



# Familial thoracic aortic aneurysms

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## Purpose of review

A lot of new data have been obtained in familial thoracic aortic aneurysms, including description of new entities and better understanding of pathophysiology. The aim of this review is to put them in perspective.

## Recent findings

The new data have been collected, put together, and allowed a new classification scheme to be proposed by the Montalcino Aortic Consortium on the basis of the role of proteins coded by the culprit gene (either protein of the extracellular matrix or protein of the transforming growth factor-beta pathway, or protein of the contractile apparatus of the smooth muscle cell). These groups of diseases include aortic aneurysm, but the extent of extra-aortic vascular risk and the presence of extra-aortic (skeletal, ophthalmologic, neurological, or immunological) features vary according to the gene involved. This understanding also sheds light on the therapeutic benefits that can be foreseen for new molecules, or old molecules used in a newer way.

## Summary

Classification of familial forms of thoracic aortic aneurysm should allow a better understanding of these diseases and therefore standardization of initial evaluation of the patients (vascular evaluation limited or not to the aorta, and extravascular evaluation, including or not skeleton, eyes, neurology, digestive tract, and immunological diseases) and individualization of therapy (adapted to both the genotype and the phenotype).

## Keywords

aorta, Marfan, transforming growth factor-beta

## INTRODUCTION

Familial thoracic aortic aneurysms (TAA) represent around 20% of all TAA. Most of the familial forms are transmitted as autosomal-dominant diseases. Among these, a mutation in a causative gene has been found in a low percentage. New genes are regularly reported. An area of progress is, therefore, the description of the phenotype and the natural history associated with mutations in these newly reported genes, often on the basis of case reports at first. Another area of research is the search for new genes in the familial forms, not related to genes previously reported. Lastly, these mutations give indications on the pathophysiological aspects of the disease (Fig. 1). We will first review recent findings in the genetic forms of TAA and a classification scheme recently proposed.

## MARFAN SYNDROME AND *FBN1* GENE

In the classical form of Marfan syndrome, defined on clinical features, a cohort study provides some support to the surgical threshold proposed for surgery in this population: aortic event rates appear

to be very low in patients with Marfan syndrome who undergo regular follow-up, take beta-blockers, and have aortic root diameter below 50 mm [1].

The cardiovascular features of Marfan syndrome include mainly aortic dilatation and mitral valve prolapse, which can be responsible for mitral regurgitation requiring surgery in a few patients. A recent report suggests that mitral valve repair in combination with aortic surgery (valve-sparing surgery or aortic valve replacement) is technically reasonable in these patients, but that such a surgery is probably unnecessary in patients with low-grade mitral regurgitation [2]. However, this study is limited by the

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## KEY POINTS

- FAA may be related to genes coding for contractile apparatus of the smooth muscle cell (e.g., *ACTA2*, *MYH11*, *MYLK*, and *PRKG1*), TGF-beta pathway proteins (e.g., *TGFB2*, *TGFB1*, *TGFB2*, and *SMAD3*), or protein of the extracellular matrix (e.g., *FBN1*).
- Phenotype characterization of the newly discovered genetic forms of TAA includes neurological features (Charcot-Marie-Tooth type II), immunological diseases, and early osteoarthritis, which could all be the reason for seeking medical advice, and should lead to evaluation of the aorta, particularly in a familial context.
- Familial TAA are often associated with arterial aneurysms outside the aorta, and complete vascular imaging is required when Marfan syndrome related to *FBN1* mutation is not diagnosed.
- Although initially thought to be responsible for the TAA, the increase in TGFβ signalling (i.e., P-Smad2) within the smooth muscle cells may actually be a compensatory mechanism present in all TAA, and its importance is related to the severity of the disease.

duration of the follow-up available, and the applicability of the results is mainly for expert centres, such as those that participated in this registry, because combined surgery in this population is technically challenging.

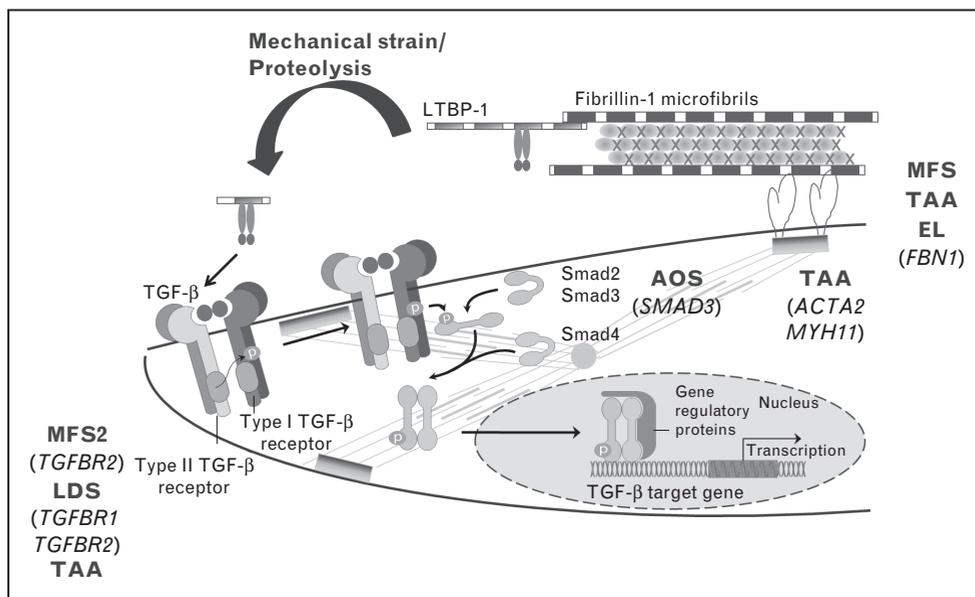
Marfan syndrome is usually related to mutations in the Fibrillin 1 (*FBN1*) gene, but mutations in this gene can also be responsible for other syndromes

(familial TAA, ectopia lentis, Shprintzen–Goldberg syndrome, and Weill–Marchesani syndrome). Missense mutations in *FBN1* exons 41 and 42 have been associated with acromicric dysplasia and geleophysic dysplasia, but not Marfan syndrome or Weill–Marchesani syndrome. A recent report indicates that aortic dissection may occur in these patients, indicating that aortic screening is necessary in all patients with *FBN1* mutation [3].

## OTHER GENES

A number of genes coding for proteins of the transforming growth factor (TGF)-beta pathways have been reported in genetic forms of TAA (vide infra).

*SMAD3* mutations have recently been associated with the newly recognized aneurysm–osteoarthritis syndrome [4]. Arthritis occurring at an early age is the hallmark of this syndrome and is thought to occur in almost every patient. The other defining feature of this syndrome is the diffusion of the arterial aneurysmal localization, which can be found on cerebral arteries, descending aorta, pulmonary artery, mesenteric artery, celiac artery, hepatic artery, splenic artery, and iliac arteries, with arterial and aortic tortuosity in many patients [5]. Internal mammary artery may also be affected. Aortic or extra-aortic arterial disease is present in 95% of the patients [6]. On the aorta, dilatation is usually present at the level of the sinuses of Valsalva, but can also be observed above, at the level of the tubular aorta, and may even be maximal there [7]. Dissection on moderately dilated aorta (less than



**FIGURE 1.** The more frequent genetic causes for familial thoracic aortic aneurysms. MFS, Marfan syndrome; LDS, Loëys–Dietz syndrome; OAS, osteoarthritis syndrome; TAA, thoracic aortic aneurysms; TGFβ, transforming growth factor beta.

40 mm) has been reported [4]. Lastly, the cardiovascular phenotype associated with mutation in this gene may also include hypoplastic left heart syndrome [8].

Apart from diffuse arterial disease, *SMAD3* mutations may also be associated with neurological features (68%), including peripheral neuropathy, with electromyography showing axonal motor and sensory neuropathy, evocative of type II Charcot-Marie-Tooth disease, and autoimmune features found in a third of the patients [6<sup>■</sup>].

*SMAD4* mutations are usually associated with juvenile polyposis syndrome and a combined juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia. Two patients were recently reported with juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia related to *SMAD4* mutations who also presented thoracic aortic dilatation [9].

*TGF $\beta$ 2* mutations cause familial TAA and dissections associated with mild skeletal features of Marfan syndrome, some degree of arterial tortuosity, and a risk for cerebrovascular disease [10<sup>■</sup>]. *TGF $\beta$ 2* encodes TGF- $\beta$ 2, and the mutations are predicted to cause haploinsufficiency for TGF $\beta$ 2; however, aortic tissue from some cases showed paradoxically increased TGF- $\beta$ 2 expression and immunostaining. This is further increased in the aortic wall of mouse carrying both *FBN1* and *TGF $\beta$ 2* mutations [11]. Aortic event has currently been reported in adulthood only.

The other great family of genes reported to be associated with the presence of aortic dilatation are genes coding for proteins involved in the contractile apparatus of the smooth muscle cells (*ACTA2*, *MYH11*, *MYLK*, and now *PRKG1*).

*ACTA2* mutations are known to be associated with TAA, but also aneurysms of other arteries, and, sometimes, early onset of coronary artery disease. A recent case report indicates that such a mutation may be responsible for paediatric stroke and cerebral vasculopathy [12].

Guo *et al.* [13] report that a recurrent mutation in the *PRKG1* gene may also be responsible for thoracic aortic disease. A recurrent mutation with gain-of-function was found in six families. In these families, dissection occurred between 17 and 51 years of age (mean 33), with full penetrance above 18 years of age, and no difference between men and women. Dissection of the coronary artery has also been reported in patients with *PRKG1* gene mutation as well as arterial tortuosity, but no skeletal features of the Marfan syndrome spectrum. Interestingly, the mutation resulting in p.Arg177Gln was associated with an increase in the activity of Protein Kinase G-1, leading to decreased phosphorylation of the myosin regulatory light chain, and is predicted to

cause decreased contraction of the vascular smooth muscle cells.

There is no clear consensus on when to operate on patients with these mutations as the experience is limited. Early dissection has been reported with all mutations (including *FBN1*) and prognosis is different in different reports. Early surgery is probably warranted when major facial abnormalities (hypertelorism, cleft palate, craniosynostosis, and bifid uvula) are present [14], and surgical threshold close to that proposed to patients with *FBN1* mutations is probably optimal in patients with no extra-aortic features [15]. Recommendations are also divergent across the ocean, and surgical threshold probably should differ between adults and children, and in adults according to age. In conclusion, referral of patient to a reference centre is probably the best option because wide variability in the clinical phenotype and the prognosis is a hallmark of all these mutations, even within families [15].

## CLASSIFICATION

These observations have led a group of experts (Montalcino Aortic Consortium) to propose a classification of familial forms of thoracic aneurysm that take into account the pathophysiology of these diseases and will probably allow the inclusion of new mutations into prespecified categories [16<sup>■</sup>]. Table 1 gives an overview of phenotypes associated with the more frequent mutations.

Mutations of genes coding for the extracellular matrix, which are responsible not only for TAA but also for extra-aortic features [*FBN1*, Collagen 3A1 (*COL3A1*), EGF-containing fibulin-like extracellular matrix protein 2 (*EFEMP2*)], are explained as follows:

- (1) The more classical form of this type of TAA is Marfan syndrome related to mutation in the *FBN1* gene, which can present a myriad of extra-aortic features, including skeletal, ophthalmological, cutaneous, pulmonary, and neurological abnormalities. Penetrance is complete.
- (2) Mutations in genes coding for collagen (Ehlers-Danlos syndrome *COL3A1*) are associated with dissection more than dilatation, not only of the aorta but also of medium-sized arteries, and extra-vascular features such as skin abnormalities and uterine and bowel ruptures.
- (3) Lastly, mutations in fibulin 4 (*EFEMP2*) may also be associated with severe arteriopathies and aortic dilatation [17].

In this group of diseases, extra-aortic features may be on the front line, and isolated familial TAA is relatively unusual.

Mutations coding for proteins of the TGF-beta pathways (*TGFB2*, *TGFBR1*, *TGFBR2*, *SMAD3*, *SMAD4*) are explained as follows:

- (1) Mutations in *TGFB2*, responsible for decreased *TGFB2* production, lead to TAA and some skeletal features.
- (2) Mutations in *TGFBR2*, which can be associated with a range of phenotypes: severe forms are called Loeys–Dietz syndrome with craniofacial malformations, including cleft palate, craniosynostosis, bifid uvula, hypertelorism, and arterial tortuosity (which is less specific because it is also observed in patients with *FBN1* mutation, *EFEMP2* mutations, Filamin A mutations, and *TGFB2* mutation). In the initial study, Loeys *et al.* [14] also reported features of vascular Ehlers–Danlos syndrome, including visceral rupture and cutaneous features (easy bruising, wide and atrophic scars, and translucent/velvety skin). Severe forms are associated with aggressive vasculopathy (and often craniofacial malformations), and the vasculopathy may also involve extra-aortic arteries. Less severe forms are responsible for a phenotype fitting clinical criteria for Marfan syndrome (Marfan syndrome type 2) [15], and familial forms of TAA without extra-aortic features may also result from these mutations [18]; also penetrance is incomplete. Because of the wide variability associated with the phenotype even within a family, complete arterial screening (including cerebral arteries) is warranted in these patients. Immunological disorders associated with these mutations have also been reported [19].
- (3) Mutations in the *TGFBR1* gene are responsible for similar phenotypes, but women are less severely affected than men, and dissections may occur for larger aortic diameter, but are rarer (half the frequency of the *TGFBR2* mutation) [20].
- (4) Mutations in *SMAD3* are responsible for diffuse arteriopathy, early osteoarthritis, neurological features, and immunological disorder.
- (5) Mutations in *SMAD4* may also present aortic disease, but this is not on the front line of the phenotype. Hereditary hemorrhagic telangiectasia and juvenile polyposis syndrome are more classical.

In this group of diseases, diffuse arterial aneurysms are observed, and extra-aortic features depending on the gene, but often with skeletal features observed in Marfan syndrome.

Mutations coding for proteins of the contractile apparatus of the smooth muscle cell (*ACTA2*, *MYH11*, *PRKG1*, *MYLK*) are explained as follows:

- (1) Mutations in *ACTA2* are responsible for 14% of genetic forms of TAA in the USA, but are rarer in France. Their phenotype combines thoracic aortic aneurysm, usually involving aortic root and tubular aorta, extra-aortic arterial aneurysms, and iris flocculi. Early atherosclerosis and myomamyoma diseases have also been reported.
- (2) Mutations in *MYH11* are very rare and combine TAA and patent ductus arteriosus.
- (3) Mutations in *PRKG1* are responsible for familial TAA, as are mutations in *MYLK*.

In this group of diseases, the presentation is often that of familial TAA without extra-vascular features.

It is therefore possible to choose the molecular genetic screening to be done on the basis of clinical features [21]. It is also apparent from this classification that arterial visualization beyond the aorta, including the cerebral vasculature, should be performed in familial TAA not related to *FBN1*. Lastly, phenotypic overlap between these different mutations is illustrated in Table 1, and renders molecular genetics particularly useful in these patients, at least until more experience is gained.

## THErapy

A second area of intense research is therapy in patients with TAA. The importance of the TGF-beta pathway has been recognized for many years (the first mutation in the *TGFBR2* gene was reported in 2004). However, the relationship between TGF-beta and TAA is still unclear.

Activation of the TGF-beta pathway in the aortic wall of patients with TAA has been suggested in animals (mouse model for Marfan Syndrome, KI for a mutation in *FBN1*) and in the aortic wall of humans with TAA because of the increase in P-Smad2 in the aortic tissue. Smad2 is phosphorylated into P-Smad2 following activation of *TGFBR* (Fig. 1). It has been proposed that the activation of the TGF-beta pathway could be responsible for the development of TAA, so that its blockade would be beneficial. This was after the report by John Hopkins' group of prevention of aortic dilatation with the use of specific antibodies [22].

However, activation of the TGF-beta pathway was also observed in TAA in the absence of mutation in the *FBN1* gene. Actually, it was also observed in TAA related to mutation in the *TGFBR2* gene blocking the transmission of the TGF-beta signal [23]. This leads to the development of an alternate interpretation: the TGF-beta pathway could play a role in the healing process, and therefore could just be a marker of the aortic dilatation.

**Table 1.** The different forms of heritable thoracic disorders, including Marfan syndrome and related diseases

	Extracellular matrix		TGFB signalling				SMC contractile			
	<i>FBN1</i>	<i>COL3A1</i>	<i>TGFB2</i>	<i>TGFBR1</i>	<i>TGFB2</i>	<i>SMAD3</i>	<i>ACTA2</i>	<i>MYH11</i>	<i>MYLK</i>	<i>PRKG1</i>
Nonsyndromic	x	x	xx	xx	xx	x	xx	xx	xx	xx
Skeletal features (pectus, scoliosis, arachnodactyly)	xxx		xx	x	xx	xx				
Ectopia lentis	xxx		?	NR	?	NR				
Dural ectasia	xx		xx	xx	xx	xx				
EDS cutaneous findings (easy bruising, wide and atrophic scars, and translucent/velvety skin)	NR	xxx	x	xx	xx	x				
Abnormal uvula				xxx	xxx	x/xx				
Craniofacial score				xxx	xxx	?				
Cerebral aneurysm/dissection	NR		R	R	R	R	R	NR	NR	NR
Abdominal aneurysm/dissection (frequency)	x		?	x	x	xx				
Peripheral aneurysm/dissection (frequency)	+/-		?	xx	xx/xxx	xxx				x
Mitral valve disease	xxx		xxx	x	xx	xxx				
BAV	x			x	xx		x			
PDA	0		0	xx	x	0	x	xxx	NR	
Arterial tortuosity (severity)	x		x	xx	xx	xx	x	x	x	
Cardiomyopathy	x				xx	x				
Osteoarthritis	x					xxx				
Autoimmune	?				x	xx				
Neurological (peripheral neuropathy)						xx				

BAV, bicuspid aortic valve; EDS, ehlers danlos syndrome; NR, non-reported; PDA, patent ductus arteriosus; R, reported; SMC, smooth muscle cells; TGFB, transforming growth factor beta.

Reported are the phenotypical features that may be observed, but it must be kept in mind that a wide variability is observed with all these syndromes.

Craniofacial score was reproduced from [14].

In fact, it was recently demonstrated that the increased Smad2 production by cultured aortic smooth muscle cells obtained from TAA was the result of an epigenetic modification of the promoter of the *SMAD2* gene within the smooth muscle cell: increased Smad2 production was present in smooth muscle cells but not in fibroblasts isolated from the aortic wall of aneurysmal aorta, and was maintained after smooth muscle cell division. The role of p53 has been highlighted [24]. This indicates that the increased Smad2 is not directly the result of the increased TGF-beta activation, but is part of the modification of the smooth muscle cell occurring in TAA.

Besides, conditional *TGFB2* disruption in post-natal smooth muscle impairs aortic wall homeostasis in a mouse model, suggesting that basal TGF-beta signalling in smooth muscle is, in fact, required to preserve structural integrity. Furthermore, this inactivation exacerbates aortic disease in a model of Marfan syndrome [25]. Of note, this disruption

impaired the contractile apparatus of vascular smooth muscle, and fits into the 'contractile' hypothesis of TAA [26].

This discussion is important for the interpretation of the results of many losartan trials that are ongoing or have been recently terminated. Losartan was initially thought to specifically interfere with the supposed pathogenic activation of the TGF-beta pathway secondary to *FBN1* mutation because, in the mouse model, P-Smad2 decreased within the aortic wall as the dilatation was prevented. If this were true, the applicability of positive clinical trial results would be limited. However, if one considers that the beneficial effect of losartan may result from its vasodilatory properties, and the observed decrease in P-Smad2 is simply the consequence of lesser dilatation, the applicability of the results would be much wider. One should remember that a positive result in an animal model does not always translate into benefit in man.

The population included in the ongoing American Marfan trial comparing losartan vs. atenolol has just been published [27]. Six hundred and eight patients fulfilling Ghent1 criteria for Marfan syndrome, aged 6 months to 25 years, with aortic dilatation were randomized to receive either atenolol or losartan. The partly positive result (negative in the whole population, but positive in subgroups) of the study from the Netherlands, including adult patients with and without aortic surgery, has been reported in the *European Heart Journal* [28].

Beyond Smad2 synthesis, epigenetic modification of protease synthesis may also occur, and has been suggested to differentiate aortic dissection from aortic aneurysm [29<sup>\*</sup>].

## POLYGENIC DISEASES

Although much progress is being made in the understanding of TAA of genetic origin, most of the familial forms of TAA are not related to a known mutation. Apart from monogenic diseases, the familial TAA may also be associated with susceptibility genes. Lemaire *et al.* [30] have reported on the association between single nucleotide polymorphism within the *FBN1* gene and thoracic diseases [30], which was recently confirmed in a different population [31]. Inversely, *SMAD3* responsible for the aneurysm-osteoarthritis syndrome appears to be associated with the total burden of radiographic osteoarthritis in generalized osteoarthritis [32].

TAA associated with bicuspid aortic valve (BAV) may also be familial [33], and the familial screening of first-degree relatives is recommended. However, the interpretation of the increased diameter of the aorta in patients with bicuspid aortic valve remains difficult; it may reflect either altered anatomy of the aortic root, which is probably predominant at the level of the sinus of Valsalva and related to the BAV morphology, or progressive dilatation of the aorta, which is probably predominant in the tubular junction and is independent of the BAV anatomy [34<sup>\*</sup>].

## CONCLUSION

Familial TAA remains a subject for intense research and tremendous progress is being made, which should hopefully soon translate into improved patient care.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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