



Genes Associated with Thoracic Aortic Aneurysm and Dissection: 2019 Update and Clinical Implications

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Abstract

Thoracic aortic aneurysm is a typically silent disease characterized by a lethal natural history. Since the discovery of the familial nature of thoracic aortic aneurysm and dissection (TAAD) almost 2 decades ago, our understanding of the genetics of this disorder has undergone a transformative amplification. To date, at least 37 TAAD-causing genes have been identified and an estimated 30% of the patients with familial nonsyndromic TAAD harbor a pathogenic mutation in one of these genes. In this review, we present our yearly update summarizing the genes associated with TAAD and the ensuing clinical implications for surgical intervention. Molecular genetics will continue to bolster this burgeoning catalog of culprit genes, enabling the provision of personalized aortic care.

Keywords

- ▶ genetics
- ▶ thoracic aortic aneurysm
- ▶ aortic dissection

Introduction

This review presents an annual update to the article “Genes Associated with Thoracic Aortic Aneurysm and Dissection: Update and Clinical Implications” originally published in 2017 and updated in 2018 in AORTA.^{1,2} We have updated the list of genes with identified genetic variants predisposing individuals to a thoracic aortic aneurysm or dissection (TAAD) in ▶ **Table 1**, and the recommendation for individualized surgical interventions for specific genetic mutations is presented in ▶ **Fig. 1**.

Thoracic aortic aneurysm (TAA) affects 1% of the general population³ and its natural history is to enlarge an average of 0.14 cm per year.⁴ Prior to often lethal dissection or rupture, TAAs are usually asymptomatic. However, if identified and treated with appropriate blood pressure control and surgical intervention, life expectancy is improved.

Report of inherited TAAD in the 1990s⁵ has led to the discovery and understanding of genetic and molecular mechanisms of TAAD.⁶ To date, variants in 37 genes have been associated with TAAD (▶ **Table 1**; ▶ **Fig. 1**). These genes explain approximately 30% of the familial nonsyndromic

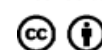


Table 1 Genes associated with syndromic and nonsyndromic thoracic aortic aneurysm and/or dissection, associated vascular characteristics, and size criteria for elective surgical intervention (any gene newly reported during the past year to be associated with TAAD is highlighted in red)

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 α -actin	Yes ²⁰	+	+	AAT6 + multisystemic smooth muscle dysfunction + MYMY5	TAAD, early aortic dissection ¹ , CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV ^{21,22}	4.5–5.0 ^{a,23–25}	AD	611788 613834 614042
ARH1	Ariadne RBR E3 ubiquitin protein ligase 1¹⁵	No	+	+	FTAA	Aortic and intracranial aneurysm¹⁵	Standard	Unknown	605624
BGN	Biglycan	Yes ²⁶	+	–	Meester-Loeys syndrome	ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity ²⁷	Standard	X-linked	300989
COL1A2	Collagen 1 $\alpha 2$ chain	No	+	–	EDS, arthrochalasia Type (Vllb) + cardiac valvular type	Borderline aortic root enlargement ^{22,28}	Standard	AD + AR	130060 225320
COL3A1	Collagen 3 $\alpha 1$ chain	Yes ^{29,30}	+	–	EDS, vascular Type (IV)	TAAD, early aortic dissection ¹ , visceral arterial dissection, vessel fragility, IA ^{31–33}	5.0 ^{b,33}	AD	130050
COL5A1	Collagen 5 $\alpha 1$ chain	No ^e	+	–	EDS, classic Type I	ARD, rupture/dissection of medium-sized arteries ^{34–36}	Standard	AD	130000
COL5A2	Collagen 5 $\alpha 2$ chain	Partially ^f	+	–	EDS, classic Type II	ARD ³⁷	Standard	AD	130000
EFEMP2	Fibulin-4	Yes ^{38,39}	+	–	Cutis laxa, AR Type Ib	Ascending aortic aneurysms, other arterial aneurysms, arterial tortuosity, and stenosis ⁴⁰	Standard	AR	614437
ELN	Elastin	No	+	–	Cutis laxa, AD	ARD, ascending aortic aneurysm and dissection, BAV, IA possibly associated with SVAS ^{41–43}	Standard	AD	123700 185500
EMILIN1	Elastin microfibril inter-facer 1	No	+	–	CTD and peripheral neuropathy	Ascending and descending aortic aneurysm ⁴⁴	Standard	AD	Unassigned
FBN1	Fibrillin-1	Yes ^{45–49}	+	+	Marfan syndrome	ARD, TAAD, AAA, other arterial aneurysms, pulmonary artery dilatation, arterial tortuosity ⁵⁰	5.0 ^{25,51}	AD	154700
FBN2	Fibrillin-2	No	+	–	Contractural arachnodactyly	Rare ARD and aortic dissection, ⁵² BAV, PDA	Standard	AD	121050
FLNA	Filamin A	Yes ^{53,54}	+	–	Periventricular nodular heterotopia and otopalatodigital syndrome	Aortic dilatation/aneurysms, peripheral arterial dilatation, ⁵⁵ PDA, IA, ⁵⁶ BAV	Standard	XLD	300049
FOXE3	Forkhead box 3	Yes ⁵⁷	–	+	AAT11	TAAD (primarily Type A dissection) ⁵⁷	Standard	AD	617349
HCM4	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	No	–	+	Noncompaction cardiomyopathy, bradycardia, and mitral valve disease	Ascending aorta dilation ⁵⁸	Standard	AD	163800
LOX	Lysyl oxidase	Yes ^{59–62}	–	+	AAT10	TAAD, AAA, hepatic artery aneurysm, BAV, CAD	Standard	AD	617168
LTPBP19	Latent TGF-β binding protein	No^{h,10}	+	–	Aortic dilation with associated musculoskeletal findings	TAAD¹⁰	Standard	AD	150390
LTPBP3	Latent TGF-β binding protein	Yes^{1,12}	+	–	Dental anomalies and short stature	TAAD, AAA, visceral and peripheral arterial aneurysm¹²	Standard	AR	602090
MAT2A	Methionine adenosyltransferase II α	No ⁶³	–	+	FTAA	Thoracic aortic aneurysms, BAV ⁶³	Standard	AD	Unassigned
MFAP5	Microfibril-associated glycoprotein 2	Partially ^{k,64}	–	+	AAT9	ARD, TAAD ⁶⁵	Standard	AD	616166

Table 1 (Continued)

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAO	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 ⁶⁶	-	+	AAT4	TAAO, early aortic dissection [†] , PDA, CAD, peripheral vascular occlusive disease, carotid IA ⁶⁷	4.5–5.0 ^{25,67}	AD	132900
MYLK	Myosin light chain kinase	No ^{m,68}	-	+	AAT7	TAAO, early aortic dissections [†] 17,69,70	4.5–5.0 ^{25,68}	AD	613780
NOTCH1	NOTCH1	Partially ⁿ	-	+	AOVD1	BAV/TAAD ^{71,72}	Standard	AD	109730
PRKG1	Type I cGMP-dependent protein kinase	No	-	+	AAT8	TAAO, early aortic dissection [†] , AAA, coronary artery aneurysm/dissection, aortic tortuosity, small vessel CVD	4.5–5.0 ⁷³	AD	615436
ROBO4	Roundabout guidance receptor 4	Yes	-	+	BAV	BAV/TAAD ⁹	Standard	AD	607528
SKI	Sloan Kettering proto-oncoprotein	No ^o	+	-	Shprintzen-Goldberg syndrome	ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysms ⁴	Standard	AD	182212
SICZAT10	Glucose transporter 10	No ^p	+	-	Arterial tortuosity syndrome	ARD, ⁷⁵ ascending aortic aneurysms, ⁷⁵ 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 ^{76,77}	Standard	AD	Unassigned
SMAD3	SMAD3	Partially ^{d,78}	+	+	LDS Type III	ARD, TAAO, early aortic dissection [†] , AAA, arterial tortuosity, other arterial aneurysms/dissections, IA, BAV ^{9,80}	4.0–4.2 ^{25,51}	AD	613795
SMAD4	SMAD4	Yes ⁸¹	+	-	JP/HHT syndrome	ARD, TAAO, AVMs, IA ^{82,83}	Standard	AD	175050
SMAD6	SMAD6	No ^r	-	+	AOVD2	BAV/TAAD ⁸⁴	Standard	AD	602931
TIMP3	Tissue inhibitors of metalloproteinase 3	No	+	-	AOVD	BAV/TAAD ¹⁶	Standard	XLD	188826
TIMP1	Tissue inhibitors of metalloproteinase 1	No	-	-	AOVD	BAV/TAAD ¹⁶	Standard	XLD	305370
TGFβ2	TGF-β2	Yes ⁸⁵	+	+	LDS Type IV	ARD, TAAO, arterial tortuosity, other arterial aneurysms, BAV ^{85,86}	4.5–5.0 ⁸⁷	AD	614816
TGFβ3	TGF-β3	No ^s	+	-	LDS Type V	ARD, TAAO, AAA/dissection, other arterial aneurysms, IA/dissection ⁸⁸	Standard	AD	615582
TGFβR1	TGF-β receptor type I	Yes ⁸⁹	+	+	LDS Type I + AAT5	TAAO, early aortic dissection [†] , AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV ⁹⁰	4.0–4.5 ^{4,25,51,91}	AD	609192
TGFβR2	TGF-β receptor Type II	Yes ^{81,89}	+	+	LDS Type II + AAT3	TAAO, early aortic dissection [†] , AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV ⁹⁰	4.0–4.5 ^{4,25,51,91}	AD	610168

Abbreviations: 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; 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; MMYM, moyamoya disease; OMIM, Online Mendelian Inheritance in Man; PDA, patent ductus arteriosus; SVAS, supraaortic arterial stenosis; TGF, transforming growth factor; TAAO, thoracic aortic aneurysm and/or dissection; TGFβR, TGF-β receptor; XLD, X-linked dominant.

Note: 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 the intervention of 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 5.0–5.5 cm; Early aortic dissection¹ = dissection at aortic diameters <5.0 cm.

^aIndividuals with MYLK and ACTA2 mutations have been shown to have aortic dissections at a diameter of 4.0 cm.^{23,68}

^bThere are no data to set threshold diameters for surgical intervention for EDS Type IV.⁵¹ 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.⁵²

^cThere are limited data concerning the timing of surgical intervention for LDS Type IV. However, there has been a case of a Type A aortic dissection at an aortic diameter <5.0 cm,⁸⁷ hence the recommended threshold range of 4.5–5.0 cm.

^dCurrent U.S. guidelines recommend prophylactic surgery for LDS Types I and II at ascending aortic diameters of 4.0–4.2 cm.^{25,51} However, the European guidelines state that more clinical data are required.³³ Patients with TGFBR2 mutations have similar outcomes to patients with FBN1 mutations once their disease is diagnosed,⁹³ and the clinical course of LDS 1 and 2 does not appear to be as severe as originally reported.^{91,94,95} 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.²¹ Individuals with TGFBR2 mutations are more likely to have aortic dissections at diameters <5.0 cm than those with TGFBR1 mutations.^{91,95} 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.⁹¹ 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.⁹¹

^eWenstrup et al found that mice heterozygous for an inactivating mutation in Col5a1 exhibit decreased aortic compliance and tensile strength relative to wild type mice.⁹⁶

^fPark 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.³⁷ 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.⁹⁷

^gChromosome 2p22 deletion.

^hTodorovic et al⁹⁸ showed that LTBP1 plays an important role in cardiac and bone development. Knockout mice displayed interrupted aortic arch, patent truncus arteriosus, hyperplastic semilunar valves, and atrial septal defects. However, aortic measurements were not mentioned.¹⁰

ⁱGuo et al showed that the knockout mice have larger aortic roots and ascending aortas than wild type, however, no aneurysms or dissections were reported.

^jGuo et al found that the knockdown of MATZAA in zebrafish led to defective aortic arch development.⁶³

^kCombs et al demonstrated that MFAP2 and MFAP5 double knockout (MFAP2^{-/-};MFAP5^{-/-}) mice exhibit age-dependent aortic dilation, though this is not the case with MFAP5 single knockout mice.

^lWhile Kuang et al reported that a mouse knock-in model (Myh11^{R247C/R247C}) does not lead to a severe vascular phenotype under normal conditions,⁹⁹ 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).

^mWang 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.

ⁿKoenig et al recently found that Notch1 haploinsufficiency exacerbates the aneurysmal aortic root dilation in a mouse model of MFS and that Notch1 heterozygous mice exhibited aortic root dilation, abnormal smooth muscle cell morphology, and reduced elastic laminae.¹⁰⁰

^oDoyle 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.⁷⁴ 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.¹⁰¹

^pMice with homozygous missense mutations in Slc2a10 have not been shown to have the vascular abnormalities seen with arterial tortuosity syndrome,¹⁰² though Cheng et al did demonstrate that such mice do exhibit abnormal elastogenesis within the aortic wall.¹⁰³

^qTan 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.⁷⁸

^rGalvin 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.¹⁰⁴

^sTGFβ3 knockout mice die at birth from cleft palate,⁸⁸ but minor differences in the position and curvature of the aortic arches of these mice compared with wild type mice have been described.¹⁰⁵

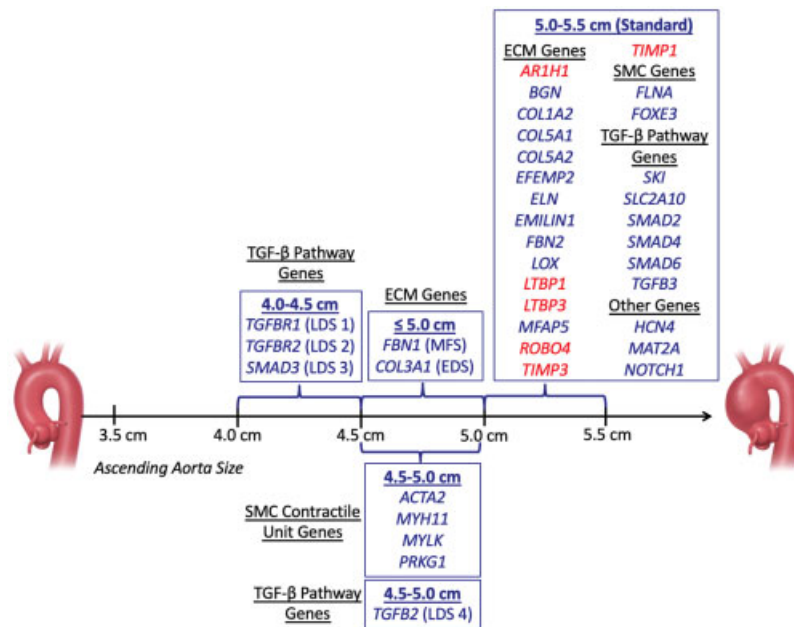


Fig. 1 Ascending aortic dimensions for prophylactic surgical intervention (Data derived from ►Table 1 and modified with permission from Brownstein et al²). Any gene newly reported during the past year to be associated with TAAD is highlighted in red. ECM, extracellular matrix; SMC, smooth muscle cell; TGF, transforming growth factor.

TAAD.⁷ These genes encode proteins of the extracellular matrix, vascular smooth muscle cell contractile unit, or transforming growth factor β (TGF- β)-signaling pathways⁸ and thus are essential to the structure and maintenance of the aortic wall.

During 2018, several important studies were published that have enhanced our understanding of the pathogenesis of TAAD. Gould et al⁹ performed whole-exome sequencing (WES) and targeted sequencing on 736 individuals with bicuspid aortic valve (BAV), non-syndromic ascending aortic aneurysm (AscAA), and 376 controls.⁹ In 13 (1.8%) of the affected individuals a heterozygous *ROBO4* mutation was identified, including two variants that segregated with disease among two affected families.⁹ *ROBO4* is well expressed in vascular endothelial cells and plays a role in endothelial barrier function.⁹ In this study, its expression was found to be diminished in the resected aorta sample of an affected individual with AscAA.⁹ To further test their hypothesis that *ROBO4* variants lead to the disruption of endothelial performance at a cellular level, thus altering vascular permeability, the authors cultured human aortic endothelial cells and either silenced *ROBO4* or expressed *ROBO4* variants. They confirmed that *ROBO4* abnormalities did indeed induce endothelial barrier dysfunction. Lastly, the authors created homozygous *ROBO4* knockout mice and a knock-in mouse with an *ROBO4* splice donor site mutation; the affected mice presented with a mix of aortic valve dysfunction (BAV and/or aortic regurgitation or stenosis) and AscAA, confirming their suspicion that a heterozygous mutation in *ROBO4* can lead to a nonsyndromic presentation of BAV/AscAA.⁹

Latent transforming growth factor binding proteins (LTBP), a family of extracellular matrix glycoproteins, have been shown to play a significant role in TGF- β regulation.¹⁰

LTBP1, in particular, can bind to fibrillin-1 and inactivate TGF- β .^{10,11} Quiñones-Pérez et al described a case series involving a three-generation family with TAA found to have a chromosome 2p22.3-p22.2 deletion involving *LTBP1*, amongst other genes.¹⁰ Despite multiple genes being involved in the deletion, *LTBP1* was considered the likely culprit given its relationship to TGF- β . In addition to TAA, the affected individuals displayed additional features of Marfan syndrome (MFS) and Loeys-Dietz syndrome, even though none of them met the criteria for diagnosis.

Mutations of the latent TGF- β binding protein-3 (*LTBP3*) gene have been associated with TAAD in a WES study of 271 individuals from unrelated families with heritable thoracic aortic disease (multiple affected family members) without a known genetic etiology for aortopathy.¹² In this study, compound heterozygous variants in one family and a homozygous insertion/deletion variant in *LTBP3* in a second family were identified. Sequencing of 338 additional individuals with non-syndromic TAAD found nine additional heterozygous *LTBP3* rare variants. The authors also demonstrated that *LTBP3* knockout mice manifested enlarged aortic roots and ascending aortas compared with wild type mice. These findings demonstrate that individuals with *LTBP3* are at increased risk for TAAD, in addition to the already established risk for skeletal and dental abnormalities.¹²⁻¹⁴

Rare mutations in the Parkin-like E3 ubiquitin ligase Ariadne-1 (*ARIH1*) have been observed in patients with early-onset or familial TAAD.¹⁵ *ARIH1* encodes a protein of the LINC (linker of nucleoskeleton and cytoskeleton), a protein complex essential for anchoring myocyte nuclei to the cytoskeleton.¹⁵ Aortic tissues from patients with these mutations exhibit affected nuclear morphology in vascular smooth muscle cells.

It is well known there is an increased risk for BAV and TAA among individuals with Turner syndrome, although the precise etiology has thus far remained elusive. Corbitt et al¹⁶ demonstrated that Turner syndrome patients with putatively-deleterious mutations in *TIMP3* are associated with a greater incidence of BAV and TAA than the patients without *TIMP3* variants. Hemizygoty for coincident *TIMP1/TIMP3* variants, synergistically increased the risk for BAV and TAA,¹⁶ due to *TIMP1*'s functional redundancy with *TIMP3*.

Numerous mutations of the myosin light chain kinase (*MYLK*) gene have been associated with TAAD. Shalata et al have identified an additional *MYLK* missense mutation in a single pedigree.¹⁷ Myosin light chain kinase phosphorylates myosin regulatory light chains to facilitate actin-myosin generation of contraction. The mutation was shown to be functional, reducing kinase activity.

Insights to the pathogenesis of TAAD are as important as identifying TAAD variants. Nogi et al¹⁸ found the protein expression of small GTP-binding protein GDP dissociation stimulator (*SmgGDS*) in aortic smooth muscle cells was decreased in TAAD patients compared with controls.¹⁸ *SmgGDS* is encoded by the *RAP1GDS1* gene and known to be involved in the contraction of vascular smooth muscle cell (VSMC).¹⁸ Using a heterozygous *SmgGDS*^{+/-} mouse model, since the complete knockout (*SmgGDS*^{-/-}) was embryologically lethal, they observed that the downregulation of *SmgGDS* was causing "pathological phenotype changes in VSMC" via the angiotensin-II pathway.¹⁸ Furthermore, they demonstrated that when *SmgGDS* was overexpressed in the *SmgGDS*^{+/-}, the mice had less aortic growth and fewer aortic ruptures, suggesting that *SmgGDS* could be used as a biomarker or a therapeutic agent.

Conclusion

Advances in 2018 have increased our understanding of the pathogenesis of TAAD. The number of genes with genetic variants or mutations associated with TAAD has increased from 29 in our original 2017 report² to 37 in this 2019 update. Advances in genetic techniques and bioinformatics tools have enabled rapid progress in the genetic and molecular understanding of TAA. As the cost for genome sequencing decreases, we anticipate accelerating progress. With our greater understanding of the genetics of the individuals affected with TAAD and their specific genetic mutations or susceptibility variants, we can provide a personalized aortic care, tailoring surgical recommendations for each patient depending on their individual genetic profiles. Because most families that have multiple affected members with TAAD still have not had known genetic variants identified in the aortopathy genes, we expect many new genes harboring variants for TAAD will be discovered in the foreseeable future and thereby enhance our genetic dictionary. Furthermore, it is important to remind ourselves that every disease-causing mutation starts out as a variant of unknown significance (VUS).¹⁹ Only after extensive functional studies it is possible to confidently state that a VUS is a disease-causing mutation. Such work requires multidisciplinary collaboration.

We will continue to report annual updates regarding the "TAA genetic dictionary" with updates to the Table and

Figure below and provide suggested surgical intervention criteria for each identified mutation.

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None.

Conflict of Interest

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

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None.

References

- 1 Brownstein AJ, Kostiuk V, Ziganshin BA, et al. Genes associated with thoracic aortic aneurysm and dissection: 2018 update and clinical implications. *Aorta (Stamford)* 2018;6(01):13–20
- 2 Brownstein AJ, Ziganshin BA, Kuivaniemi H, Body SC, Bale AE, Elefteriades JA. Genes associated with thoracic aortic aneurysm and dissection: an update and clinical implications. *Aorta (Stamford)* 2017;5(01):11–20
- 3 Verstraeten A, Luyckx I, Loeys B. Aetiology and management of hereditary aortopathy. *Nat Rev Cardiol* 2017;14(04):197–208
- 4 Zafar MA, Li Y, Rizzo JA, et al. Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. *J Thorac Cardiovasc Surg* 2018;155(05):1938–1950
- 5 Ziganshin BA, Elefteriades JA. Genetic impact on thoracic aortic aneurysms. In: Eskandari MK, Pearce WK, Yao JST, eds. *Current Vascular Surgery: Northwestern Vascular Symposium*. Raleigh, NC: PMPH USA; 2017:461480
- 6 Pinard A, Jones GT, Milewicz DM. Genetics of thoracic and abdominal aortic diseases. *Circ Res* 2019;124(04):588–606
- 7 Milewicz DM, Regalado E. Heritable thoracic aortic disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*®. Seattle, WA:1993
- 8 Elefteriades J, Brownstein AJ, Ziganshin BA. Clinical and molecular genetics of thoracic aortic aneurysm and dissection. In: Melissano G, Chiesa R, eds. *Aortic Dissection: Patients True Stories and the Innovations that Saved Their Lives*. Milan, Italy: Edi.Ermes; 2016:49–79
- 9 Gould RA, Aziz H, Woods CE, et al; Baylor-Hopkins Center for Mendelian Genomics; MIBAVA Leducq Consortium. *ROBO4* variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. *Nat Genet* 2019;51(01):42–50
- 10 Quiñones-Pérez B, VanNoy GE, Towne MC, et al. Three-generation family with novel contiguous gene deletion on chromosome 2p22 associated with thoracic aortic aneurysm syndrome. *Am J Med Genet A* 2018;176(03):560–569
- 11 Takeda N, Komuro I. Genetic basis of hereditary thoracic aortic aneurysms and dissections. *J Cardiol* 2019;74(02):136–143
- 12 Guo DC, Regalado ES, Pinard A, et al; University of Washington Center for Mendelian Genomics. *LTBP3* pathogenic variants predispose individuals to thoracic aortic aneurysms and dissections. *Am J Hum Genet* 2018;102(04):706–712
- 13 Morkmued S, Hemmerle J, Mathieu E, et al. Enamel and dental anomalies in latent-transforming growth factor beta-binding protein 3 mutant mice. *Eur J Oral Sci* 2017;125(01):8–17
- 14 Dabovic B, Chen Y, Colarossi C, et al. Bone abnormalities in latent TGF- β binding protein (*LTBP*)-3-null mice indicate a role for *Ltbp-3* in modulating TGF- β bioavailability. *J Cell Biol* 2002;156(02):227–232
- 15 Tan KL, Haelterman NA, Kwartler CS, et al; University of Washington Center for Mendelian Genomics. *Ari-1* regulates myonuclear organization together with *Parkin* and is associated with aortic aneurysms. *Dev Cell* 2018;45(02):226–244.e8

- 16 Corbitt H, Morris SA, Gravholt CH, et al; GenTAC Registry Investigators. TIMP3 and TIMP1 are risk genes for bicuspid aortic valve and aortopathy in Turner syndrome. *PLoS Genet* 2018;14(10):e1007692
- 17 Shalata A, Mahroom M, Milewicz DM, et al. Fatal thoracic aortic aneurysm and dissection in a large family with a novel MYLK gene mutation: delineation of the clinical phenotype. *Orphanet J Rare Dis* 2018;13(01):41
- 18 Nogi M, Satoh K, Sunamura S, et al. Small GTP-binding protein GDP dissociation stimulator prevents thoracic aortic aneurysm formation and rupture by phenotypic preservation of aortic smooth muscle cells. *Circulation* 2018;138(21):2413–2433
- 19 Kwartler CS, Gong L, Chen J, et al. Variants of unknown significance in genes associated with heritable thoracic aortic disease can be low penetrant “risk variants”. *Am J Hum Genet* 2018;103(01):138–143
- 20 Milewicz DM, Prakash SK, Ramirez F. Therapeutics targeting drivers of thoracic aortic aneurysms and acute aortic dissections: insights from predisposing genes and mouse models. *Annu Rev Med* 2017;68:51–67
- 21 Milewicz D, Hostetler E, Wallace S, et al. Precision medical and surgical management for thoracic aortic aneurysms and acute aortic dissections based on the causative mutant gene. *J Cardiovasc Surg (Torino)* 2016;57(02):172–177
- 22 Bradley TJ, Bowdin SC, Morel CF, Pyeritz RE. The expanding clinical spectrum of extracardiovascular and cardiovascular manifestations of heritable thoracic aortic aneurysm and dissection. *Can J Cardiol* 2016;32(01):86–99
- 23 Disabella E, Grasso M, Gambarin FI, et al. Risk of dissection in thoracic aneurysms associated with mutations of smooth muscle alpha-actin 2 (ACTA2). *Heart* 2011;97(04):321–326
- 24 Guo DC, Pannu H, Tran-Fadulu V, et al. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. *Nat Genet* 2007;39(12):1488–1493
- 25 Andelfinger G, Loeys B, Dietz H. A decade of discovery in the genetic understanding of thoracic aortic disease. *Can J Cardiol* 2016;32(01):13–25
- 26 Heegaard AM, Corsi A, Danielsen CC, et al. Biglycan deficiency causes spontaneous aortic dissection and rupture in mice. *Circulation* 2007;115(21):2731–2738
- 27 Meester JA, Vandeweyer G, Pintelon I, et al. Loss-of-function mutations in the X-linked biglycan gene cause a severe syndromic form of thoracic aortic aneurysms and dissections. *Genet Med* 2017;19(04):386–395
- 28 Schwarze U, Hata R, McKusick VA, et al. Rare autosomal recessive cardiac valvular form of Ehlers-Danlos syndrome results from mutations in the COL1A2 gene that activate the nonsense-mediated RNA decay pathway. *Am J Hum Genet* 2004;74(05):917–930
- 29 Smith LB, Hadoke PW, Dyer E, et al. Haploinsufficiency of the murine Col3a1 locus causes aortic dissection: a novel model of the vascular type of Ehlers-Danlos syndrome. *Cardiovasc Res* 2011;90(01):182–190
- 30 D'hondt S, Guillemin B, Syx D, et al. Type III collagen affects dermal and vascular collagen fibrillogenesis and tissue integrity in a mutant Col3a1 transgenic mouse model. *Matrix Biol* 2018;70:72–83
- 31 De Paepe A, Malfait F. The Ehlers-Danlos syndrome, a disorder with many faces. *Clin Genet* 2012;82(01):1–11
- 32 Germain DP. Ehlers-Danlos syndrome type IV. *Orphanet J Rare Dis* 2007;2:32
- 33 Erbel R, Aboyans V, Boileau C, et al; ESC Committee for Practice Guidelines; The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. *Eur Heart J* 2014;35(41):2873–2926
- 34 Monroe GR, Harakalova M, van der Crabben SN, et al. Familial Ehlers-Danlos syndrome with lethal arterial events caused by a mutation in COL5A1. *Am J Med Genet A* 2015;167(06):1196–1203
- 35 Mehta S, Dhar SU, Birnbaum Y. Common iliac artery aneurysm and spontaneous dissection with contralateral iatrogenic common iliac artery dissection in classic Ehlers-Danlos syndrome. *Int J Angiol* 2012;21(03):167–170
- 36 Wenstrup RJ, Meyer RA, Lyle JS, et al. Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. *Genet Med* 2002;4(03):112–117
- 37 Park AC, Phan N, Massoudi D, et al. Deficits in Col5a2 expression result in novel skin and adipose abnormalities and predisposition to aortic aneurysms and dissections. *Am J Pathol* 2017;187(10):2300–2311
- 38 Huang J, Davis EC, Chapman SL, et al. Fibulin-4 deficiency results in ascending aortic aneurysms: a potential link between abnormal smooth muscle cell phenotype and aneurysm progression. *Circ Res* 2010;106(03):583–592
- 39 Igocheva O, Alexeev V, Halabi CM, et al. Fibulin-4 E57K knock-in mice recapitulate cutaneous, vascular and skeletal defects of recessive cutis laxa 1B with both elastic fiber and collagen fibril abnormalities. *J Biol Chem* 2015;290(35):21443–21459
- 40 Loeys B, De Paepe A, Urban Z. EFEMP2-related cutis laxa. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*®. Seattle, WA 1993
- 41 Jelsing AM, Urban Z, Huchtagowder V, Nissen H, Ousager LB. Novel ELN mutation in a family with supravalvular aortic stenosis and intracranial aneurysm. *Eur J Med Genet* 2017;60(02):110–113
- 42 Callewaert B, Renard M, Huchtagowder V, et al. New insights into the pathogenesis of autosomal-dominant cutis laxa with report of five ELN mutations. *Hum Mutat* 2011;32(04):445–455
- 43 Szabo Z, Crepeau MW, Mitchell AL, et al. Aortic aneurysmal disease and cutis laxa caused by defects in the elastin gene. *J Med Genet* 2006;43(03):255–258
- 44 Capuano A, Buccioti F, Farwell KD, et al. Diagnostic exome sequencing identifies a novel gene, EMILIN1, associated with autosomal-dominant hereditary connective tissue disease. *Hum Mutat* 2016;37(01):84–97
- 45 Pereira L, Andrikopoulos K, Tian J, et al. Targeting of the gene encoding fibrillin-1 recapitulates the vascular aspect of Marfan syndrome. *Nat Genet* 1997;17(02):218–222
- 46 Pereira L, Lee SY, Gayraud B, et al. Pathogenetic sequence for aneurysm revealed in mice underexpressing fibrillin-1. *Proc Natl Acad Sci U S A* 1999;96(07):3819–3823
- 47 Judge DP, Biery NJ, Keene DR, et al. Evidence for a critical contribution of haploinsufficiency in the complex pathogenesis of Marfan syndrome. *J Clin Invest* 2004;114(02):172–181
- 48 Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006;312(5770):117–121
- 49 Lima BL, Santos EJ, Fernandes GR, et al. A new mouse model for Marfan syndrome presents phenotypic variability associated with the genetic background and overall levels of Fbn1 expression. *PLoS One* 2010;5(11):e14136
- 50 Morris SA, Orbach DB, Geva T, Singh MN, Gauvreau K, Lacro RV. Increased vertebral artery tortuosity index is associated with adverse outcomes in children and young adults with connective tissue disorders. *Circulation* 2011;124(04):388–396
- 51 Hiratzka LF, Bakris GL, Beckman JA, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American College of Radiology; American Stroke Association; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of Thoracic Surgeons; Society for Vascular Medicine. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients

- with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol* 2010;55(14):e27–e129
- 52 Takeda N, Morita H, Fujita D, et al. Congenital contractural arachnodactyly complicated with aortic dilatation and dissection: case report and review of literature. *Am J Med Genet A* 2015;167A(10):2382–2387
 - 53 Retailleau K, Arhatte M, Demolombe S, et al. Smooth muscle filamin A is a major determinant of conduit artery structure and function at the adult stage. *Pflugers Arch* 2016;468(07):1151–1160
 - 54 Feng Y, Chen MH, Moskowitz IP, et al. Filamin A (FLNA) is required for cell-cell contact in vascular development and cardiac morphogenesis. *Proc Natl Acad Sci U S A* 2006;103(52):19836–19841
 - 55 Reinstein E, Frentz S, Morgan T, et al. Vascular and connective tissue anomalies associated with X-linked periventricular heterotopia due to mutations in Filamin A. *Eur J Hum Genet* 2013;21(05):494–502
 - 56 Lange M, Kasper B, Bohring A, et al. 47 patients with FLNA associated periventricular nodular heterotopia. *Orphanet J Rare Dis* 2015;10:134
 - 57 Kuang SQ, Medina-Martinez O, Guo DC, et al. FOXE3 mutations predispose to thoracic aortic aneurysms and dissections. *J Clin Invest* 2016;126(03):948–961
 - 58 Vermeer AMC, Lodder EM, Thomas D, et al. Dilation of the aorta ascendens forms part of the clinical spectrum of HCN4 mutations. *J Am Coll Cardiol* 2016;67(19):2313–2315
 - 59 Lee VS, Halabi CM, Hoffman EP, et al; Brigham Genomic Medicine. Loss of function mutation in LOX causes thoracic aortic aneurysm and dissection in humans. *Proc Natl Acad Sci U S A* 2016;113(31):8759–8764
 - 60 Hornstra IK, Birge S, Starcher B, Bailey AJ, Mecham RP, Shapiro SD. Lysyl oxidase is required for vascular and diaphragmatic development in mice. *J Biol Chem* 2003;278(16):14387–14393
 - 61 Mäki JM, Räsänen J, Tikkanen H, et al. Inactivation of the lysyl oxidase gene *Lox* leads to aortic aneurysms, cardiovascular dysfunction, and perinatal death in mice. *Circulation* 2002;106(19):2503–2509
 - 62 Ren W, Liu Y, Wang X, et al. β -Aminopropionitrile monofumarate induces thoracic aortic dissection in C57BL/6 mice. *Sci Rep* 2016;6:28149
 - 63 Guo DC, Gong L, Regalado ES, et al; GenTAC Investigators, National Heart, Lung, and Blood Institute Go Exome Sequencing Project; Montalcino Aortic Consortium. *MAT2A* mutations predispose individuals to thoracic aortic aneurysms. *Am J Hum Genet* 2015;96(01):170–177
 - 64 Combs MD, Knutsen RH, Broekelmann TJ, et al. Microfibril-associated glycoprotein 2 (*MAGP2*) loss of function has pleiotropic effects in vivo. *J Biol Chem* 2013;288(40):28869–28880
 - 65 Barbier M, Gross MS, Aubart M, et al. *MFAP5* loss-of-function mutations underscore the involvement of matrix alteration in the pathogenesis of familial thoracic aortic aneurysms and dissections. *Am J Hum Genet* 2014;95(06):736–743
 - 66 Bellini C, Wang S, Milewicz DM, Humphrey JD. *Myh11*(R247C/R247C) mutations increase thoracic aorta vulnerability to intramural damage despite a general biomechanical adaptivity. *J Biomech* 2015;48(01):113–121
 - 67 Pannu H, Tran-Fadulu V, Papke CL, et al. *MYH11* mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. *Hum Mol Genet* 2007;16(20):2453–2462
 - 68 Wang L, Guo DC, Cao J, et al. Mutations in myosin light chain kinase cause familial aortic dissections. *Am J Hum Genet* 2010;87(05):701–707
 - 69 Hannuksela M, Stattin EL, Klar J, et al. A novel variant in *MYLK* causes thoracic aortic dissections: genotypic and phenotypic description. *BMC Med Genet* 2016;17(01):61
 - 70 Luyckx I, Proost D, Hendriks JMH, et al. Two novel *MYLK* nonsense mutations causing thoracic aortic aneurysms/dissections in patients without apparent family history. *Clin Genet* 2017;92(04):444–446
 - 71 McKellar SH, Tester DJ, Yagubyan M, Majumdar R, Ackerman MJ, Sundt TM III. Novel *NOTCH1* mutations in patients with bicuspid aortic valve disease and thoracic aortic aneurysms. *J Thorac Cardiovasc Surg* 2007;134(02):290–296
 - 72 Proost D, Vandeweyer G, Meester JA, et al. Performant mutation identification using targeted next-generation sequencing of 14 thoracic aortic aneurysm genes. *Hum Mutat* 2015;36(08):808–814
 - 73 Guo DC, Regalado E, Casteel DE, et al; GenTAC Registry Consortium; National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project. Recurrent gain-of-function mutation in *PRKG1* causes thoracic aortic aneurysms and acute aortic dissections. *Am J Hum Genet* 2013;93(02):398–404
 - 74 Doyle AJ, Doyle JJ, Bessling SL, et al. Mutations in the TGF- β repressor *SKI* cause Shprintzen-Goldberg syndrome with aortic aneurysm. *Nat Genet* 2012;44(11):1249–1254
 - 75 Callewaert BL, Willaert A, Kerstjens-Frederikse WS, et al. Arterial tortuosity syndrome: clinical and molecular findings in 12 newly identified families. *Hum Mutat* 2008;29(01):150–158
 - 76 Micha D, Guo DC, Hilhorst-Hofstee Y, et al. *SMAD2* mutations are associated with arterial aneurysms and dissections. *Hum Mutat* 2015;36(12):1145–1149
 - 77 Zhang W, Zeng Q, Xu Y, et al. Exome sequencing identified a novel *SMAD2* mutation in a Chinese family with early onset aortic aneurysms. *Clin Chim Acta* 2017;468:211–214
 - 78 Tan CK, Tan EH, Luo B, et al. *SMAD3* deficiency promotes inflammatory aortic aneurysms in angiotensin II-infused mice via activation of iNOS. *J Am Heart Assoc* 2013;2(03):e000269
 - 79 van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic *SMAD3* variants. *J Am Coll Cardiol* 2012;60(05):397–403
 - 80 van de Laar IM, van der Linde D, Oei EH, et al. Phenotypic spectrum of the *SMAD3*-related aneurysms-osteoarthritis syndrome. *J Med Genet* 2012;49(01):47–57
 - 81 Zhang P, Hou S, Chen J, et al. *Smad4* deficiency in smooth muscle cells initiates the formation of aortic aneurysm. *Circ Res* 2016;118(03):388–399
 - 82 Heald B, Rigelsky C, Moran R, et al. Prevalence of thoracic aortopathy in patients with juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia due to *SMAD4*. *Am J Med Genet A* 2015;167A(08):1758–1762
 - 83 Wain KE, Ellingson MS, McDonald J, et al. Appreciating the broad clinical features of *SMAD4* mutation carriers: a multicenter chart review. *Genet Med* 2014;16(08):588–593
 - 84 Gillis E, Kumar AA, Luyckx I, et al; Mibava Leducq Consortium. Candidate gene resequencing in a large bicuspid aortic valve-associated thoracic aortic aneurysm cohort: *SMAD6* as an important contributor. *Front Physiol* 2017;8:400
 - 85 Lindsay ME, Schepers D, Bolar NA, et al. Loss-of-function mutations in *TGFB2* cause a syndromic presentation of thoracic aortic aneurysm. *Nat Genet* 2012;44(08):922–927
 - 86 Boileau C, Guo DC, Hanna N, et al; National Heart, Lung, and Blood Institute (NHLBI) Go Exome Sequencing Project. *TGFB2* mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. *Nat Genet* 2012;44(08):916–921

- 87 Renard M, Callewaert B, Malfait F, et al. Thoracic aortic-aneurysm and dissection in association with significant mitral valve disease caused by mutations in TGF β 2. *Int J Cardiol* 2013;165(03):584–587
- 88 Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF- β ligand, TGF β 3, cause syndromic aortic aneurysms and dissections. *J Am Coll Cardiol* 2015;65(13):1324–1336
- 89 Gallo EM, Loch DC, Habashi JP, et al. Angiotensin II-dependent TGF- β signaling contributes to Loeys-Dietz syndrome vascular pathogenesis. *J Clin Invest* 2014;124(01):448–460
- 90 MacCarrick G, Black JH III, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med* 2014;16(08):576–587
- 91 Jondeau G, Ropers J, Regalado E, et al; Montalcino Aortic Consortium. International registry of patients carrying TGFBR1 or TGFBR2 mutations: results of the MAC (Montalcino Aortic Consortium). *Circ Cardiovasc Genet* 2016;9(06):548–558
- 92 Boodhwani M, Andelfinger G, Leipsic J, et al; Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement on the management of thoracic aortic disease. *Can J Cardiol* 2014;30(06):577–589
- 93 Attias D, Stheneur C, Roy C, et al. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. *Circulation* 2009;120(25):2541–2549
- 94 Teixidó-Tura G, Franken R, Galuppo V, et al. Heterogeneity of aortic disease severity in patients with Loeys-Dietz syndrome. *Heart* 2016;102(08):626–632
- 95 Tran-Fadulu V, Pannu H, Kim DH, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. *J Med Genet* 2009;46(09):607–613
- 96 Wenstrup RJ, Florer JB, Davidson JM, et al. Murine model of the Ehlers-Danlos syndrome. *col5a1* haploinsufficiency disrupts collagen fibril assembly at multiple stages. *J Biol Chem* 2006;281(18):12888–12895
- 97 Park AC, Phillips CL, Pfeiffer FM, et al. Homozygosity and heterozygosity for null Col5a2 alleles produce embryonic lethality and a novel classic Ehlers-Danlos syndrome-related phenotype. *Am J Pathol* 2015;185(07):2000–2011
- 98 Todorovic V, Friendewy D, Gutstein DE, Chen Y, Freyer L, Finnegan E, Rifkin DB. Long form of latent TGF-beta binding protein 1 (Ltbp1L) is essential for cardiac outflow tract septation and remodeling. *Development* 2007;134:3723–3732
- 99 Kuang SQ, Kwartler CS, Byanova KL, et al. Rare, nonsynonymous variant in the smooth muscle-specific isoform of myosin heavy chain, MYH11, R247C, alters force generation in the aorta and phenotype of smooth muscle cells. *Circ Res* 2012;110(11):1411–1422
- 100 Koenig SN, LaHaye S, Feller JD, et al. Notch1 haploinsufficiency causes ascending aortic aneurysms in mice. *JCI Insight* 2017;2(21):91353
- 101 Berk M, Desai SY, Heyman HC, Colmenares C. Mice lacking the ski proto-oncogene have defects in neurulation, craniofacial, patterning, and skeletal muscle development. *Genes Dev* 1997;11(16):2029–2039
- 102 Zoppi N, Chiarelli N, Cinquina V, Ritelli M, Colombi M. GLUT10 deficiency leads to oxidative stress and non-canonical $\alpha\beta$ 3 integrin-mediated TGF β signalling associated with extracellular matrix disarray in arterial tortuosity syndrome skin fibroblasts. *Hum Mol Genet* 2015;24(23):6769–6787
- 103 Cheng CH, Kikuchi T, Chen YH, et al. Mutations in the SLC2A10 gene cause arterial abnormalities in mice. *Cardiovasc Res* 2009;81(02):381–388
- 104 Galvin KM, Donovan MJ, Lynch CA, et al. A role for smad6 in development and homeostasis of the cardiovascular system. *Nat Genet* 2000;24(02):171–174
- 105 Azhar M, Schultz Jel J, Grupp I, et al. Transforming growth factor beta in cardiovascular development and function. *Cytokine Growth Factor Rev* 2003;14(05):391–407