

# Genes Associated with Thoracic Aortic Aneurysm and Dissection

## An Update and Clinical Implications

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### Abstract

**Thoracic aortic aneurysm (TAA) is a lethal disease, with a natural history of enlarging progressively until dissection or rupture occurs. Since the discovery almost 20 years ago that ascending TAAs are highly familial, our understanding of the genetics of thoracic aortic aneurysm and dissection (TAAD) has increased exponentially. At least 29 genes have been shown to be associated with the development of TAAD, the majority of which encode proteins involved in the extracellular matrix, smooth muscle cell contraction or metabolism, or the transforming growth factor- $\beta$  signaling pathway. Almost one-quarter of TAAD patients have a mutation in one of these genes. In this review, we provide a summary of TAAD-associated genes, associated clinical features of the vasculature, and implications for surgical treatment of TAAD. With the widespread use of next-generation sequencing and development of novel functional assays, the future of the genetics of TAAD is bright, as both novel TAAD genes and variants within the genes will continue to be identified.**

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### Key Words:

**Thoracic aortic aneurysm and dissection (TAAD) • Genetics • Aortic aneurysm**

Thoracic aortic aneurysms (TAAs), which have an estimated annual incidence of 10.4 per 100,000 people [1], are typically clinically silent yet potentially fatal, as their natural history is to progressively expand until dissection or rupture occurs. Our genetic understanding of thoracic aortic aneurysm and dissection (TAAD) has rapidly advanced since the identification of the *FBN1* gene as the cause of Marfan syndrome in 1991 [2] and the discovery of the familial nature of TAAD in the late 1990s. While studies demonstrate that 20% of individuals with non-syndromic TAAD have a positive family history [3, 4], this percentage is most likely a marked underestimation, as not all family members of affected individuals undergo routine aortic imaging [5]. Of the 29 TAAD-associated genes identified to date, the majority encode proteins involved in the extracellular matrix, smooth muscle cell contraction or



**Table 1.** Genes associated with syndromic and non-syndromic thoracic aortic aneurysm and dissection, associated vascular characteristics, and size criteria for elective surgical intervention.

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Non-syndromic TAAD	Associated disease/syndrome	Associated clinical characteristics of the vasculature	Ascending aorta size (cm) for surgical intervention	Mode of inheritance	OMIM
<b>ACTA2</b>	Smooth muscle $\alpha$ -actin	No [30]	+	+	AAT6 + multysystemic smooth muscle dysfunction + MYMY5	TAAD, early aortic dissection*, CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV [6, 9]	4.5-5.0 <sup>a</sup> [10, 31, 32]	AD	611788 613834 614042
<b>BGN</b>	Biglycan	Yes [33]	+	-	Meester-Loeys syndrome	ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity [34]	Standard	X-linked	300989
<b>COL1A2</b>	Collagen 1 $\alpha$ 2 chain	No	+	-	EDS, arthrochalasia type (VIIb) + cardiac valvular type	Borderline aortic root enlargement [9, 35]	Standard	AD + AR	130060 225320
<b>COL3A1</b>	Collagen 3 $\alpha$ 1 chain	Yes [36]	+	-	EDS, vascular type (IV)	TAAD, early aortic dissection*, visceral arterial dissection, vessel fragility, IA [29, 37, 38]	5.0 <sup>b</sup> [29]	AD	130050
<b>COL5A1</b>	Collagen 5 $\alpha$ 1 chain	No <sup>c</sup>	+	-	EDS, classic type (I)	ARD, rupture/dissection of medium-sized arteries [39-41]	Standard	AD	130000
<b>COL5A2</b>	Collagen 5 $\alpha$ 2 chain	No <sup>d</sup>	+	-	EDS, classic type (II)	ARD	Standard	AD	130000
<b>EFEMP2</b>	Fibulin-4	Yes [42, 43]	+	-	Cutis laxa, AR type Ib	Ascending aortic aneurysm, other arterial aneurysm, arterial tortuosity and stenosis	Standard	AR	614437
<b>ELN</b>	Elastin	No	+	-	Cutis laxa, AD	ARD, ascending aortic aneurysm/dissection, BAV, IA, possibly associated with SVAS [44-46]	Standard	AD	123700 185500
<b>EMILIN1</b>	Elastin microfibril interfacer 1	No	+	-	Unidentified CTD	Ascending and descending aortic aneurysm [47]	Standard	AD	Unassigned
<b>FBN1</b>	Fibrillin-1	Yes [48-52]	+	+	Marfan syndrome	ARD, TAAD, AAA, other arterial aneurysm, pulmonary artery dilatation, arterial tortuosity [53]	5.0 [10, 28]	AD	154700
<b>FBN2</b>	Fibrillin-2	No	+	-	Contractural arachnodactyly	Rare ARD and aortic dissection [54], BAV, PDA	Standard	AD	121050

(table continues)

Table 1. (Continued)

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Non-syndromic TAAD	Associated disease/syndrome	Associated clinical characteristics of the vasculature	Ascending aorta size (cm) for surgical intervention	Mode of inheritance	OMIM
<i>FLNA</i>	Filamin A	Yes [55, 56]	+	-	Periventricular nodular heterotopia	Aortic dilatation/aneurysm, peripheral arterial dilatation [57], PDA, IA [58], BAV	Standard	XLD	300049
<i>FOXE3</i>	Forkhead box 3	Yes [59]	-	+	AAT11	ARD, TAAD (primarily type A dissection) [59]	Standard	AD	617349
<i>LOX</i>	Lysyl oxidase	Yes [60–63]	-	+	AAT10	TAAD, AAA, hepatic artery aneurysm, BAV, CAD	Standard	AD	617168
<i>MAT2A</i>	Methionine adenosyltransferase II alpha	No <sup>e</sup> [64]	-	+	FTAA	Thoracic aortic aneurysm, BAV [64]	Standard	AD	Unassigned
<i>MFAP5</i>	Microfibril-associated glycoprotein 2	Partially <sup>f</sup> [65]	-	+	AAT9	ARD, TAAD	Standard	AD	616166
<i>MYH11</i>	Smooth muscle myosin heavy chain	Partially <sup>g</sup> [66]	-	+	AAT4	TAAD, early aortic dissection*, PDA, CAD, peripheral vascular occlusive disease, carotid IA	4.5–5.0 [10, 67]	AD	132900
<i>MYLK</i>	Myosin light chain kinase	No <sup>h</sup> [68]	-	+	AAT7	TAAD, early aortic dissection*	4.5–5.0 <sup>a</sup> [10, 68]	AD	613780
<i>NOTCH1</i>	NOTCH1	No	-	+	AOVD1	BAV/TAAD [69, 70]	Standard	AD	109730
<i>PRKG1</i>	Type 1 cGMP-dependent protein kinase	No	-	+	AAT8	TAAD, early aortic dissection*, AAA, coronary artery aneurysm/dissection, aortic tortuosity, small vessel CVD	4.5–5.0 [71]	AD	615436
<i>SKI</i>	Sloan Kettering proto-oncoprotein	No <sup>i</sup>	+	-	Shprintzen-Goldberg syndrome	ARD, arterial tortuosity, pulmonary artery dilatation, other (splenic) arterial aneurysm [72]	Standard	AD	182212
<i>SLC2A10</i>	Glucose transporter 10	No <sup>j</sup>	+	-	Arterial tortuosity syndrome	ARD [73], ascending aortic aneurysm [73], other arterial aneurysm, arterial tortuosity, elongated arteries, aortic/pulmonary artery stenosis	Standard	AR	208050

(table continues)

**Table 1. (Continued)**

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Non-syndromic TAAD	Associated disease/syndrome	Associated clinical characteristics of the vasculature	Ascending aorta size (cm) for surgical intervention	Mode of inheritance	OMIM
SMAD2	SMAD2	No	+	-	Unidentified CTD with arterial aneurysm/dissection	ARD, ascending aortic aneurysm, vertebral/carotid aneurysm/dissection [74]	Standard	AD	Unassigned
SMAD3	SMAD3	Partially* [75]	+	+	LDS type 3	ARD, TAAD, early aortic dissection*, AAA, arterial tortuosity, other arterial aneurysm/dissection, IA, BAV [76, 77]	4.0-4.2 [10, 28]	AD	613795
SMAD4	SMAD4	Yes [78]	+	-	JP/HHT syndrome	ARD, TAAD, AVM, IA [79, 80]	Standard	AD	175050
TGFβ2	TGF-β2	Yes [81]	+	+	LDS type 4	ARD, TAAD, arterial tortuosity, other arterial aneurysm, BAV [81, 82]	4.5-5.0 [83]	AD	614816
TGFβ3	TGF-β3	No <sup>m</sup>	+	-	LDS type 5	ARD, TAAD, AAA/dissection, other arterial aneurysm, IA/dissection [84]	Standard	AD	615582
TGFBR1	TGF-β receptor type 1	Yes [85]	+	+	LDS type 1 + AAT5	TAAD, early aortic dissection*, AAA, arterial tortuosity, other arterial aneurysm/dissection, IA, PDA, BAV [86]	4.0-4.5 <sup>n</sup> [10, 26, 28]	AD	609192
TGFBR2	TGF-β receptor type 2	Yes [78, 85]	+	+	LDS type 2 + AAT3	TAAD, early aortic dissection*, AAA, arterial tortuosity, other arterial aneurysm/dissection, IA, PDA, BAV [86]	4.0-4.5 <sup>n</sup> [10, 26, 28]	AD	610168

It is important to note that as mutations in many of these genes are rare and have only recently been implicated in TAAD, there are a lack of adequate prospective clinical studies. Therefore, it is difficult to establish threshold diameters for intervention for TAA, and each individual must be considered on a case-by-case basis, taking into account the rate of change in aneurysm size (> 0.5 cm per year is considered rapid) and any family history of aortic dissection.

A "+" symbol in the syndromic or non-syndromic TAAD column indicates that mutations in the gene have been found in patients with syndromic or non-syndromic TAAD, respectively. A "-" symbol in the syndromic or non-syndromic TAAD column indicates that mutations in the gene have not been found in patients with syndromic or non-syndromic TAAD, respectively. A reference is provided for each of the associated vascular characteristics not reported in the OMIM entry for that gene.

(table continues)

**Table 1. (Continued)**

AAA = abdominal aortic aneurysm; AAT = aortic aneurysm = familial thoracic; AD = autosomal dominant; AOVd = aortic valve disease; AR = autosomal recessive; ARD = aortic root dilatation; AVM = arteriovenous malformation; BAV = bicuspid aortic valve; CAD = coronary artery disease; CTD = connective tissue disease; CVD = cerebrovascular disease; EDS = Ehlers-Danlos syndrome; FTA = familial thoracic aortic aneurysm; HHT = hereditary hemorrhagic telangiectasia; IA = intracranial aneurysm; JP = juvenile polyposis; LDS = Loeys-Dietz syndrome; MMY = moyamoya disease; OMIM = Online Mendelian Inheritance in Man; PDA = patent ductus arteriosus; SVAS = supravalvular aortic stenosis; TGF = transforming growth factor; TAAD = thoracic aortic aneurysm and dissection; TGFBR = TGF- $\beta$  receptor; XLD = X-linked dominant

Standard = surgical intervention at 5.0-5.5 cm

\* Early aortic dissection = dissection at aortic diameter < 5.0 cm

<sup>a</sup> Individuals with MYLK and ACTA2 mutations have been shown to have aortic dissections at a diameter of 4.0 cm [31, 68].

<sup>b</sup> There are no data to set threshold diameters for surgical intervention for EDS Type IV [28]. The Canadian guidelines recommend surgery for aortic root sizes of 4.0-5.0 cm and ascending aorta sizes of 4.2-5.0 cm, though these patients are at high risk of surgical complications due to poor-quality vascular tissue [87].

<sup>c</sup> Wenstrup et al. found that mice heterozygous for an inactivating mutation in Col5a1 exhibit decreased aortic compliance and tensile strength relative to wildtype mice [91].

<sup>d</sup> Park et al. illustrated that mice heterozygous for a null allele in Col5a2 exhibited increased aortic compliance and reduced tensile strength compared to wildtype mice [92].

<sup>e</sup> Guo et al. found that knockdown of mat2aa in zebrafish led to defective aortic arch development [64].

<sup>f</sup> Combs et al. demonstrated that Mfap2 and Mfap5 double knockout (Mfap2<sup>-/-</sup>/Mfap5<sup>-/-</sup>) mice exhibit age-dependent aortic dilation, though this is not the case with Mfap5 single knockout mice.

<sup>g</sup> While Kuang et al. reported that a mouse knock-in model (Myh11<sup>REM/REM</sup>) does not lead to a severe vascular phenotype under normal conditions [93], Bellini et al. demonstrated that induced hypertension in this mouse model led to intramural delaminations (separation of aortic wall layers without dissection) or premature deaths (due to aortic dissection based on necropsy according to unpublished data by Bellini et al.) in over 20% of the R247C mice, accompanied by focal accumulation of glycosaminoglycans within the aortic wall (a typical histological feature of TAAD).

<sup>h</sup> Wang et al. demonstrated that SMC-specific knockdown of Mylk in mice led to histopathological changes (increased pools of proteoglycans) and altered gene expression consistent with medial degeneration of the aorta, though no aneurysm formation was observed.

<sup>i</sup> Doyle et al. found that knockdown of paralogs of mammalian Ski in zebrafish led to craniofacial and cardiac anomalies, including failure of cardiac looping and malformations of the outflow tract [72]. Berk et al. showed that mice lacking Ski exhibit craniofacial, skeletal muscle, and central nervous system abnormalities, which are all features of Shprintzen-Goldberg syndrome, but no evidence of aneurysm development was reported [94].

<sup>j</sup> Mice with homozygous missense mutations in Sic2a10 have not been shown to have the vascular abnormalities seen with arterial tortuosity syndrome [95], though Cheng et al. did demonstrate that such mice do exhibit abnormal elastogenesis within the aortic wall [96].

<sup>k</sup> Tan et al. demonstrated that Smad3 knockout mice only developed aortic aneurysms with angiotensin II-induced vascular inflammation, though the knockout mice did have medial dissections evident on histological analysis of their aortas and exhibited aortic dilation relative to wildtype mice prior to angiotensin II infusion [75].

<sup>l</sup> There are limited data concerning the timing of surgical intervention for LDS type 4. However, there has been a case of a Type A aortic dissection at an aortic diameter < 5.0 cm [83], hence the recommended threshold range of 4.5-5.0 cm.

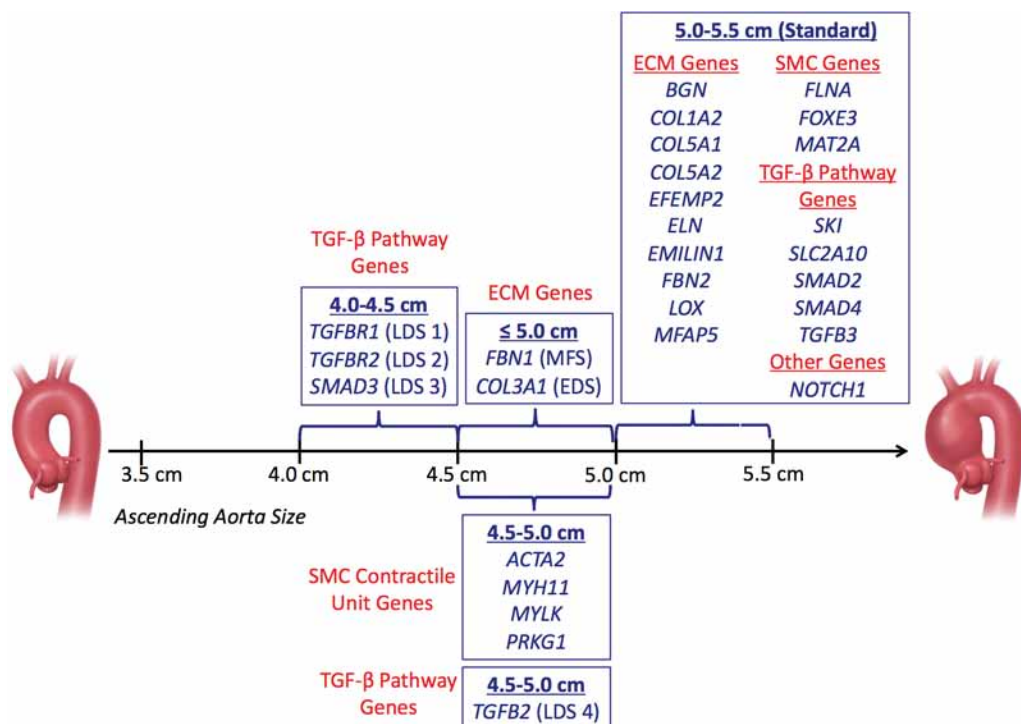
<sup>m</sup> Tgfb3 knockout mice die at birth from cleft palate [84], but minor differences in the position and curvature of the aortic arches of these mice compared to wildtype mice have been described [97].

<sup>n</sup> Current U.S. guidelines recommend prophylactic surgery for LDS types 1 and 2 at ascending aortic diameters of 4.0-4.2 cm [10, 28]. However, the European guidelines state that more clinical data are required [29]. Patients with TGFBR2 mutations have similar outcomes to patients with FBN1 mutations once their disease is diagnosed [88], and the clinical course of LDS 1 and 2 does not appear to be as severe as originally reported [26, 89, 90]. Therefore, medically treated adult patients with LDS 1 or 2 may not require prophylactic surgery at ascending aortic diameters of 4.0-4.2 cm [6]. Individuals with TGFBR2 mutations are more likely to have aortic dissections at diameters < 5.0 cm than those with TGFBR1 mutations [26, 90]. A more nuanced approach proposed by Jondeau et al. utilizing the presence of TGFBR2 mutations (vs. TGFBR1 mutations), the co-occurrence of severe systemic features (arterial tortuosity, hypertelorism, wide scarring), female gender, low body surface area, and a family history of dissection or rapid aortic root enlargement, which are all risk factors for aortic dissection, may be beneficial for LDS 1 and 2 patients to avoid unnecessary surgery at small aortic diameters [26]. Therefore, in LDS 1 or 2 individuals without the above features, Jondeau et al. maintain that 4.5 cm may be an appropriate threshold, but females with TGFBR2 mutations and severe systemic features may benefit from surgery at 4.0 cm [26].

metabolism, or the transforming growth factor (TGF- $\beta$ ) signaling pathway (Table 1) (reviewed in [6-14]). Almost one-quarter of patients with TAAD possess a mutation in one of these genes [6], the majority of which are inherited in an autosomal dominant fashion with reduced penetrance and variable expressivity [15, 16]. It is of interest to note that most genetic risk factors for aneurysms in other locations of the body (e.g., in intracranial arteries or the abdominal aorta) are different from those for TAAD [17-19].

TAAD has been classified into syndromic (associated with abnormalities of other organ systems) and non-syndromic (manifestations restricted to the aorta) [12, 20] categories, yet there is significant overlap in the genetic basis of syndromic and non-syndromic familial TAAD. Mutations in *FBN1* and Loey-Dietz syndrome (LDS) type 1-4 genes (*TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2*) are estimated to account for 10% of familial non-syndromic TAAD [6]. Also, mutations in *ACTA2* are estimated to cause 12-21% of familial TAAD, whereas mutations in other genes may each account for only 1-2% or less of

non-syndromic TAAD [6]. The identification of specific mutated genes in patients with TAAD is crucial because it permits targeted genetic testing of apparently unaffected but currently undiagnosed family members. Furthermore, genetic information helps determine the patient's risk for aortic dissection and rupture, especially mutations associated with vascular events at an ascending aorta size < 5.0 cm (Figure 1), which does not usually necessitate aortic resection in the absence of such mutations, a family history of aortic dissection, or rapid aneurysmal growth (> 0.5 cm/year). Identification of specific genetic variants associated with TAAD clinical outcomes may help predict how aortic disease will manifest and estimate the risk of other vascular diseases [6] (Table 1). Moreover, genotype-phenotype correlations have been established for both syndromic (*FBN1*, *COL3A1*, *TGFBR1*, and *TGFBR2*) and non-syndromic (*ACTA2*) TAAD, meaning that the specific genetic variant in TAAD-affected individuals can help predict the course and severity of disease [21-27].



**Figure 1.** Simplified schematic illustration of ascending aorta dimensions for prophylactic surgical intervention divided by gene category: ECM genes, SMC contractile unit and metabolism genes, and TGF- $\beta$  signaling pathway genes (data derived from Table 1). ECM, extracellular matrix; LDS, Loey-Dietz syndrome; MFS, Marfan syndrome; SMC, smooth muscle cell; EDS, Ehlers-Danlos syndrome.

As stated in the most recent United States and European guidelines [28, 29], personalized care based on underlying genetic mutations is and will continue to be a critical aspect of high-quality patient care. As genetic testing becomes more widespread, individuals at genetic risk for TAAAD may be identified earlier so that prophylactic medical and surgical intervention can be implemented to avert potentially fatal complications of TAAAD. Furthermore, the utilization of next-generation sequencing could lead to the development of a comprehensive library of pathogenic genetic variants. As the genetic basis of TAAAD is still a highly dynamic and burgeoning field, we present the most up-to-date list of genes associated with TAAAD (Table 1). We plan to update this report annually, adding new genes, intervention criteria, and manage-

ment recommendations as they become available.

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### Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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