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-β 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.

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          |
|----------|----------------------------------|---------------------------------------------|----------------|-------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|---------------------|-----------------|
| ACTA2    | Smooth muscle α-actin            | No [30]                                     | +              | +                 | RAAS + multisystemic smooth muscle dysfunction + MYMYS                                    | TAAD, early aortic dissection*, CAD, stroke ( moyamoya disease), PDA, pulmonary artery dilation, BAV [6, 9]               | 4.5-5.0* [10, 31, 32] | AD               | 611788         |
| BGN      | Biglycan                         | Yes [33]                                    | +              | -                 | Meester-Loeys syndrome                                                                   | ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity [34]                                                      | Standard X-linked | X-linked | 300989         |
| COL1A2   | Collagen 1 α2 chain              | No                                          | +              | -                 | EDS, arthrochalasia type (VIIb) + cardiac valvular type                                 | Borderline aortic root enlargement [9, 35]                                                                               | Standard AD + AR | 130060          |
| COL3A1   | Collagen 3 α1 chain              | Yes [36]                                    | +              | -                 | EDS, vascular type (IV)                                                                  | TAAD, early aortic dissection*, visceral arterial dissection, vessel fragility, IA [29, 37, 38]                         | 5.0* [29]            | AD               | 130050          |
| COL5A1   | Collagen 5 α1 chain              | No*                                         | +              | -                 | EDS, classic type (I)                                                                   | ARD, rupture/dissection of medium-sized arteries [39-41]                                                            | Standard AD     | 130000          |
| COL5A2   | Collagen 5 α2 chain              | No*                                         | +              | -                 | EDS, classic type (II)                                                                  | ARD                                                                                                                      | Standard AD     | 130000          |
| EFEMP2   | Fibulin-4                        | Yes [42, 43]                                | +              | -                 | Cutis laxa, AR type Ib                                                                 | Ascending aortic aneurysm, other arterial aneurysm, arterial tortuosity and stenosis                                  | Standard AR     | 614437          |
| ELN      | Elastin                          | No                                          | +              | -                 | Cutis laxa, AD                                                                         | ARD, ascending aortic aneurysm/dissection, BAV, IA possibly associated with SVAS [44-46]                              | Standard AD     | 123700          |
| EMILIN1  | Elastin microfibril interfacere 1| No                                          | +              | -                 | Unidentified CTD                                                                       | Ascending and descending aortic aneurysm [47]                                                                      | Standard AD     | Unassigned       |
| FBN1     | 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          |
| FBN2     | Fibrillin-2                      | No                                          | +              | -                 | Contractural arachnodacty                                                              | Rare ARD and aortic dissection [54], BAV, PDA                                                                     | Standard AD     | 121050          |

* (table continues)
| 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       |
|----------|----------------------------------|---------------------------------------------|---------------|-------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------|---------------------|------------|
| FLNA     | Filamin A                        | Yes [55, 56]                                | +             | -                 | Periventricular nodular heterotopia             | Aortic dilatation/aneurysm, peripheral arterial dilatation [57], PDA, IA [58], BAV      | Standard            | XLD       | 300049    |
| FOXE3    | Forkhead box 3                   | Yes [59]                                    | -             | +                 | AAT11                                          | ARD, TAAD (primarily type A dissection) [59]                                            | Standard            | AD        | 617349    |
| LOX      | Lysyl oxidase                    | Yes [60–63]                                  | -             | +                 | AAT10                                          | TAAD, AAA, hepatic artery aneurysm, BAV, CAD                                              | Standard            | AD        | 617168    |
| MAT2A    | Methionine adenosyltransferase II alpha | No[64]                                  | -             | +                 | FTAA                                           | Thoracic aortic aneurysm, BAV [64]                                                      | Standard            | AD        | Unassigned |
| MFAP5    | Microfibril-associated glycoprotein 2 | Partially[65]                              | -             | +                 | AAT9                                           | ARD, TAAD                                                                                  | Standard            | AD        | 616166    |
| MYH11    | Smooth muscle myosin heavy chain | Partially[66]                                | -             | +                 | AAT4                                           | TAAD, early aortic dissection*, PDA, CAD, peripheral vascular occlusive disease, carotid IA | 4.5-5.0 [10, 67]    | AD        | 132900    |
| MYLK     | Myosin light chain kinase        | No[68]                                      | -             | +                 | AAT7                                           | TAAD, early aortic dissection*                                                            | 4.5-5.0* [10, 68]   | AD        | 613780    |
| NOTCH1   | NOTCH1                           | No                                          | -             | +                 | AOVD1                                          | BAV/TAAD [69, 70]                                                                          | Standard            | AD        | 109730    |
| PRKG1    | 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    |
| SKI      | Sloan Kettering proto-oncoprotein | No[69]                                      | +             | -                 | Shprintzen-Goldberg syndrome                  | ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysm [72] | Standard            | AD        | 182212    |
| SLC2A10  | Glucose transporter 10           | No[70]                                      | +             | -                 | 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*
| 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     |
| TGFB2  | TGF-β2  | Yes [81]                                   | +              | +                  | LDS type 4                  | ARD, TAAD, arterial tortuosity, other arterial aneurysm, BAV [81, 82] | 4.5-5.0^[83]       | AD          | 614816     |
| TGFB3  | TGF-β3  | No^[n]                                     | +              | -                  | 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^[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^[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)
Individuals with MYLK and ACTA2 mutations have been shown to have aortic dissections at a diameter of 4.0 cm [31, 68].

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].

Park et al. illustrated that mice heterozygous for a null allele in Col5a1 exhibit decreased aortic compliance and reduced tensile strength compared to wildtype mice [91].

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]

D. Park et al. found that knockdown of mat2a1 in zebrafish led to defective aortic arch development [64].

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].

Guo et al. found that knockdown of mat2a1 in zebrafish led to defective aortic arch development [64].

Combs et al. demonstrated that mice heterozygous for a null allele in Col5a2 exhibited increased aortic compliance and reduced tensile strength compared to wildtype mice [92].

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 [94].

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].

Mice with homozygous missense mutations in Sck2a10 have not been shown to have the vascular abnormalities seen with arterial tortuosity syndrome [55], though Cheng et al. did demonstrate that such mice do exhibit abnormal elastogenesis within the aortic wall [86].

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 [94].

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metabolism, or the transforming growth factor (TGF-B)-β 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 TGFBR2) 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-β 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.](image)
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 TAAD may be identified so that prophylactic medical and surgical intervention can be implemented to avert potentially fatal complications of TAAD. 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 TAAD is still a highly dynamic and burgeoning field, we present the most up-to-date list of genes associated with TAAD (Table 1). We plan to update this report annually, adding new genes, intervention criteria, and management 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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