GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Loeys-Dietz Syndrome

[*Loeys-Dietz Aortic Aneurysm Syndrome. Includes: TGFBR1-Related Loeys-Dietz Syndrome, TGFBR2-Related Loeys-Dietz Syndrome*]

Bart L Loeys, MD, PhD
Center Medical Genetics
Ghent University Hospital
Gent, Belgium
bart.loeys@ugent.be

Harry C Dietz, MD
Victor A McKusick Professor of Medicine and Genetics
Institute of Genetic Medicine
Departments of Pediatrics, Medicine, and Molecular Biology and Genetics
Johns Hopkins University School of Medicine
Baltimore, MD
hdietz@jhmi.edu

Initial Posting: February 28, 2008.

Summary

Disease characteristics. Loeys-Dietz syndrome (LDS) is characterized by vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections) and skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus). Approximately 75% of affected individuals have LDS type I with craniofacial manifestations (ocular hypertelorism, bifid uvula/cleft palate, craniosynostosis); approximately 25% have LDS type II with cutaneous manifestations (velvety and translucent skin; easy bruising; widened, atrophic scars). LDSI and LDSII form a clinical continuum. The natural history of LDS is characterized by aggressive arterial aneurysms (mean age at death 26.1 years) and high incidence of pregnancy-related complications including death and uterine rupture.

Diagnosis/testing. The diagnosis of LDS is based on characteristic clinical findings in the proband and family members and molecular genetic testing of *TGFBR1* and *TGFBR2*, the only two genes known to be associated with LDS. Such testing is available on a clinical basis. No differences in phenotype are observed between individuals with mutations in *TGFBR1* and *TGFBR2*.

Management. *Treatment of manifestations:* 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; beta-adrenergic 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 spinal cord damage. Standard treatment of club feet and severe pes planus. Standard treatment of cleft palate and craniosynostosis; management by a craniofacial team is preferred. *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. *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 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; activities that cause joint injury or pain. *Testing of relatives at risk:* If the causal *TGFBR1* or *TGFBR2* mutation is known in the proband, molecular genetic testing can be used to clarify genetic status of family members at risk; if the mutation 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.

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* gene mutation. Each child of an individual with LDS has a 50% chance of inheriting the mutation and the disorder. Prenatal diagnosis for pregnancies at increased risk for LDS is possible if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

Loeys-Dietz syndrome (LDS) is characterized by four major groups of clinical findings that include the following [Loeys et al 2005]:

Vascular

- **Dilatation or dissection of the aorta.** Aortic root dilation is present in more than 95% of probands.
- **Other arterial aneurysms and tortuosity.** Evaluation is best done with magnetic resonance angiography (MRA) or CT scan with 3D reconstruction from head to pelvis to identify arterial aneurysms and arterial tortuosity throughout the arterial tree.

  Note: 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
- Arachnodactyly
- Talipes equinovarus

Craniofacial

- Ocular hypertelorism
- Bifid uvula/cleft palate
- Craniosynostosis, in which all sutures can be involved: most commonly the sagittal suture (resulting in dolichocephaly), but also the coronal suture (resulting in brachycephaly) and metopic suture (resulting in trigonocephaly)

Cutaneous. In persons without craniofacial features, important cutaneous findings include the following:

- Translucent skin

- Easy bruising
- Dystrophic scars

Two clinical presentations were initially identified. It is now recognized that LDS is a continuum that includes the following:

- LDS type I (~75% of individuals) with vascular, skeletal, and craniofacial findings
- LDS type II (~25% of individuals) with vascular, skeletal, and cutaneous findings

Note: (1) Minimal diagnostic criteria have not been established. (2) Molecular genetic testing of *TGFBR1* and *TGFBR2* plays an important role in diagnosis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. *TGFBR1* and *TGFBR2* (transforming growth factor beta receptor genes 1 and 2) are the genes known to harbor mutations in individuals with LDS.

Note: No differences in phenotype are observed between individuals with mutations in *TGFBR1* and *TGFBR2*.

Clinical testing

- **Sequence analysis.** More than 95% of individuals with findings typical of LDS (arterial tortuosity/aortic aneurysm, ocular hypertelorism, bifid uvula, and translucent skin) have a *TGFBR1* or *TGFBR2* mutation [Author, personal observation].
- **Deletion analysis.** Deletion testing using a variety of methods to detect exonic, multiexonic, and whole-gene deletions for *TGFBR1* and *TGFBR2* is available on a clinical basis. Mutation detection frequency by deletion analysis is as yet unknown.

  Note: To date, the authors have not identified *TGFBR1* or *TGFBR2* deletions in individuals with LDS [personal observation].

Table 1 summarizes molecular genetic testing for this disorder.

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

Gene Symbol	Proportion of LDS Attributed to Mutations in This Gene	Test Method	Mutation Detection Frequency by Test Method	Test Availability
TGFBR1	~25%	Sequence analysis	95%	Clinical Testing
TGFBR2	~75%	Sequence analysis	95%	Clinical Testing
		Deletion analysis [1]	Unknown	

1. Use of a variety of techniques to detect exonic, multiexonic, or whole-gene deletions

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirmation of the diagnosis in a proband relies on identification of a disease-causing mutation:

- Molecular genetic testing can begin with sequence analysis of *TGFBR2*, which accounts for approximately 75% of causative mutations.
- If no *TGFBR2* mutation is identified, *TGFBR1*, which accounts for approximately 25% of causative mutations, can be sequenced.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

A number of disorders have been thought to be caused by mutations in *TGFBR1* or *TGFBR2* (see Differential Diagnosis). To date, however, mutations in the two genes have only been associated with LDS.

Clinical Description

Natural History

The clinical and molecular characterization of 52 families with *TGFBR1* and *TGFBR2* mutations has been described [Loeys et al 2006]. Approximately 75% had Loeys-Dietz syndrome type 1 (LDS type I) with typical vascular, skeletal, and craniofacial manifestations. Approximately 25% had LDS type II with typical vascular, skeletal, and cutaneous manifestations including velvety and translucent skin, easy bruising, widened atrophic scars; uterine rupture; and arterial aneurysms/dissections within the cerebral, thoracic, and abdominal vascular trees. The current belief that LDS types I and II are part of a clinical continuum is supported by the observation that identical mutations can lead to LDS type I or type II.

The natural history of LDS types I and II is characterized by aggressive arterial aneurysms (mean age at death 26.1 years) and high incidence of pregnancy-related complications including death and uterine rupture (6/11 pregnant women). Individuals with LDS type I had earlier cardiovascular surgery (13.0 vs. 26.9 years) and death (22.1 vs. 31.8 years) compared to those with LDS type II. Of the 54 vascular surgeries in the cohort of 52 individuals with LDS, the one intraoperative mortality represented a much lower rate than that in EDS, vascular type [Loeys et al 2006]. Although these figures may be somewhat biased by the clinical severity of individuals initially ascertained as having LDS, catastrophic complications of pregnancy have also been observed in women at the milder end of the clinical spectrum.

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. The arterial involvement is widespread and arterial tortuosity is present in most individuals with a *TGFBR1* or *TGFBR2* mutation. Most affected individuals have multiple arterial anomalies.

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. 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.

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.

Other recurrent findings include patent ductus arteriosus, atrial septal defects, and bicuspid aortic valve. Although all of these findings are common in the general population, the incidence in LDS exceeds by at least five times that seen in the general population.

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

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. This picture of cystic medial necrosis does not distinguish LDS from other causes of aortic aneurysm.

Skeletal. The skeletal findings are characterized by Marfan syndrome-like skeletal features and joint laxity or contractures:

- 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 (club feet).

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

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 at least about one-third 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; however, it 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.

Craniofacial. In its most typical presentation, LDS presents with ocular 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.

Skin. 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.

Eye. Myopia is less frequent and less severe than that seen in Marfan syndrome. Significant refractive errors can lead to amblyopia. Retinal detachment has been reported rarely. Other common ocular features include strabismus and blue sclerae. 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. Complications include aortic dissection/rupture or uterine rupture during pregnancy and delivery, or aortic dissection/rupture in the immediate postpartum period.

Genotype-Phenotype Correlations

Few genotype-phenotype correlations exist in LDS. The current belief that LDS type I and II are part of a clinical continuum suggests that modifying genetic or stochastic factors govern phenotypic expression.

No differences in phenotype are observed between individuals with mutations in *TGFBR1* and *TGFBR2* and no apparent phenotype-genotype correlations explain the distinction between LDS type I and LDS type II.

Mutations cluster in the intracellular part of both receptors (serine-threonine kinase domains). Few mutations have been described in the extracellular domain.

Most mutations are missense mutations that substitute highly conserved amino acids of either receptor. However, a splice-site mutation in the extracellular domain and a nonsense mutation in the penultimate exon, predicted to generate a stable transcript but a protein product lacking the terminal half of the kinase domain, lead to LDS phenotypes that are indistinguishable from those associated with missense mutations.

No differences are apparent between the mutations that the authors and others have found in persons with LDS versus those described as causing typical Marfan syndrome or familial thoracic aortic aneurysm and dissection (FTAAD). Indeed, many of the identical mutations described as causing Marfan syndrome or FTAAD were found in persons with typical LDS type I or LDS type II [Loeys et al 2006, unpublished data].

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.

Anticipation

Anticipation has not been observed in LDS.

Nomenclature

Marfan syndrome type 2 (MFS2). Some confusion exists in the current literature regarding use of the term "Marfan syndrome, type 2" (MFS2). An opinion expressed by others and shared by the authors is that the term "LDS" (rather than "MFS2") most efficiently conveys the following information to health care providers [Arbustini et al 2006]:

- The term MFS2 was initially applied by Mizuguchi et al (2004) to describe individuals with "classic" Marfan syndrome caused by mutations in *TGFBR2*. At the time of this report other discriminating features of LDS had not been described.
- Genotyping of 93 individuals presenting with classic Marfan syndrome identified *FBN1* mutations in 86 (93%); none of the remainder had mutations in either *TGFBR1* or *TGFBR2* [Loeys et al 2004, Loeys et al 2005]. (See Marfan Syndrome.)
- In the authors' experience, no individual with a *TGFBR1* or *TGFBR2* mutation has had clinical manifestations diagnostic of Marfan syndrome [Loeys et al 2006; authors, personal observation].
- Consensus is emerging that all individuals with *TGFBR1* or *TGFBR2* mutations have a more aggressive vascular course than that observed in Marfan syndrome with routine involvement of vascular segments distant from the aortic root.

Prevalence

The prevalence of LDS is unknown. No apparent enrichment in any ethnic or racial group and no gender preference have been reported.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The clinical and molecular characterization of 52 families with *TGFBR1* and *TGFBR2* mutations has been described [Loeys et al 2006]:

- Approximately 75% had Loeys-Dietz syndrome type 1 (LDS type I) with typical vascular, skeletal, and craniofacial manifestations of LDS. Virtually all had clinical features distinct from those of MFS and familial thoracic arterial aneurysms (FTAA), including ocular hypertelorism, cleft palate/bifid uvula, arterial tortuosity, aneurysms beyond the aortic root, skin abnormalities, and craniosynostosis.
- Approximately 25% had LDS type II with cutaneous features similar to vascular Ehlers-Danlos syndrome (EDS), i.e., velvety and translucent skin, easy bruising, widened atrophic scars, uterine rupture, and arterial aneurysms/dissections within the cerebral, thoracic, and abdominal circulations.

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 et al 2005]. *FBN1* mutations associate with a broad phenotypic continuum, ranging from isolated features of Marfan syndrome [Dietz et al 1991] to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. Myopia is the most common ocular feature; displacement of the lens from the center of the pupil, seen in approximately 60% of affected individuals, is a hallmark feature. People with Marfan syndrome are at increased risk for retinal detachment, glaucoma, and early cataract formation. Skeletal involvement is characterized by bone overgrowth and joint laxity. The extremities are disproportionately long for the size of the trunk (dolichostenomelia). Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum). Scoliosis is common and can be mild or severe and progressive. The major sources of morbidity and early mortality in the Marfan syndrome relate to the cardiovascular system. 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. With proper management, the life expectancy of someone with Marfan syndrome approximates that of the general population.

Molecular genetic testing of *FBN1*, the only gene known to be associated with Marfan syndrome, detects mutations in 70%-93% of probands. Inheritance is autosomal dominant. About one-third of individuals have a *de novo* mutation.

MASS phenotype 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 mutations in *FBN1* can be causative. Inheritance is autosomal dominant.

Shprintzen-Goldberg syndrome (SGS) is characterized by craniosynostosis (involving the coronal, sagittal, or lambdoid sutures), distinctive craniofacial features, skeletal changes (dolichostenomelia, arachnodactyly, camptodactyly, pes planus, pectus excavatum or carinatum, scoliosis, joint hypermobility, or contractures), neurologic abnormalities, mild-to-moderate intellectual disability, and brain anomalies (hydrocephalus, dilatation of the lateral ventricles, and Chiari 1 malformation). Cardiovascular anomalies (mitral valve prolapse, mitral regurgitation, and aortic regurgitation) may occur, but aortic root dilatation is most likely not

found. Minimal subcutaneous fat, abdominal wall defects, cryptorchidism in males, and myopia are also characteristic findings.

The diagnosis of Shprintzen-Goldberg syndrome is suspected in individuals with characteristic clinical findings and radiographic findings showing C1-C2 abnormality, wide anterior fontanel, thin ribs, 13 pairs of ribs, square-shaped vertebral bodies, and osteopenia. The causative gene is unknown. Molecular analysis of a series of individuals with typical SGS did not reveal mutations in the *TGFBR1* or *TGFBR2* [Loeys et al 2005]. Inheritance is unknown.

Discriminating factors, characteristic of LDS but rare or absent in SGS, include aortic aneurysm/dissection, arterial tortuosity, cleft palate/bifid uvula, and prominent skin manifestations. Another distinguishing feature of LDS is the low incidence of developmental delay.

Note: A patient 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].

The Ehlers-Danlos syndromes (EDS) are a heterogeneous group of disorders that are currently classified according to the Villefranche nosology [Beighton et al 1998], in which the former numbered classification system has been replaced by one that describes the major clinical symptoms. The former types I/II, III, IV, and VI are now called the classic, hypermobile, vascular, and kyphoscoliotic type of EDS, respectively.

- **EDS, classic type** is often caused by mutations in the genes encoding for type V collagen *(COL5A1*, *COL5A2*); tenascin X *(TNX*); and, rarely, type I collagen *(COL1A1*). A proportion of individuals with EDS, classic type and **EDS, hypermobility type** have had aortic root enlargement, but progression of the dilatation associated with these diseases or a predisposition for aortic dissection has not been established [Wenstrup et al 2002]. Arguing against the progressive nature of these aortic dilatations is the absence of a history of sudden death in individuals with these disorders.
- **EDS, vascular type (EDS IV)** is characterized by thin, translucent skin, easy bruising, characteristic facial appearance, and arterial, intestinal, and/or uterine fragility [Pepin et al 2000]. Vascular rupture or dissection and gastrointestinal perforation or organ rupture are the presenting signs in 70% of adults. Arterial rupture may be preceded by aneurysm, arteriovenous fistulae, or dissection, or it may occur spontaneously. Neonates may present with clubfoot and/or congenital dislocation of the hips. In childhood, inguinal hernia, pneumothorax, and recurrent joint dislocation or subluxation are common. The median age of death is 48 years.

  The diagnosis of EDS, vascular type is based on clinical findings and confirmed by abnormal type III collagen biosynthesis and/or identification of a disease-causing mutation in *COL3A1*, the only gene known to be associated with EDS, vascular type. Inheritance is autosomal dominant.

  In individuals with a clinical suspicion of EDS, vascular type, normal collagen biochemistry, and absence of *COL3A1* mutations, the diagnosis of LDS type II should be considered and molecular analysis of the *TGFBR1* and *TGFBR2* genes should be performed.

  Arginine-to-cysteine mutations in *COL1A1* have been identified in a recently described subset of affected individuals who typically present with aneurysms of the abdominal aorta and iliac arteries reminiscent of vascular EDS. Distinct abnormalities on collagen electrophoresis are observed [Malfait et al 2007].

- **EDS, valvular type,** caused by mutations in *COL1A2*, is an autosomal recessive form of EDS with joint hypermobility, skin hyperextensibility, and severe cardiac valvular defects [Schwarze et al 2004].
- **EDS, kyphoscoliotic form (EDS VI)** is a generalized connective tissue disorder characterized by kyphoscoliosis, joint laxity, muscle hypotonia, and, in some individuals, ocular problems. Intelligence is normal; life span may be normal, but affected individuals are at risk for rupture of medium-sized arteries and respiratory compromise if kyphoscoliosis is severe. Aortic dilation and rupture can also be seen.

  EDS, kyphoscoliotic form is caused by deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1: lysyl hydroxylase 1). The diagnosis of EDS, kyphoscoliotic form relies on the demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by HPLC, a highly sensitive and specific test. Assay of lysyl hydroxylase enzyme activity in skin fibroblasts is also available. Mutations in *PLOD1*, the gene encoding the enzyme lysyl hydroxylase 1, are causative. Inheritance is autosomal recessive.

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). Most affected individuals have "crumpled" ears that present as a folded upper helix of the external ear; most have contractures of major joints (knees and ankles) at birth. The proximal interphalangeal joints also have flexion contractures (i.e., camptodactyly), as do the toes. Hip contractures, adducted thumbs, and club foot may occur. The majority of affected individuals have muscular hypoplasia. Contractures usually improve with time. Kyphosis/scoliosis is present in about half of all affected individuals. It begins as early as infancy, is progressive, and causes the greatest morbidity in CCA. 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 diagnosed on the basis of clinical findings. *FBN2*, the gene encoding the extracellular matrix microfibril fibrillin 2, is the only gene known to be associated with CCA [Putnam et al 1995]. Inheritance is autosomal dominant.

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]. In addition, skeletal and skin involvement is common. The underlying genetic defect is homozygosity for loss-of-function mutations in *SLC2A10*, the gene encoding the facilitative glucose transporter GLUT10 [Coucke et al 2006]. Although it is a surprising finding that a glucose transporter defect causes 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 dilation 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; broad or webbed neck; unusual chest shape with superior pectus carinatum, inferior pectus excavatum, and apparently low-set nipples; developmental delay of variable degree; cryptorchidism; and characteristic facies. Varied coagulation defects and lymphatic dysplasias are frequently observed. 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. Mild intellectual disability is seen in up to one-third of affected individuals. Ocular abnormalities, including strabismus, refractive errors, amblyopia, and nystagmus, occur in up to 95% of affected individuals.

Diagnosis of Noonan syndrome is made on clinical grounds. *PTPN11*, *KRAS*, and *SOS1* are the three genes known to be associated with the disorder. Mutations in these genes account for 50%, fewer than 5%, and approximately 10% of affected individuals, respectively. 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:

- Heterozygous mutations in the elastin gene *(ELN*) cause ADCL. However, it is now known that persons with *ELN* mutations can also have aortic aneurysms that require aortic root replacement or lead to aortic rupture in early adulthood. The aortic pathology of these aneurysms was indistinguishable from that seen in Marfan syndrome. It remains to be seen whether *ELN* is mutated in persons with TAAD [Urban et al 2005].
- Mutations in the gene encoding fibulin-4 cause ARCL with arterial tortuosity and a predisposition for aneurysms and dissections [Hucthagowder et al 2006].
- Mutations in the gene encoding fibulin-5 also cause ARCL with typical skin and pulmonary manifestations (emphysema) and arterial tortuosity, but not aneurysms [Loeys et al 2002].

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 dilation 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, mutations have been identified in *NOTCH1* and *KCNJ2* in rare individuals with additional congenital cardiac malformations. *NOTCH1* mutations 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].

Persistent patent ductus arteriosus with thoracic aortic aneurysm (PDA/TAA). A recent report describing a single large family with 179 members that have a high incidence of 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]. The causal gene is *MYH11*, encoding the myosin heavy chain protein 11, a specific contractile protein of smooth muscle cells. 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) 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.

Familial thoracic aortic aneurym/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]:

- *TAAD1* was the first locus to be mapped. In a study of 15 families in which TAAD segregated in an autosomal dominant manner with reduced penetrance, nine showed linkage to 5q13-q14 [Guo et al 2001]. *TAAD1* has been confirmed as a major predisposition locus for TAAD by a subsequent study in which seven of 11 Finnish families showed linkage to the same locus [Kakko et al 2003].
- *FAA1* was the second locus to be mapped. A single large family showed linkage to 11q23-q24 [Vaughan et al 2001]. In contrast to *TAAD1*, the disease associated with

FAA1 is characterized by a more diffuse vascular disease, with aneurysms affecting both the thoracic and abdominal aorta as well as other arteries.

- *TAAD2*, the third locus to be mapped (3p24-p25) [Hasham et al 2003], is now known to be *TGFBR2* [Pannu et al 2005]. *TGFBR2* mutations all affecting the same codon (Arg460His and 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* mutations 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* mutation 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 *TGFBR2* mutation does not seem appropriate.
- Mutations in *ACTA2*, encoding for the smooth muscle actin alpha 2, have been identified in approximately 14% of families with autosomal dominant thoracic aortic aneurysm. Selected individuals also presented with livido reticularis, iris flocculi, cerebral aneurysm, bicuspid aortic valve, and persistent ductus arteriosus [Guo et al 2007].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Loeys-Dietz syndrome (LDS), the following evaluations are recommended:

- Echocardiography. Aortic root measurements must be interpreted based on consideration of normal values for age and body size [Roman et al 1989]. Select findings may require the immediate attention of a cardiologist or cardiothoracic surgeon (e.g., severe aortic dilatation).
- 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 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 that includes: 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 and blue sclerae

Treatment of Manifestations

Management of LDS is most effective through the coordinated input of a multidisciplinary team of specialists including a medical geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon.

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 other medications are used to reduce hemodynamic stress.
- Aneurysms are amenable to early and aggressive surgical intervention (in contrast to EDS, vascular type, in which surgery is used as a last resort because of the extremely high rate of intraoperative complications and death). Many individuals can receive 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 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 cm, allowing the placement of a graft of sufficient size to accommodate growth.
  - 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 individual patients.

Note: This practice may not eliminate risk of dissection and death, and earlier intervention based on family history or the patient'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.

Eye. 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 the risks associated with pregnancy is recommended.

Prevention of Secondary Complications

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

Because of a high risk of cervical spine instability, an 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
- 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)

Testing of Relatives at Risk

If the causal *TGFBR1* or *TGFBR2* mutation is identified in the proband, molecular genetic testing can be used to clarify genetic status of family members at risk.

If the causal mutation is not known, relatives at risk should be evaluated for signs of the disorder. 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.

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 are underway to determine whether TGFβ antagonizing agents, such as angiotensin II receptor type 1 blockers, can slow or prevent manifestations of LDS. The safety and efficacy of such interventions has not been addressed for persons with LDS.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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* gene mutation.

- If the *TGFBR1* or *TGFBR2* mutation in a proband is known, molecular genetic testing of both parents is indicated. If the mutation is unknown, it is appropriate to evaluate both parents for manifestations of LDS, including a comprehensive clinical examination.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the 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 but greater than that of the general population because of reported (although rare) cases of somatic and germline mosaicism.

Offspring of a proband

- Each child of an individual with LDS has a 50% chance of inheriting the mutation and the disorder.
- The penetrance of disease-causing *TGFBR1* and *TGFBR2* mutations is reported to be near 100%; thus, offspring who inherit a mutant allele 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 genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

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

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal 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. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for LDS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be

performed. Linkage analysis should be used with caution unless *TGFBR1* or *TGFBR2* marker alleles can be shown to cosegregate with disease in a large family.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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

Requests for prenatal testing for LDS are uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Loeys-Dietz Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
TGFBR1	9q33-q34	TGF-beta receptor type-1
TGFBR2	3p22	TGF-beta receptor type-2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Loeys-Dietz Syndrome

190181	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I; TGFBR1
190182	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE II; TGFBR2
609192	LOEYS-DIETZ SYNDROME; LDS

Table C. Genomic Databases for Loeys-Dietz Syndrome

Gene Symbol	Entrez Gene	HGMD
TGFBR1	7046 (MIM No. 190181)	TGFBR1
TGFBR2	7048 (MIM No. 190182)	TGFBR2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *TGFBR1* consists of nine exons coding for 503 amino acids. *TGFBR1* is also referred to as activin receptor like kinase 5 (ALK-5). Few or no polymorphisms have been described in *TGFBR1*. Coding SNPs are uncommon except for the polymorphic polyalanine stretch in exon 1. However, dbSNP lists more than 200 intronic entries.

TGFBR2 consists of seven exons coding for 567 amino acids. Some polymorphisms have been identified in *TGFBR2*.

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

Normal gene product: 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: In the initial description of *TGFBR2* mutations causing Marfan syndrome [Mizuguchi et al 2004] it was observed that recombinantly expressed mutant 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 co-expressed wild-type receptor. These data were interpreted to infer haploinsufficiency and consequent reduced TGFβ signaling as the relevant pathogenic mechanisms. In keeping with this hypothesis, one of the original Marfan syndrome-like patients was shown to harbor a translocation breakpoint within *TGFBR2*. Complicating this hypothesis, however, is the observation of a distinct paucity of nonsense or frameshift mutations in either of the TGFβ receptor genes in persons with LDS or related phenotypes. The mutant receptor subunits may not traffick to the cell surface or may not cycle, resulting in "functional haploinsufficiency." Furthermore, the only reported nonsense mutation occurs at the very distal margin of the penultimate exon. As opposed to more proximal nonsense mutations, this context is not predicted to induce nonsense-mediated mRNA decay (NMD) and clearance of the mutant transcripts. As a result, most (if not all) mutations in the TGFβ receptor genes associated with vascular phenotypes are predicted to give rise to a mutant 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. Furthermore, 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 mutant receptors may not be informative for the situation in vivo when affected individuals are heterozygous for these mutations. 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 mutant, 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 mutant TGFβ receptors in LDS.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Heart Association
7272 Greenville Avenue
Dallas TX 75231
Phone: 1-800-242-8721
american heart association: aortic aneurysms

Medline Plus
Abdominal aortic aneurysm

National Marfan Foundation
The National Marfan Foundation provides education and support for other heritable connective tissue disorders that share some features of Marfan syndrome.
22 Manhasset Avenue
Port Washington NY 11050
Phone: 800-8-MARFAN ext 10 (800-862-7326); 516-883-8712
Fax: 516-883-8040
Email: staff@marfan.org
Related Disorders: Loeys-Dietz

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Arbustini E, Marziliano N, Magrassi L. Aneurysm syndromes and TGFbeta receptor mutations. N Engl J Med. 2006;355:2155. [PubMed: 17108349]

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998;77:31–7. [PubMed: 9557891]

Coady MA, Davies RR, Roberts M, Goldstein LJ, Rogalski MJ, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Familial patterns of thoracic aortic aneurysms. Arch Surg. 1999;134:361–7. [PubMed: 10199307]

Coucke PJ, Willaert A, Wessels MW, Callewaert B, Zoppi N, De Backer J, Fox JE, Mancini GM, Kambouris M, Gardella R, Facchetti F, Willems PJ, Forsyth R, Dietz HC, Barlati S, Colombi M, Loeys B, De Paepe A. Mutations in the facilitative glucose transporter GLUT10 alter angiogenesis and cause arterial tortuosity syndrome. Nat Genet. 2006;38:452–7. [PubMed: 16550171]

Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, Puffenberger EG, Hamosh A, Nanthakumar EJ, Curristin SM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature. 1991;352:337–9. [PubMed: 1852208]

Guo D, Hasham S, Kuang SQ, Vaughan CJ, Boerwinkle E, Chen H, Abuelo D, Dietz HC, Basson CT, Shete SS, Milewicz DM. Familial thoracic aortic aneurysms and dissections: genetic heterogeneity with a major locus mapping to 5q13-14. Circulation. 2001;103:2461–8. [PubMed: 11369686]

Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, Avidan N, Bourgeois S, Estrera AL, Safi HJ, Sparks E, Amor D, Ades L, McConnell V, Willoughby CE, Abuelo D, Willing M, Lewis RA, Kim DH, Scherer S, Tung PP, Ahn C, Buja LM, Raman CS, Shete SS, Milewicz DM. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007;39:1488–93. [PubMed: 17994018]

Gupta PA, Putnam EA, Carmical SG, Kaitila I, Steinmann B, Child A, Danesino C, Metcalfe K, Berry SA, Chen E, Delorme CV, Thong MK, Ades LC, Milewicz DM. Ten novel FBN2 mutations in congenital contractural arachnodactyly: delineation of the molecular pathogenesis and clinical phenotype. Hum Mutat. 2002;19:39–48. [PubMed: 11754102]

Hasham SN, Willing MC, Guo DC, Muilenburg A, He R, Tran VT, Scherer SE, Shete SS, Milewicz DM. Mapping a locus for familial thoracic aortic aneurysms and dissections (TAAD2) to 3p24-25. Circulation. 2003;107:3184–90. [PubMed: 12821554]

Hucthagowder V, Sausgruber N, Kim KH, Angle B, Marmorstein LY, Urban Z. Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. Am J Hum Genet. 2006;78:1075–80. [PubMed: 16685658]

Judge DP, Dietz HC. Marfan's syndrome. Lancet. 2005;366:1965–76. [PubMed: 16325700]

Kakko S, Raisanen T, Tamminen M, Airaksinen J, Groundstroem K, Juvonen T, Ylitalo A, Uusimaa P, Savolainen MJ. Candidate locus analysis of familial ascending aortic aneurysms and dissections confirms the linkage to the chromosome 5q13-14 in Finnish families. J Thorac Cardiovasc Surg. 2003;126:106–13. [PubMed: 12878945]

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: 15998682]

Kosaki K, Takahashi D, Udaka T, Kosaki R, Matsumoto M, Ibe S, Isobe T, Tanaka Y, Takahashi T. Molecular pathology of Shprintzen-Goldberg. Am J Med Genet A. 2006;140:104–8. [PubMed: 16333834]

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: 15731757]

Loeys B, De Backer J, Van Acker P, Wettinck K, Pals G, Nuytinck L, Coucke P, De Paepe A. Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. Hum Mutat. 2004;24:140–6. [PubMed: 15241795]

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: 16928994]

Loeys B, Van Maldergem L, Mortier G, Coucke P, Gerniers S, Naeyaert JM, De Paepe A. Homozygosity for a missense mutation in fibulin-5 (FBLN5) results in a severe form of cutis laxa. Hum Mol Genet. 2002;11:2113–8. [PubMed: 12189163]

Loscalzo ML, Goh DL, Loeys B, Kent KC, Spevak PJ, Dietz HC. Familial thoracic aortic dilation and bicommissural aortic valve: a prospective analysis of natural history and inheritance. Am J Med Genet A. 2007;143:1960–7. [PubMed: 17676603]

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: 17211858]

Martin LJ, Ramachandran V, Cripe LH, Hinton RB, Andelfinger G, Tabangin M, Shooner K, Keddache M, Benson DW. Evidence in favor of linkage to human chromosomal regions 18q, 5q and 13q for bicuspid aortic valve and associated cardiovascular malformations. Hum Genet. 2007;121:275–84. [PubMed: 17203300]

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: 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: 10377302]

Pannu H, Fadulu VT, Chang J, Lafont A, Hasham SN, Sparks E, Giampietro PF, Zaleski C, Estrera AL, Safi HJ, Shete S, Willing MC, Raman CS, Milewicz DM. Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. Circulation. 2005;112:513–20. [PubMed: 16027248]

Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med. 2000;342:673–80. [PubMed: 10706896]

Putnam EA, Zhang H, Ramirez F, Milewicz DM. Fibrillin-2 (FBN2) mutations result in the Marfan-like disorder, congenital contractural arachnodactyly. Nat Genet. 1995;11:456–8. [PubMed: 7493032]

Robinson P, Neumann L, Tinschert S. Response to Kosaki et al, Molecular Pathology of Shprintzen-Goldberg. Am J Med Genet A. 2006;140:109–10. [PubMed: 16333834]

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: 2773795]

Schwarze U, Hata RI, McKusick VA, Shinkai H, Hoyme HE, Pyeritz RE, Byers PH. Rare autosomal recessive cardiac valvular form of Ehlers-Danlos syndrome results from mutations in the COL1A2 gene that activate the nonsense-mediated RNA decay pathway. Am J Hum Genet. 2004;74:917–30. [PubMed: 15077201]

Urban Z, Gao J, Pope FM, Davis EC. Autosomal dominant cutis laxa with severe lung disease: synthesis and matrix deposition of mutant tropoelastin. J Invest Dermatol. 2005;124:1193–9. [PubMed: 15955094]

Vaughan CJ, Casey M, He J, Veugelers M, Henderson K, Guo D, Campagna R, Roman MJ, Milewicz DM, Devereux RB, Basson CT. Identification of a chromosome 11q23.2-q24 locus for familial aortic aneurysm disease, a genetically heterogeneous disorder. Circulation. 2001;103:2469–75. [PubMed: 11369687]

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: 12180144]

Wessels MW, Catsman-Berrevoets CE, Mancini GM, Breuning MH, Hoogeboom JJ, Stroink H, Frohn-Mulder I, Coucke PJ, Paepe AD, Niermeijer MF, Willems PJ. Three new families with arterial tortuosity syndrome. Am J Med Genet A. 2004;131:134–43. [PubMed: 15529317]

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: 17470566]

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: 16444274]

Suggested Readings

Akutsu K, Morisaki H, Takeshita S, Sakamoto S, Tamori Y, Yoshimuta T, Yokoyama N, Nonogi H, Ogino H, Morisaki T. Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations in the transforming growth factor-beta receptor genes. Circ J. 2007;71:1305–9. [PubMed: 17652900]

Johnson PT, Chen JK, Loeys BL, Dietz HC, Fishman EK. Loeys-Dietz syndrome: MDCT angiography findings. AJR Am J Roentgenol189:W29-35. 2007 [PubMed: 17579132]

Ki CS, Jin DK, Chang SH, Kim JE, Kim JW, Park BK, Choi JH, Park IS, Yoo HW. Identification of a novel TGFBR2 gene mutation in a Korean patient with Loeys-Dietz aortic aneurysm syndrome; no mutation in TGFBR2 gene in 30 patients with classic Marfan's syndrome. Clin Genet. 2005;68:561–3. [PubMed: 16283890]

LeMaire SA, Pannu H, Tran-Fadulu V, Carter SA, Coselli JS, Milewicz DM. Severe aortic and arterial aneurysms associated with a TGFBR2 mutation. Nat Clin Pract Cardiovasc Med. 2007;4:167–71. [PubMed: 17330129]

Matyas G, Arnold E, Carrel T, Baumgartner D, Boileau C, Berger W, Steinmann B. Identification and in silico analyses of novel TGFBR1 and TGFBR2 mutations in Marfan syndrome-related disorders. Hum Mutat. 2006;27:760–9. [PubMed: 16791849]

Mizuguchi T, Matsumoto N. Recent progress in genetics of Marfan syndrome and Marfan-associated disorders. J Hum Genet. 2007;52:1–12. [PubMed: 17061023]

Sakai H, Visser R, Ikegawa S, Ito E, Numabe H, Watanabe Y, Mikami H, Kondoh T, Kitoh H, Sugiyama R, Okamoto N, Ogata T, Fodde R, Mizuno S, Takamura K, Egashira M, Sasaki N, Watanabe S, Nishimaki S, Takada F, Nagai T, Okada Y, Aoka Y, Yasuda K, Iwasa M, Kogaki S, Harada N, Mizuguchi T, Matsumoto N. Comprehensive genetic analysis of relevant four genes in 49 patients with Marfan syndrome or Marfan-related phenotypes. Am J Med Genet A. 2006;140:1719–25. [PubMed: 16835936]

Singh KK, Rommel K, Mishra A, Karck M, Haverich A, Schmidtke J, Arslan-Kirchner M. TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loeys-Dietz syndrome. Hum Mutat. 2006;27:770–7. [PubMed: 16799921]

Williams JA, Loeys BL, Nwakanma LU, Dietz HC, Spevak PJ, Patel ND, Francois K, DeBacker J, Gott VL, Vricella LA, Cameron DE. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg. 2007;83:S757–63. [PubMed: 17257922]

Chapter Notes

Revision History

- 28 February 2008 (me) Review posted to live Web site
- 2 July 2007 (bl) Original submission