CURRENT OPINION

Heritable thoracic aortic disorders

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Purpose of review
Disease of the wall of the thoracic aorta has many causes: inflammation, infection and atherosclerosis are the most common 'acquired' causes, but even these have genetic predispositions. This article deals with aortic disease due to mutations in specific genes. The conditions can affect tissues and organs other than the aorta (syndromic) or be limited to the aorta (nonsyndromic).

Recent findings
A classification scheme based on the gene is emerging, those that affect primarily the extracellular matrix (e.g., *FBN1*, *COL3A1*), TGF-β signaling (e.g., *TGFBR1*, *TGFB2*), or vascular smooth muscle cell contractility (e.g., *ACTA2*, *MYH11*).

Summary
Understanding pathogenesis is driving the development of novel therapies, such as angiotensin receptor blockade, which is in clinical trial. However, recurrent imaging, restriction of exercise, β-adrenergic blockade, and prophylactic surgery remain effective in preventing dissection and sudden death.

Keywords
Loeys–Dietz syndrome, Marfan syndrome, TGF-β signalling, thoracic aortic aneurysm, thoracic aortic dissection

'Aneurism (*sic*) of any part of the thoracic aorta is a very hopeless disease.'
William Osler, *Principles and Practice of Medicine*, 1903.

INTRODUCTION

Disease of the wall of the thoracic aorta can present as dilatation, dissection or both. When the dilatation is beyond an arbitrary size, perhaps 45–50 mm in an adult, it is termed an aneurysm. Complications of aortic aneurysm kill at least 50 000 people in the United States annually. Acute aortic dissection, specially involving the ascending aorta, can lead to sudden death and may be unrecognized in the absence of pre-mortem imaging or post-mortem examination. Intramural hematoma, in the absence of an intimal tear, can present with the same symptoms as dissection and has a similarly morbid course [1]. Aortopathy has many causes. Inflammation, infection, and atherosclerosis are the most common 'acquired' causes, but even these have genetic predispositions. In older people, hypertension and cigarette smoking are clear risk factors. Several factors mitigate against thoracic aortic aneurysm (TAA); females are less prone to being diagnosed with TAA [2■] and diabetes mellitus is independently associated with decreased rate of hospitalization for

TAA and dissection (TAAD) [3]. Aortic disease associated with congenital heart defects is usually multifactorial, although Turner syndrome is due to the absence of a crucial segment of the X chromosome. Ascending TAA is commonly associated with bicuspid aortic valve, and recurrence in some families suggests autosomal dominant inheritance; however, identification of a gene or genes has been frustrating. This article deals with aortic disease due to mutations in specific genes.

The conditions due to mutations in single genes can affect tissues and organs other than the aorta (syndromic), be limited to the aorta, or involve other arteries (nonsyndromic). In general, in about 20% of cases, nonsyndromic TAAD is familial (FTAAD). About one dozen genes are available for clinical molecular testing in both groups. Mutations in some genes can produce either syndromic or nonsyndromic thoracic aortic disease.

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KEY POINTS

- At least 20% of patients presenting with thoracic aortic disease have an affected relative, and a detailed family history is an essential component of the evaluation.

- More than a dozen genes can cause, when mutated, Mendelian forms of thoracic aortic disease; clinical molecular testing is often appropriate after pretest genetic counseling.

- Genes encoding components of the ECM, TGF-β and other signaling pathways, and vascular smooth muscle cytoskeleton are all involved in thoracic aortopathies, and more genes will soon be discovered.

Disease of the thoracic aorta carries high morbidity and mortality. Fortunately, over the past few decades, substantial progress has been made in diagnosis, follow-up, medical therapy and surgery that has reduced the occurrence of acute dissection and prolonged life. Understanding the genetic cause of many forms of thoracic aortic disease has contributed to this progress, mainly by enabling relatives of the proband to be screened before they suffer a major complication.

How can the clinician, specially in primary care, be kept up-to-date on diagnosis and management of this group of conditions? In 2010, a number of professional societies sponsored and then endorsed Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease [4]. Unfortunately, most of the recommendations were based on expert opinion (Level of Evidence C). Nonetheless, they provide a starting point for designing clinical trials that will lead to improved standards of care in the future. With these guidelines as a baseline, this article reviews recent developments.

Table 1 lists the various conditions discussed, classified by the specific gene affected. This new classification system of heritable thoracic aortic disorders is based on the Montalcino Aortic Consortium, an ad-hoc group that is attempting to bring some nosological order to an increasingly confusing group of aortopathies.

Table 1. Classification of heritable thoracic aortic conditions

Gene symbol	Protein	Phenotypes	OMIM no. for locus
Genes specifying components of the extracellular matrix			
FBN1	Fibrillin-1	Marfan syndrome	134797
COL3A1	Type 3 procollagen	Vascular Ehlers–Danlos syndrome	120180
COL4A5	Type 4 procollagen	Alport syndrome	303630
EFEMP2	Fibulin-4	Cutis laxa	604633
Genes specifying components of TGF-β/BMP signaling			
TGFBR1	TGF-β receptor-1	LDS	190181
		FTAAD	
TGFBR2	TGF-β receptor-2	LDS syndrome	190182
		FTAAD	
TGFB2	TGF-β2	FTAAD	190220
SMAD3	SMAD3	FTAAD	603109
Genes specifying components of contractility of vascular smooth muscle cells			
ACTA2	α-actin	FTAAD	102620
MYH11	Myosin heavy chain-11	FTAAD	160745
MYLK	Myosin light chain kinase	FTAAD	600922
PRKG1	cGMP-dependent	FTAAD	176894
Receptor kinase (PKG I)			
FLNA	Filamin-A	Cerebral heterotopias/ aortic aneurysm	3000017
TSC2	Tuberin	Tuberous sclerosis complex	191092
Genes specifying components of other signaling pathways			
JAG1	JAGGED-1	Alagille syndrome	601920
NOTCH1	NOTCH-1	Bicuspid aortic valve/aortic aneurysm	190198
SLC2A10	Glucose transporter 10	Arterial tortuosity syndrome	606145

BMP, bone morphogenic protein; FTAAD, familial aortic aneurysm and dissection; LDS, Loeys–Dietz syndrome; OMIM, Online Mendelian Inheritance in Man; TGF, transforming growth factor.

GENES SPECIFYING COMPONENTS OF THE EXTRACELLULAR MATRIX

The *FBN1* gene that encodes for the extracellular matrix (ECM) protein, fibrillin-1, was first associated with the archetypal syndromic form of thoracic aortic disease, the Marfan syndrome (MFS) [5]. This condition has been the model for the studies of pathogenesis, medical therapy, and prophylactic surgery that has been applied widely in other aortopathies. The defect in fibrillin-1, an important component of elastic fibers, was once thought to 'weaken' connective tissue, thereby leading to the characteristic progressive dilatation of the sinuses of Valsalva and ascending aorta. However, this theory never could explain other features of the syndrome, such as disproportionately tall stature, hypoplasia of skeletal muscle and adipose tissue, and cysts in the kidneys and liver. The recognition that fibrillin-1 plays a role in regulating activation of transforming growth factor-beta (TGF-β) provided not only an explanation for the pleiotropic features, but a potential novel therapy. Because TGF-β is hyperactive in most tissues, an angiotensin receptor blocking (ARB) drug held promise of reducing this over-activity and was impressively effective in a mouse model of MFS. At least 10 randomized trials of an ARB versus standard therapy (typically, a β-adrenergic blocking drug) are in progress. Two small trials have reported positive results for the ARB, but the power was low [6,7■]. A large trial comparing losartan and atenolol in predominantly children and adolescents will not report findings until 2014 [8■].

Prophylactic surgery to replace the aortic root remains standard of care [9,10]. The criteria for when to operate remain an absolute maximal diameter of 50 mm, a rate of change of more than 5 mm per year, or a diameter of 45 mm, if there is a family history of aortic dissection. If the aortic valve is not too dysfunctional (severe aortic regurgitation, large fenestrations in the cusps), then a valve-sparing approach shows excellent promise [11,12■■]. The long-term complication of most concern in patients undergoing elective root repair is type B dissection; determining postoperative wall stress holds promise of predicting risk [13]. In this regard, chronic β-adrenergic blockade remains the medical treatment of choice [14]. Any distal segment of the Marfan aorta that is dissected is subject to progressive dilatation and the need for surgical management [15■], much as in nonsyndromic aortic dissection [16■■]. Pregnancy remains an important risk factor for acute dissection in MFS, specially when the syndrome is not recognized and managed appropriately [17].

Mutations in *FBN1* cause a dozen other phenotypes, but few are associated with TAAD. Only rare families with nonsyndromic TAAD have *FBN1* mutations [18].

COL3A1

Deficiency of type III collagen in the ECM is the cause of the vascular form of Ehlers–Danlos syndrome. Saccular aneurysms and spontaneous rupture of the aorta and its branches are a common cause of death, along with bowel and uterine rupture [19]. Although the thoracic aorta is not the most common site of vascular involvement, TAAD does occur, and it is worth imaging the entire aorta on a periodic basis. One trial in Europe suggested that chronic β-blockade can reduce arterial complications [20], but bias in assignment to study groups may have biased the results. Vascular cannulation is hazardous, as is prophylactic surgery, but operation in emergency situations is even more fraught with morbidity and mortality. Endovascular repairs of arteries other than the aorta can be successful in experienced hands [21]. The most serious phenotypes are due to heterozygous missense mutations that disrupt the triple helix. Heterozygous null mutations result in a vascular phenotype that may be more prone to aneurysms and less severe skin, joint, and visceral manifestations [22]. Studies of murine models of this condition implicate a role for angiotensin II in stimulating vascular complications, which suggests a common pathogenesis with a number of the disorders discussed in this chapter [23■].

GENES SPECIFYING COMPONENTS OF TGF-B/BMP SIGNALING

A number of genes whose protein products are directly involved in TGF-β signaling have been implicated in syndromic and nonsyndromic TAAD.

TGFBR1

This gene encodes a cell wall receptor for TGF-β. Heterozygous missense mutations that would be expected to reduce downstream TGF-β signaling paradoxically increase it. In 2005, mutations in this gene were first described as a cause of a 'new' condition, Loeys–Dietz syndrome (LDS), a pleiotropic condition characterized by craniosynostosis, hypertelorism, cleft palate or bifid uvula, club foot, arachnodactyly, loose-jointedness, arterial tortuosity, and TAAD. At about the same time, *TGFBR1* mutations were described in Furlong syndrome, which had been first described phenotypically in 1987. Now, LDS and Furlong are considered the same condition. Dissection in LDS can occur at

smaller aortic diameters than in MFS, so the recommendation has been to perform prophylactic surgery earlier, at a maximal diameter of 40 mm [24].

Some patients diagnosed with MFS but who were negative for mutations in *FBN1* have mutations in *TGFBR1*. They more often have mutations in *TGFBR2*.

Mutations in *TGFBR1* can also cause nonsyndromic FTAAD, which is quite genetically heterogeneous. There is an increased incidence of fusiform or saccular dilatation of intracerebral arteries, specially among women [25].

TGFBR2

Mutations in this gene were first associated with the various forms of cancer. Subsequently, in several families and individuals felt to have a variant form of MFS, missense mutations in *TGFBR2* were described in 2004. Individuals with the Furlong–LDS phenotype were found to have mutations in 2005.

Families with nonsyndromic autosomal dominant TAAD also can have mutations in *TGFBR2*; the course of their aortic disease, specially the risk of dissection, is not nearly as aggressive as in LDS. There is an increased incidence of fusiform or saccular dilatation of intracerebral arteries, specially among women [25].

TGFB2

Autosomal dominant FTAAD can be due to mutations in this gene. Although the mutations cause haploinsufficiency for the ligand, TGF-β signaling in aortic tissue is paradoxically increased, which is hypothesized to result from a secondary increase in the synthesis of TGFB2 in tissue [26▪▪].

SMAD3

Mutations in this gene were originally reported in families showing autosomal dominant inheritance of both TAAD and early-onset osteoarthritis [27]. The gene product, Smad3, is an intracellular component of the TGF-β pathway. Subsequently, mutations in *SMAD3* have been found in nonsyndromic FTAAD. In addition to TAAD, some individuals are prone to intracranial aneurysms, abdominal aortic aneurysms or both [28].

SLC2A10

Mutations in both alleles of this gene cause arterial tortuosity syndrome, which can be lethal in infancy, primarily because of pulmonic stenosis, or be compatible with survival to adulthood [29]. As the syndromic name suggests, arteries, including the aorta, are unusually tortuous. However, there is little predisposition to dilatation or dissection. The protein product, GLUT10, is a nuclear membrane facilitated glucose transporter. Signaling through the TGF-β pathway is enhanced in samples from arterial wall.

GENES SPECIFYING COMPONENTS OF CONTRACTILITY OF VASCULAR SMOOTH MUSCLE CELLS

A third class of genes that predispose to TAAD are involved in nonvascular and vascular smooth muscle cell (vsmc) contractility [30,31]. Mutations in these genes produce not only an aortopathy associated with dilatation and dissection, but occlusion of smaller muscular arteries.

ACTA2

This gene encodes the smc isoform of α-actin. In families with TAAD due to mutations in *ACTA2*, penetrance of aortopathy is about 50%, but all heterozygotes are prone to coronary artery disease and aortic stroke [32]. Moyamoya malformation and livedo reticularis are other manifestations of the diffuse vasculopathy. Up to 10% of FTAAD is due to mutations in *ACTA2*.

One mutation, R179H, is associated with a diffuse vasculopathy and myopathy [33]. One patient presented with megacystitis and prune belly sequence [34▪].

MYH11

Mutations in this gene are an uncommon cause of FTAAD, but when they occur are often associated with patent ductus arteriosus [35]. A variant in *MYH11*, R247C, which does not cause FTAAD, may be a risk factor for vasculopathy in the general population [36].

PRKG1

The protein product of *PRKG1* is involved in regulating vsmc contractility. One mutation, R177Q, is associated with FTAAD in multiple families [37]. The mutation leads to gain-of-function, which results in decreased vsmc contractility.

FLNA

This gene on the X chromosome encodes filamin-A, a protein of the cytoplasm that is expressed diffusely

and assists in anchoring actin to the cell membrane. The majority of humans detected as having *FLNA* mutations are women, suggesting that hemizygosity can be lethal *in utero* in males. Affected women often present with seizures due to cerebral heterotopias. They are also prone to joint hypermobility and some may be diagnosed with a form of Ehlers–Danlos syndrome. Dilatation of the proximal aorta and its branches is a common finding [38,39■], and any person with the joint and central nervous system features should have computed tomographic angiography or magnetic resonance angiography of the entire aorta and its branches.

GENES SPECIFYING COMPONENTS OF OTHER SIGNALING PATHWAYS

Several genes that encode transmembrane signaling molecules that are not part of the TGF-β pathway have also been implicated in aortic disease.

JAG1

Mutations in this gene disrupt Jagged1, a ligand in the Notch pathway. One consequence is Alagille syndrome, which is defined by decreased interlobular bile ducts, characteristic facies, butterfly vertebrae, and posterior embryotoxon [40]. The most common vascular anomaly is peripheral pulmonic stenosis, but some patients have a diffuse arteriopathy that can affect the aorta [41]. Tetralogy of Fallot is also associated with mutations in this gene.

NOTCH1

Rare families with calcific bicuspid aortic valve associated with ascending aortic aneurysm have a mutation in this gene, which encodes the cellular receptor for Jagged1 and other ligands [42]. Large studies of both familial and sporadic bicuspid aortic valve have failed to detect many causative mutations in *NOTCH1* [43].

CONCLUSION

Perhaps one-quarter of all patients who present with TAA, dissection or intramural hematoma have a positive family history of aortic disease. The younger the proband, the greater the chance of having affected relatives. We now know that simply asking about aortic disease is insufficient; one needs to query about intracerebral arterial disease, precocious coronary artery disease, congenital heart disease (specially, coarctation and patent ductus), and bicuspid aortic valve. Syndromic and nonsyndromic forms of FTAAD occur, and mutations in more than a dozen genes are now known to explain about 25% of probands. These genes can be grouped into several classes, including those specifying components of the ECM, various signaling pathways (specially TGF-β), and vascular smooth muscle contractile proteins [44,45]. Understanding both the underlying cause and pathogenesis of a patient with FTAAD will guide therapy to some extent now, but more so in the future [46]

Conflicts of interest

There are no conflicts of interest.

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