

# Genes Associated with Thoracic Aortic Aneurysm and Dissection: 2018 Update and Clinical Implications

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AORTA 2018;6:13–20.

## Abstract

Thoracic aortic aneurysms, with an estimated prevalence in the general population of 1%, are potentially lethal, via rupture or dissection. Over the prior two decades, there has been an exponential increase in our understanding of the genetics of thoracic aortic aneurysm and/or dissection (TAAD). To date, 30 genes have been shown to be associated with the development of TAAD and ~30% of individuals with nonsyndromic familial TAAD have a pathogenic mutation in one of these genes. This review represents the authors' yearly update summarizing the genes associated with TAAD, including implications for the surgical treatment of TAAD. Molecular genetics will continue to revolutionize the approach to patients afflicted with this devastating disease, permitting the application of genetically personalized aortic care.

## Keywords

- genetics
- thoracic aortic aneurysm
- thoracic aortic dissection

This review is the update to the 2017 paper "Genes Associated with Thoracic Aortic Aneurysm and Dissection" published in AORTA.<sup>1</sup> We have updated both ► **Table 1** listing the genes known to predispose to thoracic aortic aneurysm or dissection (TAAD) and ► **Fig. 1**, with the recommended sizes for surgical intervention for each specific mutation, based upon published findings in 2017.

Thoracic aortic aneurysms, with an estimated prevalence in the general population of 1%,<sup>2</sup> are potentially lethal, via rupture or dissection. Although significant progress has been made in decreasing the mortality of type A and type B aortic

dissections, particularly among individuals who are diagnosed and undergo surgical repair,<sup>3</sup> almost 50% of patients with a type A aortic dissection still die before hospital admission.<sup>4</sup> Therefore, it is critical for clinicians to identify those individuals at risk of TAAD and to perform clinical and genetic risk stratification so that appropriate and personalized management can be provided.

To date, 30 genes have been found to be associated with TAAD (► **Table 1** and ► **Fig. 1**) and ~30% of individuals with familial nonsyndromic TAAD (clinical manifestations restricted to the aorta) have a pathogenic variant in one or more of these

**Table 1** Genes associated with syndromic and nonsyndromic thoracic aortic aneurysm and/or dissection, associated vascular characteristics, and size criteria for elective surgical intervention (SMAD6 is the only gene that has been added to this table since publication of our 2017 AORTA review paper.)

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Nonsyndromic FTAAD	Associated disease/syndrome	Associated clinical characteristics of the vasculature	Ascending Aorta Size (cm) for Surgical Intervention	Mode of inheritance	OMIM
ACTA2	Smooth muscle $\alpha$ -actin	Yes <sup>10</sup>	+	+	AAT6 + multisystemic smooth muscle dysfunction + MYMY5	TAAD, early aortic dissection,* CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV <sup>11,12</sup>	4.5–5.0 <sup>a,13–15</sup>	AD	611788 613834 614042
BGN	Biglycan	Yes <sup>16</sup>	+	–	Meester-Loeys syndrome	ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity <sup>17</sup>	Standard	X-linked	300989
COL1A2	Collagen 1 $\alpha 2$ chain	No	+	–	EDS, arthrochalasia type (VIIb) + cardiac valvular type	Borderline aortic root enlargement <sup>12,18</sup>	Standard	AD + AR	130060 225320
COL3A1	Collagen 3 $\alpha 1$ chain	Yes <sup>19</sup>	+	–	EDS, vascular type (IV)	TAAD, early aortic dissection,* visceral arterial dissection, vessel fragility, IA <sup>20–22</sup>	5.0 <sup>b,22</sup>	AD	130050
COL5A1	Collagen 5 $\alpha 1$ chain	No <sup>e</sup>	+	–	EDS, classic type 1	ARD, rupture/dissection of medium sized arteries <sup>23–25</sup>	Standard	AD	130000
COL5A2	Collagen 5 $\alpha 2$ chain	Partially <sup>f</sup>	+	–	EDS, classic type 2	ARD	Standard	AD	130000
EFEMP2	Fibulin-4	Yes <sup>26,27</sup>	+	–	Cutis laxa, AR type 1b	Ascending aortic aneurysms, other arterial aneurysms, arterial tortuosity and stenosis	Standard	AR	614437
ELN	Elastin	No	+	–	Cutis laxa, AD	ARD, ascending aortic aneurysm and dissection, BAV, IA possibly associated with SVAS <sup>28–30</sup>	Standard	AD	123700 185500
EMILIN1	Elastin microfibril interfacier 1	No	+	–	Unidentified CTD	Ascending and descending aortic aneurysm <sup>31</sup>	Standard	AD	Unassigned
FBN1	Fibrillin-1	Yes <sup>32–36</sup>	+	+	Marfan syndrome	ARD, TAAD, AAA, other arterial aneurysms, pulmonary artery dilatation, arterial tortuosity <sup>37</sup>	5.0 <sup>15,38</sup>	AD	154700
FBN2	Fibrillin-2	No	+	–	Contractual arachnodactyly	Rare ARD and aortic dissection, <sup>39</sup> BAV, PDA	Standard	AD	121050
FLNA	Filamin A	Yes <sup>40,41</sup>	+	–	Periventricular nodular heterotopia	Aortic dilatation/aneurysms, peripheral arterial dilatation, PDA, IA, <sup>43</sup> BAV	Standard	XLD	300049
FOXE3	Forkhead box 3	Yes <sup>44</sup>	–	+	AAT11	TAAD (primarily Type A dissection) <sup>44</sup>	Standard	AD	617349
LOX	Lysyl oxidase	Yes <sup>45–48</sup>	–	+	AAT10	TAAD, AAA, hepatic artery aneurysm, BAV, CAD	Standard	AD	617168
MAT2A	Methionine adenosyltransferase II $\alpha$	No <sup>g,49</sup>	–	+	FTAA	Thoracic aortic aneurysms, BAV <sup>49</sup>	Standard	AD	Unassigned
MFAP5	Microfibril-associated glycoprotein 2	Partially <sup>h,50</sup>	–	+	AAT9	ARD, TAAD	Standard	AD	616166

Table 1 (Continued)

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Nonsyndromic FTAAD	Associated disease/syndrome	Associated clinical characteristics of the vasculature	Ascending Aorta Size (cm) for Surgical Intervention	Mode of inheritance	OMIM
MYH11	Smooth muscle myosin heavy chain	Partially <sup>51</sup>	-	+	AAT4	TAAD, early aortic dissection,* PDA, CAD, peripheral vascular occlusive disease, carotid IA	4.5-5.0 <sup>15,52</sup>	AD	132900
MYLK	Myosin light chain kinase	No <sup>53</sup>	-	+	AAT7	TAAD, early aortic dissections*	4.5-5.0 <sup>a,15,53</sup>	AD	613780
NOTCH1	NOTCH1	Partially <sup>k</sup>	-	+	AOVD1	BAV/TAAD <sup>54,55</sup>	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 <sup>56</sup>	AD	615436
SKI	Sloan Kettering proto-oncoprotein	No <sup>l</sup>	+	-	Shprintzen-Goldberg syndrome	ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysms <sup>57</sup>	Standard	AD	182212
SLC2A10	Glucose transporter 10	No <sup>m</sup>	+	-	Arterial tortuosity syndrome	ARD, <sup>58</sup> ascending aortic aneurysms, <sup>58</sup> other arterial aneurysms, arterial tortuosity, elongated arteries aortic/pulmonary artery stenosis	Standard	AR	208050
SMAD2	SMAD2	No	+	-	Unidentified CTD with arterial aneurysm/dissections	ARD, ascending aortic aneurysms, vertebral/carotid aneurysms and dissections, AAA <sup>59,60</sup>	Standard	AD	Unassigned
SMAD3	SMAD3	Partially <sup>n,61</sup>	+	+	LDS type 3	ARD, TAAD, early aortic dissection,* AAA, arterial tortuosity, other arterial aneurysms/dissections, IA, BAV <sup>62,63</sup>	4.0-4.2 <sup>15,38</sup>	AD	613795
SMAD4	SMAD4	Yes <sup>64</sup>	+	-	JP/HHT syndrome	ARD, TAAD, AVMs, IA <sup>65,66</sup>	Standard	AD	175050
SMAD6	SMAD6	No <sup>o</sup>	-	+	AOV2	BAV/TAAD <sup>6</sup>	Standard	AD	602931
TGFβ2	TGF-β2	Yes <sup>67</sup>	+	+	LDS type 4	ARD, TAAD, arterial tortuosity, other arterial aneurysms, BAV <sup>67,68</sup>	4.5-5.0 <sup>69</sup>	AD	614816
TGFβ3	TGF-β3	No <sup>p</sup>	+	-	LDS type 5	ARD, TAAD, AAA/dissection, other arterial aneurysms, IA/dissection <sup>70</sup>	Standard	AD	615582
TGFβR1	TGF-β receptor type 1	Yes <sup>71</sup>	+	+	LDS type 1 + AAT5	TAAD, early aortic dissection,* AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV <sup>72</sup>	4.0-4.5 <sup>d,15,38,73</sup>	AD	609192
TGFβR2	TGF-β receptor type 2	Yes <sup>64,71</sup>	+	+	LDS type 2 + AAT3	TAAD, early aortic dissection,* AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV <sup>72</sup>	4.0-4.5 <sup>d,15,38,73</sup>	AD	610168

Abbreviations: AAA, abdominal aortic aneurysm; AAT, aortic aneurysm, familial thoracic; AD, autosomal dominant; AOV2, 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; EDS, Ehlers-Danlos syndrome; FTAAD, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and/or dissection; HHT, hereditary hemorrhagic telangiectasia; IA, intracranial aneurysm; JP, juvenile polyposis; LDS, Loews-Dietz syndrome; MMY, moyamoya

**Table 1** (Continued)

disease; OMIM, Online Mendelian Inheritance in Man; PDA, patent ductus arteriosus; SVAS, supravalvular aortic stenosis; TGF, transforming growth factor; TAAD, thoracic aortic aneurysm and/or dissection; TGFBR, TGF- $\beta$  receptor; XLD, X-linked dominant

It is important to note that since mutations in many of these genes are rare and have only recently been implicated in TAAD, there is a lack of adequate prospective clinical studies. Therefore, it is difficult to establish threshold diameters for intervention for TAAs, 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), any family history of aortic dissection at diameters < 5.0 cm, and the presence of significant aortic regurgitation, which are all indications for early repair if present.

A "\*" symbol in the syndromic TAAD column indicates that mutations in the gene have been found in patients with syndromic TAAD (same for the nonsyndromic TAAD column). A "." symbol in the syndromic TAAD column indicates that mutations in the gene have not been found in patients with syndromic TAAD (same for the nonsyndromic TAAD column). A reference is provided for each of the associated vascular characteristics not reported in the OMIM entry for that gene.

Standard = surgical intervention at 5.0 to 5.5 cm.

Early aortic dissection\* = dissection at aortic diameters < 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.<sup>13,53</sup>

<sup>b</sup>There are no data to set threshold diameters for the surgical intervention for EDS type IV.<sup>38</sup> The Canadian guidelines recommend surgery for aortic root sizes of 4.0 to 5.0 cm and ascending aorta sizes of 4.2 to 5.0 cm, though these patients are at high risk of surgical complications due to poor-quality vascular tissue.<sup>74</sup>

<sup>c</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<sup>69</sup> hence, the recommended threshold range of 4.5 to 5.0 cm.

<sup>d</sup>Current US guidelines recommend prophylactic surgery for LDS types 1 and 2 at ascending aortic diameters of 4.0 to 4.2 cm.<sup>15,38</sup> However, the European guidelines state that more clinical data are required.<sup>22</sup> Patients with TGFBR2 mutations have similar outcomes to patients with FBNI mutations once their disease is diagnosed,<sup>75</sup> and the clinical course of LDS 1 and 2 does not appear to be as severe as originally reported.<sup>73,76,77</sup> Therefore, medically treated adult patients with LDS 1 or 2 may not require prophylactic surgery at ascending aortic diameters of 4.0 to 4.2 cm.<sup>11</sup> Individuals with TGFBR2 mutations are more likely to have aortic dissections at diameters < 5.0 cm than those with TGFBR1 mutations.<sup>73,77</sup> A more nuanced approach proposed by Jondeau et al utilizing the presence of TGFBR2 mutations (versus 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.<sup>73</sup> 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.<sup>73</sup>

<sup>e</sup>Wenstrup et al found that mice heterozygous for an inactivating mutation in Col5a1 exhibit decreased aortic compliance and tensile strength relative to wild-type mice.<sup>78</sup>

<sup>f</sup>Park et al recently demonstrated that Col5a2 haploinsufficiency increased the incidence and severity of AAA and led to aortic arch ruptures and dissections in an angiotensin II-induced aneurysm mouse model.<sup>79</sup> In an earlier paper, Park et al illustrated that mice heterozygous for a null allele in Col5a2 exhibited increased aortic compliance and reduced tensile strength compared with wild-type mice.<sup>80</sup>

<sup>g</sup>Guo et al found that knockdown of mat2a in zebrafish led to defective aortic arch development.<sup>49</sup>

<sup>h</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>i</sup>While Kuang et al reported that a mouse knock-in model (Myh11<sup>R247C/R247C</sup>) does not lead to a severe vascular phenotype under normal conditions,<sup>81</sup> 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>j</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>k</sup>Koenig et al recently found that Notch1 haploinsufficiency exacerbates the aneurysmal aortic root dilation in a mouse model of Marfan syndrome and that Notch1 heterozygous mice exhibited aortic root dilation, abnormal smooth muscle cell morphology, and reduced elastic laminae.<sup>82</sup>

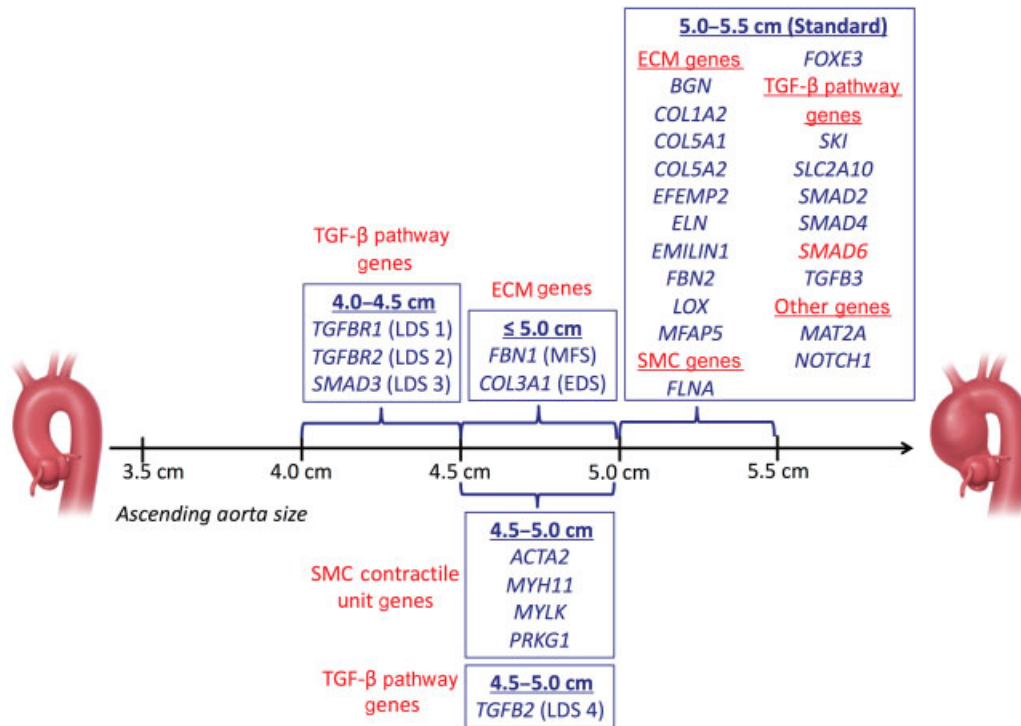
<sup>l</sup>Doyle et al found that knockdown of paralogs of mammalian SKI in zebrafish led to craniofacial and cardiac anomalies, including failure of cardiac looping and malformations of the outflow tract.<sup>57</sup> Berk et al showed that mice lacking Ski exhibit craniofacial, skeletal muscle, and central nervous system abnormalities, which are all features of Shprintzen–Goldberg syndrome, but no evidence of aneurysm development was reported.<sup>83</sup>

<sup>m</sup>Mice with homozygous missense mutations in Slc2a10 have not been shown to have the vascular abnormalities seen with arterial tortuosity syndrome,<sup>84</sup> though Cheng et al did demonstrate that such mice do exhibit abnormal elastogenesis within the aortic wall.<sup>85</sup>

<sup>n</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 dilatation relative to wild-type mice prior to angiotensin II infusion.<sup>61</sup>

<sup>o</sup>Galvin et al demonstrated that Madh6, which encodes Smad6, mutant mice exhibited defects in cardiac valve formation, outflow tract septation, vascular tone, and ossification but no aneurysm development was observed.<sup>86</sup>

<sup>p</sup>Tgfb3 knockout mice die at birth from cleft palate<sup>70</sup>, but minor differences in the position and curvature of the aortic arches of these mice compared with wild-type mice have been described.<sup>87</sup>



**Fig. 1** Ascending aorta dimensions for prophylactic surgical intervention. (Data derived from ►Table 1 and modified with permission from Brownstein et al.<sup>1</sup>) Any gene newly reported during the past year to be associated with TAAD is highlighted in red. Abbreviations: ECM, extracellular matrix; SMC, smooth muscle cell; TAAD, thoracic aortic aneurysm and/or dissection; TGF, transforming growth factor.

genes.<sup>5</sup> Mutations in these genes lead to a spectrum of risk and severity of type A and B aortic dissections,<sup>5</sup> as well as different extra-aortic manifestations. Specific mutations in *ACTA2* are estimated to account for 12 to 21% of familial nonsyndromic TAAD, while mutations in syndromic genes (*FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2*) are estimated to account for an additional 14% of cases of familial nonsyndromic TAAD.<sup>5</sup> Other genes listed in ►Table 1 are estimated to contribute to 1 to 2% each or less of familial nonsyndromic TAAD.<sup>5</sup> Given that the majority of familial nonsyndromic TAAD cannot be explained by a mutation in one of the known genes associated with TAAD, it is likely that additional genes remain to be identified.

Several important genetic findings have been reported during the past year. Using exome sequencing of 441 patients with bicuspid aortic valve and thoracic aortic aneurysm, Gillis et al identified pathogenic mutations in *SMAD6* in 11 afflicted individuals, adding to the growing list of genes associated with TAAD.<sup>6</sup> Additionally, in an exome sequencing study of 27 patients with syndromic or familial TAAD (specifically focused on three pairs of first-degree relatives with the same pathogenic TAAD variant but differing phenotypic severity from three independent families), Landis et al found that variants within two genes, *ADCK4* and *COL15A1*, segregated with mild disease severity among thoracic aortic aneurysm patients, offering clues that may help explain the reduced penetrance and variable expression observed in those with TAAD.<sup>7</sup> Lastly, though not introducing a novel association, work by Franken et al on 290 Marfan syndrome (MFS) patients recently expanded our understanding of the genotype–phenotype relationships in TAAD—by demonstrating that among individuals with MFS,

those with haploinsufficient mutations in *FBN1* have larger aortic root diameters that exhibit a more rapid dilation rate than those with dominant negative mutations.<sup>8</sup> Similarly, De Carlo et al found that the presence of certain common polymorphisms in *TGFBR1* and *TGFBR2* was associated with reduced cardiovascular disease severity among patients with MFS.<sup>9</sup>

These studies completed in 2017 illustrate the dynamic nature of the field of TAAD genetics. Through continued investigation and expanded access to genetic testing for affected patients and their family members, whole genome sequencing will undoubtedly continue to add new genes to the roster of causes for familial TAAD. Molecular genetics will continue to revolutionize the approach to patients afflicted with this devastating disease, permitting the application of genetically personalized aortic care. A major challenge in the field remains the lack of functional studies to prove the pathogenicity of identified variants.

We will continue to provide a yearly update and a revised summary table and revised intervention criterion table in AORTA at the end of each calendar year.

#### Conflict of Interest

The authors declare no conflict of interest related to this manuscript.

#### Funding

None.

#### Acknowledgements

None.



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