary manifestations of the underlying gene defect [Loscalzo et al 2007]. In family studies, reduced penetrance is common.

Thus far, pathogenic variants have been identified in *NOTCH1* (OMIM 190198) and *SMAD6* (OMIM 602931) in rare individuals with additional congenital cardiac malformations. *NOTCH1* pathogenic variants appear specific to individuals and families with significant valve calcification and stenosis, findings not observed in most families with BAV/TAA. Linkage analysis suggests genetic heterogeneity with loci identified on chromosomes 18q, 5q, and 13q [Martin et al 2007]. *SMAD6* loss-of-function variants account for about 2% of all cases of BAV/TAA [Gillis et al 2017].

Persistent patent ductus arteriosus with thoracic aortic aneurysm (PDA/TAA). A report describing a single large family with 179 members who have a high incidence of thoracic aortic aneurysm and dissection (TAAD)

in conjunction with PDA suggests that a novel genetic defect underlies both vascular conditions in this family. Linkage analysis excluded all known genes or loci implicated in familial TAAD or autosomal recessive PDA. The disease was mapped to chromosome 16p12 [Khau Van Kien et al 2005]. Mutation of *MYH11* (encoding myosin-11, a specific contractile protein of smooth muscle cells) is causative. The structural defect leads to lower aortic compliance, smooth muscle cell loss, and elastolysis, but the precise pathophysiology remains unclear [Zhu et al 2006].

Fibromuscular dysplasia (FMD) (OMIM 135580) is a nonatherosclerotic, noninflammatory 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. Macro-aneurysms 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].

Familial thoracic aortic aneurysm and dissection (FTAAD). Cardiovascular manifestations of FTAAD include the following:

- Dilatation of the aorta at the level of either the ascending aorta or the sinuses of Valsalva
- Aneurysms and dissections of the thoracic aorta involving either the ascending or descending aorta

TAAD is diagnosed based on the presence of dilatation and/or dissection of the thoracic aorta, absence of Marfan syndrome and other connective tissue abnormalities, and presence of a positive family history.

Cardiovascular manifestations are usually the only findings. Affected individuals typically have progressive enlargement of the ascending aorta leading to either aortic dissection involving the ascending aorta (type A dissection) or consequent tear or rupture. The onset and rate of progression of aortic dilatation is highly variable; however, persons with familial TAAD present with aortic disease at a mean age of 56.8 years, which is younger than that for sporadic TAAD (64.3 years) but significantly older than that for Marfan syndrome (24.8 years) [Coady et al 1999].

Table 6. Selected Causes of Heritable Thoracic Aortic Disease (HTAD)

Gene/(Locus) [1, 2]	Proportion of HTAD Attributed to Mutation of Gene	Findings
ACTA2	12%-21% [3]	In some: livido reticularis, iris flocculi, cerebral aneurysm, bicuspid aortic valve, & persistent patent ductus arteriosus
MYH11	1% [4]	Other cardiovascular finding: patent ductus arteriosus [5]
MYLK	1% [6]	Aortic dissections w/minimal enlargement but limited experience; no associated features
PRKG1	1% [7]	Type A & B aortic dissections associated w/ tortuosity & hypertension
MAT2A	1% [8]	Other cardiovascular finding: bicuspid aortic valve
FOXE3	1% [9]	Only affected males described; no associated features
MFAP5	< 1% [10]	Mild systemic features; associated w/lone paroxysmal atrial fibrillation
LOX	1% [11]	Associated w/bicuspid aortic valve, mild marfanoid features

Table 6. continued from previous page.

Gene/(Locus) [1, 2]	Proportion of HTAD Attributed to Mutation of Gene	Findings
(AAT1 or FAA1) [12]	Unknown	More diffuse vascular disease than in TAAD1, w/ aneurysms affecting both thoracic & abdominal aorta & other arteries
(AAT2 or TAAD1) [12]	Unknown	

Heritable thoracic aortic disease (HTAD) refers to thoracic aortic disease caused by mutation of a gene that confers a high risk for thoracic aortic aneurysms and aortic dissections (see Heritable Thoracic Aortic Disease Overview).
1. Locus is included when associated gene is not known.
2. TGFBR2 pathogenic variants all affecting the same codon (p.Arg460His and p.Arg460Cys) were found in four of 80 unrelated families with familial TAAD. Although the majority of vascular disease in these families involved ascending aortic aneurysms leading to type A dissections, affected family members also had characteristic findings of LDS including descending aortic disease and aneurysms of other arteries (e.g., cerebral, carotid, and popliteal arteries) and other connective tissue findings (e.g., pectus deformity and joint hypermobility). Furthermore, the identical *TGFBR2* pathogenic variants reported in FTAAD have been observed in multiple families with typical features of LDS [Loeys et al 2006; Authors, unpublished data]. Currently, it is unclear whether a *TGFBR2* pathogenic variant can lead to an isolated aortic aneurysm phenotype (i.e., FTAAD); thus, use of the term FTAAD to refer to families with TAAD and a heterozygous *TGFBR2* pathogenic variant does not seem appropriate.
3. Guo et al [2007], Morisaki et al [2009], Disabella et al [2011], Hoffjan et al [2011], Renard et al [2013]
4. Pannu et al [2007]
5. Glancy et al [2001], Khau Van Kien et al [2004], Khau Van Kien et al [2005], Zhu et al [2006], Pannu et al [2007]
6. Wang et al [2010], Luyckx et al [2017]
7. Guo et al [2013]
8. Guo et al [2015]. Two loci designated as AAT1 (FAA1) [Vaughan et al 2001] and AAT2 (TAAD1) [Guo et al 2001] are implicated in TAAD; the genes have not been identified.
9. Kuang et al [2016]
10. Barbier et al [2014]
11. Guo et al [2016]
12. Guo et al [2007]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Loeys-Dietz syndrome (LDS), the following evaluations are recommended if they were not completed as part of the evaluation that led to the diagnosis:

- Echocardiography. Aortic root measurements must be interpreted based on consideration of normal values for age and body size [Roman et al 1989]. Select findings (e.g., severe aortic dilatation) may require the immediate attention of a cardiologist or cardiothoracic surgeon.
- MRA or CT scan with 3D reconstruction from head to pelvis to identify arterial aneurysms and arterial tortuosity throughout the arterial tree

  Note: Approximately half of the individuals with LDS studied had an aneurysm distant from the aortic root that would not have been detected by echocardiography.
- Radiographs (including flexion and extension views of the cervical spine) to detect skeletal manifestations that may require attention by an orthopedist (e.g., severe scoliosis, cervical spine instability)
- Craniofacial examination for evidence of cleft palate and craniosynostosis

- Eye examination by an ophthalmologist with expertise in connective tissue disorders, including: slit-lamp examination through a maximally dilated pupil for exclusion of lens (sub)luxation; careful refraction and visual correction, especially in young children at risk for amblyopia; specific assessment for retinal detachment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Management of LDS is most effective through the coordinated input of a multidisciplinary team of specialists including a clinical geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon. An extensive review of management guidelines has been published [MacCarrick et al 2014] (full text).

Cardiovascular

All individuals with LDS should be managed in a medical center familiar with this condition.

Two important considerations when managing cardiovascular features of LDS:

- Aortic dissection occurs at smaller aortic diameters than observed in Marfan syndrome.
- Vascular disease is not limited to the aortic root. Imaging of the complete arterial tree from the head through the pelvis by MRA or CTA is necessary.

Beta-adrenergic blockers or angiotensin receptor blockers (ARBs) are used to reduce hemodynamic stress. No clinical trials evaluating the efficacy of beta-adrenergic blockers verses ARBs have been completed in individuals with LDS.

Aneurysms are amenable to early and aggressive surgical intervention (in contrast to vascular EDS, in which surgery is used as a last resort because of the extremely high rate of intraoperative complications and death). Many individuals can undergo a valve-sparing procedure that precludes the need for chronic anticoagulation.

Given the safety and the increasing availability of the valve-sparing procedure:

- For young children with the most severe systemic findings of LDS, surgical repair of the ascending aorta should be considered once the maximal dimension exceeds the 99th percentile and the aortic annulus exceeds 1.8-2.0 cm, allowing the placement of a graft of sufficient size to accommodate growth. Additional factors including family history, rate of aortic root growth, and aortic valve function can influence the timing of surgery.
- For adolescents and adults, surgical repair of the ascending aorta should be considered once the maximal dimension approaches 4.0 cm. This recommendation is based on both numerous examples of documented aortic dissection in adults with aortic root dimensions at or below 4.0 cm and the excellent response to prophylactic surgery. An extensive family history of larger aortic dimension without dissection could alter this practice for affected individuals.
- Note: This practice may not eliminate risk of dissection and death, and earlier intervention based on family history or the affected individual's personal assessment of risk versus benefit may be indicated.

Skeletal

Surgical fixation of cervical spine instability may be necessary to prevent damage to the spinal cord.

Clubfeet require surgical correction by an orthopedic surgeon.

Bone overgrowth and ligamentous laxity can lead to severe problems (including progressive scoliosis) and should be managed by an orthopedist; surgical stabilization of the spine may be required.

Pectus excavatum can be severe; rarely, surgical intervention is medically (rather than cosmetically) indicated.

Surgical intervention for protusio acetabulae is rarely indicated. Treatment focuses on pain control.

Orthotics are only indicated for severe *pes planus*. Some individuals prefer use of arch supports; others find them irritating; the choice should be left to personal preference. Surgical intervention is rarely indicated or successful.

Craniofacial

Cleft palate and craniosynostosis require management by a craniofacial team. Treatment of cleft palate and craniosynostosis is the same as in all other disorders with these malformations.

Allergic/Inflammatory

Standard treatment for allergic complications such as seasonal allergies, food allergies, asthma, and eczema should apply. Referral to an allergist/immunologist may be considered in severe cases. Inflammatory or allergic gastrointestinal findings are treated in the standard fashion with the guidance of a gastroenterologist.

Ocular

The ocular manifestations of LDS should be managed by an ophthalmologist with expertise in connective tissue disorders. Careful and aggressive refraction and visual correction is mandatory in young children at risk for amblyopia.

Other

Dural ectasia is usually asymptomatic. No effective therapies for symptomatic dural ectasia currently exist.

Hernias tend to recur after surgical intervention. A supporting mesh can be used during surgical repair to minimize recurrence risk.

Optimal management of pneumothorax to prevent recurrence may require chemical or surgical pleurodesis or surgical removal of pulmonary blebs.

Counseling regarding other life-threatening manifestations including spontaneous rupture of the spleen and bowel and pregnancy-associated risks is recommended.

Prevention of Secondary Complications

Use of subacute bacterial endocarditis prophylaxis should be considered for individuals with connective tissue disorders and documented evidence of mitral and/or aortic regurgitation who are undergoing dental work or other procedures expected to contaminate the bloodstream with bacteria.

Because of a high risk of cervical spine instability, a flexion and extension x-ray of the cervical spine should be performed prior to intubation or any other procedure involving manipulation of the neck.

Surveillance

All individuals with LDS require echocardiography at frequent intervals to monitor the status of the ascending aorta. The frequency of MRA or CTA evaluations should be tailored to clinical findings.

Individuals with cervical spine instability and severe or progressive scoliosis should be followed by an orthopedist.

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 triptans 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 appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those individuals who need regular cardiovascular screening to detect aortic aneurysms and initiate appropriate medical or surgical intervention. Evaluations can include the following:

- Molecular genetic testing if the pathogenic variant in the family is known
- Signs of the disorder if the pathogenic variant in the family is not known. Echocardiography and extensive vascular imaging of relatives is indicated upon appreciation of any suspicious signs 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 Loeys-Dietz syndrome can tolerate pregnancy and delivery [Gutman et al 2009, Frise et al 2017].

Therapies Under Investigation

Experimental evidence suggests that many manifestations of LDS relate to excess activation of and signaling by the growth factor TGFβ.

Animal trials have shown that TGFβ antagonizing agents, such as angiotensin II receptor type 1 blockers (ARBs), can slow or prevent vascular manifestations of LDS [Gallo et al 2014]. ARBs also attenuate the biochemical abnormalities in the aortic wall of mouse models of LDS. The safety and efficacy of such interventions has not been addressed for persons with LDS in a clinical trial setting, but ARBs have proven safe and comparable or superior to beta blockers in treating other vascular connective tissue disorders such as Marfan syndrome.

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) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 25% of individuals diagnosed with LDS have an affected parent.
- Approximately 75% of probands with LDS have the disorder as the result of a *de novo* pathogenic variant.
- If the *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* pathogenic variant in a proband is known, molecular genetic testing of both parents is indicated. If the pathogenic variant is unknown, it is appropriate to evaluate both parents for manifestations of LDS, including a comprehensive clinical examination.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (both parental somatic and germline mosaicism have been reported in rare cases).
- The family history of some individuals diagnosed with LDS may appear to be negative 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, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- 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.

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

- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- The sibs of a proband with clinically unaffected parents are still at increased risk for LDS because of the possibility of reduced penetrance in a parent.
- If the *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline 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 of a proband. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with LDS has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

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.

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 *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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 testing. While most centers would consider use of prenatal 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**

  www.loeysdietz.org
- **American Heart Association**

  Phone: 800-242-8721

  Types of Aneurysms
- **Medline Plus**

  Loeys-Dietz syndrome
- **National Marfan Foundation**

  The National Marfan Foundation provides education and support for other heritable connective tissue disorders that share some features of Marfan syndrome.

  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
SMAD2	18q21.1	Mothers against decapentaplegic homolog 2	Loeys-Dietz Syndrome Mutation Database - SMAD2	SMAD2	SMAD2
SMAD3	15q22.33	Mothers against decapentaplegic homolog 3	Loeys-Dietz Syndrome Mutation Database - SMAD3 CHD8 @ LOVD	SMAD3	SMAD3
TGFB2	1q41	Transforming growth factor beta-2 proprotein	Loeys-Dietz Syndrome Mutation Database - TGFB2	TGFB2	TGFB2
TGFB3	14q24.3	Transforming growth factor beta-3 proprotein	Loeys-Dietz Syndrome Mutation Database - TGFB3 TGFB3 @ LOVD ARVD/C Genetic Variants Database - TGFB3	TGFB3	TGFB3
TGFBR1	9q22.33	TGF-beta receptor type-1	Loeys-Dietz Syndrome Mutation Database - TGFBR1	TGFBR1	TGFBR1
TGFBR2	3p24.1	TGF-beta receptor type-2	Loeys-Dietz Syndrome Mutation Database - TGFBR2	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
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
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
619656	LOEYS-DIETZ SYNDROME 6; LDS6

Molecular Pathogenesis

In the initial description of *TGFBR2* pathogenic variants causing a phenotype similar to Marfan syndrome [Mizuguchi et al 2004] it was observed that recombinantly expressed mutated receptors in cells that were naïve for TGFβ receptors could not support TGFβ signaling. 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 TGFβ 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 harbor 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 TGFβ receptor genes in persons with 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 TGFβ 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 ligand, but that specifically lacks the ability to propagate the intracellular TGFβ 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 TGFβ 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 TGFβ signaling and can be attenuated or prevented by TGFβ antagonism in animal models.

Experiments exploring TGFβ 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 TGFβ receptors may initiate chronic and dysregulated compensatory mechanisms that result in too much TGFβ 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 TGFβ signaling after 24 hours of ligand deprivation and a slower decline in the TGFβ signal after restoration of ligand. An even more informative result was the observation of increased nuclear accumulation of pSmad2 in the aortic wall of persons with either Marfan syndrome or LDS, and increased expression of TGFβ-dependent gene products such as collagen and CTGF. Taken together, these data demonstrate increased TGFβ 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 TGFβ 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 TβRII leads to increased TGFβ signaling, including stimulation of the intracellular signaling cascade and increased output of TGFβ-responsive genes, clearly suggesting a gain-of-function mechanism for mutated TGFβ receptors in LDS.

SMAD2

Gene structure. NM_001003652.3 represents the longest transcript (11 exons, 10 coding) and encodes the longest isoform, NP_001003652.1. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The currently known pathogenic variants in *SMAD2* are predicted to lead to loss of function because they affect the functionally important MH2 domain [Micha et al 2015].

Normal gene product. The reference sequence NP_001003652.1 has 467 amino acids. SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signaling pathways. This protein functions as a transcriptional modulator activated by transforming growth factor-beta (provided by RefSeq, Apr 2009).

Abnormal gene product. No functional studies have been reported to date.

SMAD3

Gene structure. NM_005902.3 represents the longest transcript (9 exons) and encodes the longest isoform of 425 AA (NP_005893.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Most variants in *SMAD3* are predicted to lead to loss of function. This is supported by the fact that about half of the currently reported pathogenic variants lead to nonsense or out-of-frame frameshift variants [Wischmeijer et al 2013]

Normal gene product. The reference sequence NP_005893.1 has 425 amino acids.

SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signaling pathways. This protein functions as a transcriptional modulator activated by transforming growth factor-beta (provided by RefSeq, Apr 2009).

Abnormal gene product. Despite the predicted loss-of-function nature of most *SMAD3* pathogenic variants, a paradoxic gain of function on the overall TGFβ signaling pathway in aortic walls of affected individuals has been observed [van de Laar et al 2011].

TGFB2

Gene structure. *TGFB2* consists of eight exons (NM_001135599.2). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. As with *SMAD3*, loss of function is the predicted mechanism that leads to disease. This hypothesis is supported by the observation of whole-gene deletions, nonsense variants, and pathogenic variants affecting critical sites for the activation of the TGFB2 cytokine from its latent state [Lindsay et al 2012].

Normal gene product. The reference sequence NM_001135599.2 has 442 amino acids. TGFB2 belongs to the superfamily of TGFB ligands and has three isoforms: TGFB1, TGFB2, and TGFB3. The TGF-β family comprises three cytokines that regulate multiple aspects of cellular behavior, including proliferation, differentiation, migration, and specification of synthetic repertoire. Postnatally, TGF-β activity is most closely linked to wound healing, productive modulation of the immune system, and multiple pathologic processes including cancer progression and tissue fibrosis.

Abnormal gene product. Similar to SMAD3, despite the predicted loss of function of TGFB2 protein, increased TGFβ signaling was demonstrated in aortic walls of affected individuals who were heterozygous for a pathogenic variant in *TGFB2* [Lindsay et al 2012].

TGFB3

Gene structure. The longest transcript variant of *TGFB3* consists of seven exons (NM_003239.4). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. As with *TGFB2*, loss of function is the predicted mechanism that leads to disease. This hypothesis is supported by the observation of nonsense and out-of-frame splice site variants, and pathogenic variants affecting critical sites for the activation of the TGFB3 cytokine from its latent state [Bertoli-Avella et al 2015].

Normal gene product. The reference sequence NM_003239.4 encodes a protein of 412 amino acids (NP_003230.1). TGFB3 belongs to the superfamily of TGFB ligands and has three isoforms: TGFB1, TGFB2, and TGFB3. The TGF-β family comprises three cytokines that regulate multiple aspects of cellular behavior including proliferation, differentiation, migration, and specification of synthetic repertoire. Postnatally, TGF-β activity is most closely linked to wound healing, productive modulation of the immune system, and multiple pathologic processes including cancer progression and tissue fibrosis.

Abnormal gene product. Similar to TGFB2, despite the predicted loss of function of TGFB3 protein, increased TGFβ signaling was demonstrated in aortic walls of affected individuals who were heterozygous for a pathogenic variant in *TGFB3* [Bertoli-Avella et al 2015].

TGFBR1

Gene structure. *TGFBR1* (also referred to as activin receptor like kinase 5, or ALK-5) consists of nine exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Benign variants in the coding region of *TGFBR1* are uncommon except for the polymorphic repeats encoding polyalanine in exon 1 (reference sequence NM_004612.2).

Pathogenic variants. The large majority of pathogenic variants identified so far are located in the exons coding for the intracellular serine-threonine kinase domain of both receptors. They most commonly involve pathogenic missense variants; only a few nonsense variants have been described.

Normal gene product. *TGFBR1* encodes a protein of 503 amino acids (reference sequence NP_004603.1). TGFβ binds to three subtypes of cell surface receptors, known as the receptors type I, II, and III. Type I and II receptors are both serine/threonine kinase receptors that differ by the presence in type I of a glycine/serine-rich juxta-membrane domain (GS domain), which is critical for its activation. Upon binding of the ligand to the constitutively active type II receptor, TβRI is recruited and transphosphorylated in the GS domain, thereby stimulating its protein kinase activity. The activated type I receptor propagates the signal inside the cell through phosphorylation of receptor-regulated SMADS (R-SMADS), SMAD2, or SMAD3. Activated or phosphorylated R-SMADS form heteromeric complexes with SMAD4 that translocate to the nucleus, where they control gene expression.

Abnormal gene product. See Molecular Pathogenesis.

TGFBR2

Gene structure. *TGFBR2* consists of seven exons (NM_001024847.2). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The large majority of pathogenic variants identified so far are located in the exons coding for the intracellular serine-threonine kinase domain of both receptors. They most commonly involve pathogenic missense variants; only a few nonsense variants have been described.

Normal gene product. *TGFBR2* encodes a protein of 567 amino acids (NP_001020018.1).

Abnormal gene product. See Molecular Pathogenesis.

Chapter Notes

Revision History

- 1 March 2018 (ma) Comprehensive update posted live
- 11 July 2013 (me) Comprehensive update posted live

- 29 April 2008 (cd) Revision: deletion/duplication testing for *TGFBR1* available clinically
- 28 February 2008 (me) Review posted live
- 2 July 2007 (bl) Original submission

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