Loeys-Dietz Syndrome

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Abstract

Loeys-Dietz syndrome is an autosomal dominant aortic aneurysm syndrome characterized by multisystemic involvement. The most typical clinical triad includes hypertelorism, bifid uvula or cleft palate and aortic aneurysm with tortuosity. Natural history is significant for aortic dissection at smaller aortic diameter and arterial aneurysms throughout the arterial tree. The genetic cause is heterogeneous and includes mutations in genes encoding for components of the transforming growth factor beta (TGFβ) signalling pathway: *TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2* and *TGFB3*. Despite the loss of function nature of these mutations, the patient-derived aortic tissues show evidence of increased (rather than decreased) TGFβ signalling. These insights offer new options for therapeutic interventions.

Keywords

Loeys-Dietz syndrome · Hypertelorism · Bifid uvula/cleft palate · Craniosynostosis · Dilatation of aortic root · Aortic aneurysm with tortuosity · Aortic dissection · Mutations in *TGFBR1* · *TGFBR2* · *SMAD3* or *TGFB2* · Increased TGFβ signalling · Overlap with Marfan and Ehlers-Danlos syndrome · Pectus excavatum or pectus carinatum · Scoliosis · Joint laxity · Arachnodactyly · Talipes equinovarus · Cervical spine malformation · Spondylolisthesis · Acetabular protrusion · Pes planus · Osteoporosis · Retrognathia · Strabismus · Blue sclerae · Myopia · Amblyopia · Translucent skin · Easy bruising · Dystrophic scars · Spontaneous bowel rupture · Peripartal uterine rupture · Aneurysm- osteoarthritis syndrome · Mutations in *SKI* · Shprintzen-Goldberg syndrome · Cutis laxa · Familial thoracic aortic aneurysm · Mutations in *ACTA2* · *MYH11* and *MYLK*

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Abbreviations

AOS	Aneurysm-osteoarthritis syndrome
ARCL1	Autosomal recessive cutis laxa type 1
ASD/VSD	Atrial and ventricular septum defects
ATS	Arterial tortuosity syndrome
BAV	Bicuspid aortic valve
BMP	Bone morphogenetic protein
EDS	Ehlers-Danlos syndrome
LDS	Loeys-Dietz syndrome
MFS	Marfan syndrome
PDA	Patent ductus arteriosus
PLOD1	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1
SGS	Shprintzen-Goldberg syndrome
TAAD	Thoracic aortic aneurysms and dissections
TGFβ	Transforming growth factor β
TGFβR	Transforming growth factor β receptor

11.1 Introduction

The Loeys-Dietz syndrome (LDS, MIM#609192) was first described by Loeys and Dietz in 2005. The initial paper presented ten probands with a novel aortic aneurysm syndrome characterized by the clinical triad of hypertelorism, bifid uvula/cleft palate and aortic/arterial aneurysms and tortuosity (Loeys et al. 2005). Although these presented the most typical characteristics, a widespread involvement of different organ systems was also recognized. These included craniofacial (e.g., craniosynostosis), skeletal (joint laxity and contractures), integumental (skin hyperextensibility, dural ectasia) and ocular findings (e.g., strabismus). Although LDS shows clinical overlap with Marfan syndrome (MFS), it can be clinically distinguished from the latter. Shared features include aortic root aneurysm, pectus deformities, scoliosis and arachnodactyly. Distinguishing findings are craniosynostosis, hypertelorism, cleft palate or bifid uvula, cervical spine instability, club feet, and most importantly widespread arterial aneurysms with tortuosity and early aortic rupture. Since the initial description of LDS, families with aortic aneurysms without significant outward features have also been described (Pannu et al. 2005; Tran-Fadulu et al. 2009).

11.2 Inheritance and Mutational Spectrum

LDS is an autosomal dominant disorder. About two-thirds of cases are the consequence of *de novo* mutations, whereas the other one-third are familial. In general, the more severe cases with marked craniofacial and skeletal findings are the consequence of a *de novo* mutation, whereas the milder cases tend to be familial. Both non-penetrance (Loeys et al. 2006) and mosaicism (Watanabe et al. 2008) have been reported.

Two major genes have been initially associated with LDS. These genes encode the transforming growth factor β receptors 1 and 2, *TGFBR1* and *TGFBR2*. *TGFBR1* is located on chromosome 9q and contains 9 exons, whereas *TGFBR2* is positioned on chromosome 3p and contains 8 exons. Mutations in the gene encoding *SMAD3* have been associated with a condition called aneurysm-osteoarthritis syndrome, showing significant clinical overlap with LDS (van de Laar et al. 2011). Finally, also mutations in *SMAD2, TGFB2* and *TGFB3* have been identified in patients with LDS-like presentations (Lindsay et al. 2012; Cannaerts et al. 2019; Bertoli-Avella et al. 2015).

TGFBR1/2 mutations are primarily located in the serine-threonine kinase domain, the intracellular part of the TGFβ receptor. Although occasional nonsense mutations or small intragenic deletions have been described in *TGFBR2*, these were all predicted to escape nonsense-mediated-mRNA decay (Loeys et al. 2006). Deletions involving *TGFBR2* lead to an LDS-like phenotype but patients lack significant aortic disease (Campbell et al. 2011). Moreover, *TGFBR1* nonsense mutations or mutations predicted to cause a complete loss-of-function have been shown to lead to a skin cancer phenotype, multiple self-

healing squamous epitheliomas (Goudie et al. 2011). Haploinsufficiency and loss-of-function were suggested as mutational mechanisms for both *SMAD2/3* and *TGFB2/3* mutations. All findings hitherto suggest that although the *TGFBR*-mutations in LDS are also predicted to lead to loss-of-function (Cardoso et al. 2012), some residual protein activity seems to be required to cause the LDS phenotype (see pathogenesis).

11.3 Signs and Symptoms

An overview of the clinical features of LDS is given in Table 11.1. LDS is characterized by four major groups of clinical findings, affecting the vascular, craniofacial, skeletal and cutaneous system (Loeys et al. 2005). Although some clinical overlap with MFS exists, highly prevalent distinguishing features in LDS are cleft palate/bifid uvula, hypertelorism and arterial tortuosity. Interestingly, in some patients, the bifid uvula is the only visible marker to identify people at risk for aortic aneurysms.

11.3.1 Cardiovascular Manifestations

In the vascular system, the most common and prominent finding is the dilatation of the aortic root at the sinuses of Valsalva, which if undetected, leads to aortic dissection and rupture. These dissections have been described in patients as young as 6 months of age. Moreover, dissections have occurred at smaller diameters than those generally accepted at risk in MFS (Williams et al. 2007). In addition to the aortic root aneurysms, aneurysms throughout the arterial tree have been described, most prominently in the side branches of the aorta and the cerebral circulation. Finally, another striking finding is the presence of arterial tortuosity, which is usually most prominent in 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 (Loeys et al. 2005, 2006; Eckman et al. 2009).

Table 11.1 Clinical features at initial diagnosis of LDS

Craniofacial features:	
Craniosynostosis	15%
Hypertelorism	48%
Cleft palate/uvula	72%
Exo/esotropia	18%
Blue sclerae	23%
Skeletal features:	
Pectus deformity	51%
Joint contractures	23%
Joint hypermobility	50%
Arachnodactyly	56%
Club feet	22%
Pes planus	51%
Scoliosis	70%
Cervical spine abnormality	39%
Skin features:	
Thin, translucent	33%
Smooth, velvety	23%
Easy bruising	24%
Delayed wound healing	12%
Herniae	25%
Vascular findings	
Arterial tortuosity	92%
Most common in head and neck vessels	
Carotids (55%)	
Vertebral (56%)	
Intracranial (37%)	
Ascending aorta (5%), aortic arch (10%)	
Descending thoracic (4%) or abdominal (7%) Ao, also other vessels (e.g. iliacs)	
Aneurysms	
Aorta	
Root	87%
Ascending	27%
Arch	10%
Desc thoracic	15%
Abdominal	12%
Vessel beyond Ao	30%

11.3.2 Skeletal Manifestations

Marfanoid skeletal features can be observed, although the actual overgrowth tends to be milder in LDS patients compared to MFS patients. Most typical LDS skeletal findings include pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus and cervical spine malformation and/or instability. 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 MFS. The combined thumb and wrist signs are present in circa one-third of individuals with LDS. Joint hypermobility is very common and does 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). Other recurrent skeletal findings include spondylolisthesis, acetabular protrusion and pes planus (Loeys et al. 2005, 2006). 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).

11.3.3 (Cranio)Facial Manifestations

Most typical craniofacial features consist of ocular hypertelorism and the presence of a cleft palate, or its mildest presentation, a bifid uvula. Sometimes the uvula is not bifid but has an unusual broad appearance with or without a midline raphe. Another common presenting feature in the more severely affected patients is craniosynostosis. In the latter 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). Other common craniofacial characteristics are malar flattening and retrognathia. Besides the hypertelorism, ocular manifestations include strabismus, blue sclerae and myopia, but the latter is less frequent and less severe than in MFS. Significant refractive errors can lead to amblyopia. Retinal detachment has been reported rarely (Loeys et al. 2005, 2006). In our experience, ectopia lentis is not observed, although in the literature minimal lens(sub) luxation has been reported (Mizuguchi et al. 2004). Less common associated findings requiring further exploration include submandibular branchial cysts and defective tooth enamel (Loeys et al. 2006).

11.3.4 Cutaneous Manifestations

In persons without craniofacial features, important cutaneous findings can provide the clue towards diagnosis. These skin findings show significant overlap with those observed in Ehlers-Danlos syndrome (EDS) and include velvety, thin, translucent skin, easy bruising (other than the lower legs) and dystrophic scars. Comparable to the vascular type of EDS, life-threatening complications, such as spontaneous bowel rupture and peripartal uterine rupture have been reported (Loeys et al. 2006; Gutman et al. 2009). Although in the past, type I and II LDS have been described based on the presence of these vascular EDS-like findings, we now believe these are the representation of a continuum within the LDS spectrum of disease.

11.3.5 Other Findings

Finally, a minority of affected individuals present 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. Common neuroradiological findings are dural ectasia and Arnold-Chiari type I malformation (Rodrigues et al. 2009). The precise incidence of those two findings is unknown.

Other recurrent findings that need further documentation include muscle hypoplasia, dental problems with enamel dysplasia, allergic disease with seasonal allergies, asthma/sinusitis, eczema and important gastro-intestinal problems: food allergy, eosinophilic esophagitis, inflammatory bowel disease.

11.4 The Expanding Spectrum of LDS and Closely Related Disease

Van de Laar et al. described another autosomal dominant variant of LDS, also called aneurysm-osteoarthritis syndrome (AOS) (van de Laar et al.

2011). AOS is characterized by aneurysms, dissections and tortuosity throughout the arterial tree in addition to craniofacial (including hypertelorism and abnormal palate/uvula), skeletal (including arachnodactyly and scoliosis) and cutaneous (including striae and velvety skin) symptoms and thus perfectly fits in the phenotypic spectrum of LDS. A distinguishing feature, however, might be the presence of early-onset osteoarthritis. In the initially published series, about 50% of the patients present with osteochondritis dissecans and about 90% of patients have vertebral disc degeneration, suggesting that these findings are very common in *SMAD3* associated type of LDS (van de Laar et al. 2011). Since the initial publication, however, it has become clear that not all *SMAD3* mutation-positive patients do present with osteoarthritis (Wischmeijer et al. 2013; Regalado et al. 2011). The cardiovascular severity of AOS is similar to classical LDS with early-onset dissections at smaller diameters and marked tortuosity (van de Laar et al. 2012, 2012). As such, AOS is now classified as LDS type 3 (MIM#613795).

Subsequently, patients with mutations in the *TGFB2* gene, also present with an autosomal dominant disorder with many systemic features of both MFS and LDS, and are classified as LDS type 4 (MIM#614816). Features shared with MFS and LDS include aortic aneurysm, pectus deformity, arachnodactyly, scoliosis and skin striae. Features shared with LDS but not with MFS, consist of hypertelorism, bifid uvula, bicuspid aortic valve (BAV), arterial tortuosity, club feet and thin skin with easy bruising. Ectopia lentis was not observed (Lindsay et al. 2012). Heterozygous mutations in *TGFB3* lead to the mildest form of LDS, LDS type 5 (MIM#615582) (Bertoli-Avella et al. 2015). Although typical LDS features are observed non-penetrance is also very common. The most recently discovered gene for LDS involves *SMAD2* (LDS type 6) (Cannaerts et al. 2019). So far, few mutation-positive have been reported, so its precise position in the phenotypical spectrum still needs to be determined.

Interestingly, mutations in *SKI*, a functional repressor of TGFβ signalling, were identified as the cause of Shprintzen-Goldberg syndrome (SGS) (Doyle et al. 2012). SGS is characterized by craniosynostosis, distinctive craniofacial features with dolichocephaly, retrognathia, high arched palate, marfanoid skeletal changes including dolichostenomelia, arachnodactyly, camptodactyly, pes planus, pectus excavatum or carinatum, scoliosis, joint hypermobility, and contractures. Cardiovascular anomalies with mitral valve prolapse, mitral regurgitation, and aortic regurgitation may occur, but aortic root dilatation is usually mild. Minimal subcutaneous fat, abdominal wall defects, cryptorchidism in males, and myopia are also characteristic findings. Nearly all SGS patients present with developmental delay, a finding that is rare in LDS. Molecular analysis of a series of individuals with typical SGS did not reveal mutations in the *TGFBR1* or *TGFBR2* (Loeys et al. 2005).

The major clinical findings of MFS, LDS subtypes and SGS are summarized in a comparative table (Table 11.2).

11.5 Diagnostic Criteria for LDS

Although no formal diagnostic criteria have been developed, *LDS gene* testing (*TGFBR1/2, SMAD2/3, TGFB2/3*) should be considered in the following scenarios:

1. Patients with the typical clinical triad of hypertelorism, cleft palate/bifid uvula and arterial tortuosity/aneurysm
2. Early-onset aortic aneurysm with variable combination of other features including arachnodactyly, camptodactyly, club feet, craniosynostosis (all types), blue sclerae, thin skin with atrophic scars, easy bruising, joint hypermobility, BAV and patent ductus arteriosus (PDA), atrial and ventricular septum defects (ASD/VSD)
3. Patients with a MFS-like phenotype, especially those without ectopia lentis, but with

Table 11.2 Differential diagnostic features of MFS, LDS and SGS

	MFS	LDS			SGS
Clinical feature	*FBN1*	*TGFBR1/TGFBR2*	*SMAD2/3*	*TGFB2/3*	*SKI*
Ectopia lentis	+++	–	–	–	–
Cleft palate/bifid uvula	–	++	+	+	+
Hypertelorism	–	++	+	+	++
Craniosynostosis	–	++	+	–	+++
Tall stature	+++	+	+	++	
Arachnodactyly	+++	++	+	+	++
Pectus deformity	++	++	++	++	++
Club foot	–	++	+	++	+
Osteoarthritis	+	+	+++	+	–
Aortic root aneurysm	+++	++	++	++	+
Arterial aneurysm	–	++	+	+	+
Arterial tortuosity	–	++	++	+	+
Early dissection	+	+++	++	+	–
Bicuspid aortic valve	–	++	+	+	+
Mitral valve insufficiency	++	+	+	++	+
Striae	++	+	+	+	+
Dural ectasia	+	+	+	+	+
Developmental delay	–	–	–	–	++

aortic and skeletal features not fulfilling the MFS diagnostic criteria (Loeys et al. 2010)

4. Families with autosomal dominant thoracic aortic aneurysms, especially those families with precocious aortic/arterial dissection, aortic disease beyond the aortic root (including cerebral arteries)
5. Patients with a clinical tableau reminiscent of vascular EDS (thin skin with atrophic scars, easy bruising, joint hypermobility) and normal type III collagen biochemistry
6. Isolated young probands with aortic root dilatation/dissection

If patients present with premature onset of osteoarthritis in addition to any of the above clinical scenarios, *SMAD3* may be prioritized as the causal gene. If the clinical presentation is rather mild, mutation in *TGFB2* or *TGFB3* may also be considered. Although it should be stressed that the clinical overlap is so large, that it is impossible to predict the correct causal gene based on the clinical signs only. If craniosynostosis and intellectual disability are associated features, *SKI* might be the first gene to be analysed.

11.6 Differential Diagnosis

11.6.1 Syndromic Differential Diagnosis

11.6.1.1 Ehlers-Danlos Syndrome

EDS is a clinically and molecularly heterogeneous disorder (Beighton et al. 1998). Amongst the different subtypes, the vascular, valvular (Schwarze et al. 2004) and kyphoscoliosis type can present with significant cardiovascular complications.

The most typical clinical manifestations of vascular EDS include thin, translucent skin, characteristic facial appearance, vascular fragility demonstrated by extensive bruising and easy bleeding and spontaneous arterial/intestinal/uterine ruptures (Beighton et al. 1998). An abnormal type III collagen biochemistry confirms the diagnosis, but ultimate confirmation of the diagnosis lies in the identification of mutations in the *COL3A1* gene, encoding for the type III collagen α-chain 1. Interestingly, in a cohort of 40 patients displaying a vascular EDS-like

phenotype but normal collagen III biochemistry, 30% carried *TGFBR1/2* mutations (Loeys et al. 2006), suggesting on the one hand that vascular EDS closely resembles LDS but on the other hand that *TGFBR* mutations may cause a broad spectrum of diseases associated with aortic aneurysms. Finally, arginine-to-cysteine mutations 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 vascular EDS. For these cases, distinct abnormalities on collagen electrophoresis have been observed (Malfait et al. 2007).

The valvular type of EDS is a rare form of EDS with early-onset cardiac valvular dysfunction. This autosomal recessive condition is caused by nonsense mutations in *COL1A2*. Other recurrent findings include joint hypermobility and skin hyperextensibility (Schwarze et al. 2004).

Finally, aortic aneurysm and arterial rupture can also occur in the kyphoscoliotic form of EDS (the former type VI or Ocular-Scoliotic type). This generalized connective tissue disorder is characterized by kyphoscoliosis, joint laxity, muscle hypotonia, and, in some individuals, ocular problems. This autosomal recessive form of EDS is caused by deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1, also called lysyl hydroxylase 1). The diagnosis of EDS, kyphoscoliotic type relies on the demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine. Alternatively, an assay of lysyl hydroxylase enzyme activity in skin fibroblasts is diagnostic. Mutations in *PLOD1*, the gene encoding the enzyme lysyl hydroxylase 1, are causative (Pinnell et al. 1972).

11.6.1.2 Arterial Tortuosity Syndrome and Autosomal Recessive Cutis Laxa Type 1

Two other autosomal recessive connective tissue disorders present arterial tortuosity and aortic aneurysm as key findings.

The arterial tortuosity syndrome (ATS) is characterized by generalized tortuosity, elongation, stenosis and aneurysm formation in the major arteries. Patients often die at a young age due to cardiopulmonary complications. Features in common with LDS include arachnodactyly, hypertelorism, cleft palate and/or bifid uvula, joint laxity or contractions and micro/retrognathia. ATS is caused by loss-of-function mutations in *SLC2A10*, encoding GLUT10, which belongs to the glucose transporter family but its precise function remains unknown (Coucke et al. 2006).

Autosomal recessive cutis laxa type 1 (ARCL1) is another connective tissue disorder characterized by vascular anomalies, lung emphysema and diverticulae of the urinary and gastrointestinal tract aside from the cutaneous symptoms. As in ATS, prognosis can be severely compromised by cardiopulmonary complications. Mutations in two fibulin genes, *EFEMP2* (also called *FBLN4)* or *FBLN5*, are responsible for ARCL1 (Hucthagowder et al. 2006; Loeys et al. 2002). Arterial aneurysms and tortuosity are very prominent in patients with *FBLN4* mutations, while the cutaneous manifestations in *FBLN4* patients are limited and vascular stenosis is more pronounced in *FBLN5* patients. As such, ARCL1 caused by *FBLN4* mutations can be categorized within the LDS spectrum.

11.6.1.3 Meester-Loeys Syndrome

Loss-of-function mutations in *BGN* were identified in patients presenting with Meester-Loeys syndrome (MLS), a condition characterized by early-onset aortic dissection and LDS-associated features (i.e., hypertelorism, bifid uvula, and joint hypermobility and contractures) (Meester et al. 2016). Although most prominent in males as expected for an X-linked condition, a subset of mutation-carrying females also experience aortic aneurysm and even dissection. In other families, females were completely asymptomatic. Surprisingly skewed X-inactivation was shown not to underly this striking variability in females. *BGN* encodes the small leucine-rich proteoglycan biglycan that interacts with extracellular matrix components such as collagen I, III or elastin. Apart from this structural role, biglycan is also known to regulate cytokine activity (e.g. TGFβ and bone morphogenetic protein (BMP)).

11.6.2 Non-syndromic Differential Diagnosis

Non-syndromic types of thoracic aortic aneurysms and dissections (TAAD), or types in which only minor additional symptoms are present, exist as well. Occasionally, mutations in *FBN1* (Milewicz et al. 1996) and in *TGFBR1/2* (Pannu et al. 2005; Tran-Fadulu et al. 2009) causing TAAD have been described, perhaps representing the mildest end of the MFS/LDS phenotypic spectrum. Up to now, three genes, coding for components of the vascular smooth muscle contractile apparatus have been associated with familial thoracic aortic aneurysm: *ACTA2*, coding for vascular smooth cell specific α-actin, *MYH11* (β-myosin heavy chain 11) and *MYLK* (myosin light chain kinase) (Guo et al. 2007; Wang et al. 2010; Zhu et al. 2006). *ACTA2* -mutations have been identified in 14% of TAAD patients (Guo et al. 2007), while *MYH11* mutations have been found in TAAD patients with persistent ductus arteriosus (Zhu et al. 2006). Additional symptoms that can be found in *ACTA2* mutation positive patients include persistent ductus arteriosus, bicuspid aortic valve, iris flocculi, cerebrovascular accidents, Moya-Moya disease and coronary artery disease (Guo et al. 2009). Most recently, mutations in *MYLK, PRKG1, FOXE3* have been shown to account for a small subset of familial aortic aneurysmal disease (Wang et al. 2010; Guo et al. 2013; Kuang et al. 2016).

11.7 Pathology

Histologic examination of aortic tissue from LDS patients reveals elastic fibre fragmentation, loss of elastin content, a marked excess of collagen and accumulation of amorphous matrix components in the aortic media. Electron microscopy shows loss of the intimate spatial association between elastin deposits and vascular smooth muscle cells (Loeys et al. 2005). These findings have been reported already in very young children undergoing early aortic surgery and do occur in the absence of inflammation, suggesting a severe defect in elastogenesis rather than secondary elastic fibre destruction. LDS aortic samples had significantly more diffuse medial degeneration compared with MFS and control samples, but the changes are not specific for LDS (Loeys et al. 2005).

11.8 Biochemical Defects and Pathogenesis

For a long time, Marfan syndrome has been used as the sole paradigm for the pathogenetic study of thoracic aortic aneurysm. The study of Marfan mouse models has shifted our understanding of the pathogenetic mechanisms underlying this condition. In the past, it was believed that the structural deficiency of fibrillin-1 was responsible for many of the phenotypic characteristics, but recent work has also evoked a significant role for altered TGFβ signalling. It is now believed that deficient microfibrils fail to sequester TGFβ in an inactive state and that overactivation of the TGFβ signalling pathway contributes significantly to the disease pathogenesis. The discovery of the genetic basis of LDS has deepened our insights into the role of TGFβ in aortic aneurysm formation.

LDS is most frequently caused by mutations in the genes encoding the transforming growth factor beta (TGFβ) receptor subunits, TβRI and TβRII. The majority of LDS mutations are missense mutations positioned within the intracellular kinase domain, impairing kinase activity but not altering receptor expression or trafficking (Loeys et al. 2005, 2006). These mutations are predicted to cause loss-of-function of TβRI and TβRII. Interestingly, a recent report describes a cutaneous neoplastic phenotype without aortic or systemic involvement in people with heterozygous mutations that confer haploinsufficiency for *TGFBR1* (Goudie et al. 2011). In LDS, it was hypothesized that loss-of-function of the TGFβ receptors could lead to a paradoxical upregulation of TGFβ signalling. Indeed, aortic tissue-derived fibroblast studies documented that heterozygous patient cells show full preservation of the acute-phase response to TGFβ, and that patient-derived

tissues show evidence of increased (rather than decreased) TGFβ signalling (Loeys et al. 2005, 2006). While this finding intuitively corroborates the essential role of TGFβ in the pathogenesis of aortic aneurysm, it was not clear how a loss-of-function of the TGFβ receptors could lead to the same upregulation of TGFβ activity as seen in the Marfan mouse models.

The current data suggest that expression of a receptor with impaired kinase activity is necessary to generate the LDS phenotype and would be compatible with either a dominant-negative or complex gain-of-function mechanism of disease. On the one hand, at least two studies, either using heterozygous patient cells or co-transfection experiments, could not find evidence for dominant-negative activity (Loeys et al. 2005; Mizuguchi et al. 2004). On the other hand, a third study provided a somewhat complicated argument for a dominant-negative mechanism despite evidence that co-transfection of equal amounts (both 1X) of DNA encoding wild-type and mutant receptor subunits did not result in less than half the signalling activity seen upon transfection of a 2X complement of wild-type DNA (as expected for a dominant-negative mechanism)(Horbelt et al. 2010). Given that the TGFβ receptor complex involves association between two TβRI and two TβRII subunits, one might argue that dominant-negative activity is both intuitive and inevitable. However, recent evidence suggests that the individual TβRI:TβRII dimers within this tetrameric complex bind ligand and signal independently, yielding a dominant-negative mechanism untenable (Huang et al. 2011). When considered in combination with the repetitive observation of paradoxically increased TGFβ activity in LDS patient tissues, hypotheses have focused on the prospect of excessive and nonproductive compensatory mechanisms, most likely proximately induced by an imbalance of the various signalling functions (eg canonical versus noncanonical) supported by TGFβ receptors in a given cell type or an imbalance of TGFβ signalling in general between distinct but neighbouring cell populations (Lindsay and Dietz 2011). This hypothesis was first supported by accentuation of the aneurysm phenotype in *Fbn1*$^{C1039G/+}$ mice after the introduction of *Smad4* haploinsufficiency in the context of maintained high levels of Smad-dependent signalling and enhanced Smad-independent signalling (Holm et al. 2011). Furthermore, loss-of-function mutations in *SMAD3* or *TGFB2/3* were also associated with an overall increased TGFβ signature in the aortic wall (van de Laar et al. 2011; Lindsay et al. 2012).

Together, these findings indicate that TGFβ signalling is under the control of multiple feedback regulatory pathways. While adding to the complexity, the data support the contentions that many features of microfibril disorders likely manifest failure of proper regulation of TFGβ function, and that consideration of both primary and secondary events will be required to attain full mechanistic insight. Overall, the observations confirm the central role of TGFβ in the final common pathway leading to aortic aneurysms in different syndromes.

11.9 Treatment and Management

11.9.1 Natural History

Comparison of the natural history of Marfan syndrome and Loeys-Dietz syndrome has lead to two important lessons. First, in the most severe cases of LDS (with more outward features of LDS), aortic dissections at smaller diameters as in MFS have been observed, leading to the need for earlier surgical intervention (see below). Secondly, it has been observed that the aortic disease is far more widespread in LDS with aortic disease beyond the aortic root and prominent involvement of aortic sidebranches, necessitating a complete imaging of the arterial tree from head to pelvis.

11.9.2 Medical Treatment

Many of the treatment strategies in LDS are derived from knowledge derived from MFS patient management. The current treatment for aortic aneurysms in MFS is not causal and purely

symptomatic. Preventive treatment with beta-blockers is believed to slow down the aortic root growth but in general this does not prevent aortic surgery at later age. Based on initial experiments that demonstrated the rescue of the lung phenotype in Marfan mouse models through the use of TGFβ neutralizing antibodies (Neptune et al. 2003), it was hypothesized that similar treatments may be beneficial for the aortic phenotype in MFS patients. Proof-of-principle was obtained from a Marfan mouse trial (Habashi et al. 2006). The intraperitoneal injection of TGFβ neutralizing antibody blocked aortic root growth in these mice. Subsequently, similar results were obtained using an angiotensin II type 1 receptor blocker, losartan. Losartan does not only have an effect on the renin-angiotensin-aldosterone axis but has also an effect on TGFβ signalling. It is believed to reduce both the total and active amount of TGFβ in the extracellular matrix, probably through effects on thrombospondin, a TGFβ activator. In a placebo-controlled trial on Marfan mice, losartan resulted in significantly reduced aortic growth compared to atenolol, despite the similar hemodynamic effect. In addition to a major effect on the aortic growth, the histology of elastic fibres in the aortic wall of the losartan treated MFS mice was also indistinguishable from wild type mice (Habashi et al. 2006).

The beneficial effect of angiotensin receptor blocker treatment on aortic growth was confirmed in a preliminary observational study in severely affected pediatric MFS patients. Similar to the MFS mice, a significant decrease in rate of change of aortic root dimension after starting angiotensin receptor blocker therapy was observed. Again, as there was no difference in the effect of hemodynamic parameters, the data suggest that these achieved protective effects were likely to be attributed to TGFβ antagonism (Brooke et al. 2008). This study has provided the first evidence for a significant benefit of angiotensin receptor blocking agents over current therapies in reducing aortic root dilation in severe pediatric MFS patients.

Based on the mouse data and the preliminary human study a large, randomized clinical trial in MFS patients has been initiated. This trial, supported by the Pediatric Heart Network through the U.S. National Heart, Lung and Blood Institute (NHLBI), compares atenolol with losartan treatment in more than 600 patients for a three-year treatment (Lacro et al. 2007). In addition, a dozen other trials with different designs and inclusion criteria have been initiated in Belgium, France, Italy, The Netherlands, Taiwan and the United Kingdom (Detaint et al. 2010; Gambarin et al. 2009; Moberg et al. 2012; Radonic et al. 2010). A meta-analysis suggests that losartan is associated with a slower progression of aortic root dilation when compared with placebo and as an addition to beta-blocker therapy (Pyeritz and Loeys 2011; Al-Abcha et al. 2020; Elbadawi et al. 2019). Nevertheless, the precise mode of action of losartan is still unclear and might express its effect independently of the targeted angiotensin receptor, as a recent study in MFS murine model suggested (Sellers et al. 2018).

Taken together, in recent years, major steps have been made in elucidating the pathogenesis of thoracic aneurysm diseases and their clinical treatment. However, until now, there are only limited therapeutic prospects to completely halt its progression. This points out the need for further clinical trials including more patients and longer follow up periods in order to delineate even the minute effects that current and future treatments might express.

11.9.3 Surgical Treatment

Given the safety and the increasing availability of the valve-sparing procedure, the following recommendations have been issued for aortic surgery in LDS (Patel et al. 2011). First, for young children with severe systemic findings of LDS, surgical repair of the ascending aorta should be considered once the maximal dimension exceeds three standard deviations and the aortic annulus exceeds 1.8 cm, allowing the placement of a graft of sufficient size to accommodate growth. Second, for adolescents and adults, surgical repair of the ascending aorta should be considered once the maximal dimension approaches 4.0–4.5 cm. This advice is based on both numer-

ous examples of documented aortic dissection in adults with aortic root dimensions at or below 4.5 cm and the excellent outcome of prophylactic surgery. An extensive family history of larger aortic dimension without dissection could alter this practice for individual patients (Augoustides et al. 2009).

11.10 Genetic Counselling

LDS is inherited in an autosomal dominant manner. About one-quarter of LDS patients has an affected parent whereas approximately three-quarters of probands have LDS as the result of a *de novo* mutation. If the parent is affected, each child has a 50% chance of inheriting the mutation and thus the disorder. Prenatal diagnosis for pregnancies at increased risk for LDS is possible if the disease-causing mutation in the family is known.

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