

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

Adam J. Brownstein, BA¹ Valentyna Kostiuk, BA¹ Bulat A. Ziganshin, MD, PhD^{1,2}
Mohammad A. Zafar, MD¹ Helena Kuivaniemi, MD, PhD³ Simon C. Body, MD, MPH⁴
Allen E. Bale, MD⁵ John A. Elefteriades, MD¹

¹ Department of Surgery, Section of Cardiac Surgery, Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut

² Department of Surgical Diseases # 2, Kazan State Medical University, Kazan, Russia

³ Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, and Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

⁴ Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

⁵ Department of Genetics, Yale School of Medicine, New Haven, Connecticut

Address for correspondence John A. Elefteriades, MD, Aortic Institute at Yale-New Haven, Yale University School of Medicine, 789 Howard Avenue, Clinic Building – CB317 New Haven, CT 06519 (e-mail: john.elefteriades@yale.edu).

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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.¹ 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%,² 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,³ almost 50% of patients with a type A aortic dissection still die before hospital admission.⁴ 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 α -actin	Yes ¹⁰	+	+	AAT6 + multisystemic smooth muscle dysfunction + MYMY5	TAAD, early aortic dissection,* CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV ^{11,12}	4.5–5.0 ^{a,13–15}	AD	611788 613834 614042
BGN	Biglycan	Yes ¹⁶	+	–	Meester-Loeys syndrome	ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity ¹⁷	Standard	X-linked	300989
COL1A2	Collagen 1 $\alpha 2$ chain	No	+	–	EDS, arthrochalasia type (VIIb) + cardiac valvular type	Borderline aortic root enlargement ^{12,18}	Standard	AD + AR	130060 225320
COL3A1	Collagen 3 $\alpha 1$ chain	Yes ¹⁹	+	–	EDS, vascular type (IV)	TAAD, early aortic dissection,* visceral arterial dissection, vessel fragility, IA ^{20–22}	5.0 ^{b,22}	AD	130050
COL5A1	Collagen 5 $\alpha 1$ chain	No ^e	+	–	EDS, classic type 1	ARD, rupture/dissection of medium sized arteries ^{23–25}	Standard	AD	130000
COL5A2	Collagen 5 $\alpha 2$ chain	Partially ^f	+	–	EDS, classic type 2	ARD	Standard	AD	130000
EFEMP2	Fibulin-4	Yes ^{26,27}	+	–	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 ^{28–30}	Standard	AD	123700 185500
EMILIN1	Elastin microfibril interfacier 1	No	+	–	Unidentified CTD	Ascending and descending aortic aneurysm ³¹	Standard	AD	Unassigned
FBN1	Fibrillin-1	Yes ^{32–36}	+	+	Marfan syndrome	ARD, TAAD, AAA, other arterial aneurysms, pulmonary artery dilation, arterial tortuosity ³⁷	5.0 ^{15,38}	AD	154700
FBN2	Fibrillin-2	No	+	–	Contractual arachnodactyly	Rare ARD and aortic dissection, ³⁹ BAV, PDA	Standard	AD	121050
FLNA	Filamin A	Yes ^{40,41}	+	–	Periventricular nodular heterotopia	Aortic dilatation/aneurysms, peripheral arterial dilatation, PDA, IA, ⁴³ BAV	Standard	XLD	300049
FOXE3	Forkhead box 3	Yes ⁴⁴	–	+	AAT11	TAAD (primarily Type A dissection) ⁴⁴	Standard	AD	617349
LOX	Lysyl oxidase	Yes ^{45–48}	–	+	AAT10	TAAD, AAA, hepatic artery aneurysm, BAV, CAD	Standard	AD	617168
MAT2A	Methionine adenosyltransferase II α	No ^{g,49}	–	+	FTAA	Thoracic aortic aneurysms, BAV ⁴⁹	Standard	AD	Unassigned
MFAP5	Microfibril-associated glycoprotein 2	Partially ^{h,50}	–	+	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 ⁵¹	-	+	AAT4	TAAD, early aortic dissection,* PDA, CAD, peripheral vascular occlusive disease, carotid IA	4.5-5.0 ^{15,52}	AD	132900
MYLK	Myosin light chain kinase	No ⁵³	-	+	AAT7	TAAD, early aortic dissections*	4.5-5.0 ^{a,15,53}	AD	613780
NOTCH1	NOTCH1	Partially ^k	-	+	AOVD1	BAV/TAAD ^{54,55}	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 ⁵⁶	AD	615436
SKI	Sloan Kettering proto-oncoprotein	No ^l	+	-	Shprintzen-Goldberg syndrome	ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysms ⁵⁷	Standard	AD	182212
SLC2A10	Glucose transporter 10	No ^m	+	-	Arterial tortuosity syndrome	ARD, ⁵⁸ ascending aortic aneurysms, ⁵⁸ 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 ^{59,60}	Standard	AD	Unassigned
SMAD3	SMAD3	Partially ^{n,61}	+	+	LDS type 3	ARD, TAAD, early aortic dissection,* AAA, arterial tortuosity, other arterial aneurysms/dissections, IA, BAV ^{62,63}	4.0-4.2 ^{15,38}	AD	613795
SMAD4	SMAD4	Yes ⁶⁴	+	-	JP/HHT syndrome	ARD, TAAD, AVMs, IA ^{65,66}	Standard	AD	175050
SMAD6	SMAD6	No ^o	-	+	AOV2	BAV/TAAD ⁶	Standard	AD	602931
TGFβ2	TGF-β2	Yes ⁶⁷	+	+	LDS type 4	ARD, TAAD, arterial tortuosity, other arterial aneurysms, BAV ^{67,68}	4.5-5.0 ⁶⁹	AD	614816
TGFβ3	TGF-β3	No ^p	+	-	LDS type 5	ARD, TAAD, AAA/dissection, other arterial aneurysms, IA/dissection ⁷⁰	Standard	AD	615582
TGFβR1	TGF-β receptor type 1	Yes ⁷¹	+	+	LDS type 1 + AAT5	TAAD, early aortic dissection,* AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV ⁷²	4.0-4.5 ^{d,15,38,73}	AD	609192
TGFβR2	TGF-β receptor type 2	Yes ^{64,71}	+	+	LDS type 2 + AAT3	TAAD, early aortic dissection,* AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV ⁷²	4.0-4.5 ^{d,15,38,73}	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- β 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.

^aIndividuals with MYLK and ACTA2 mutations have been shown to have aortic dissections at a diameter of 4.0 cm.^{13,53}

^bThere are no data to set threshold diameters for the surgical intervention for EDS type IV.³⁸ 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.⁷⁴

^cThere 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 cm⁶⁹ hence, the recommended threshold range of 4.5 to 5.0 cm.

^dCurrent US guidelines recommend prophylactic surgery for LDS types 1 and 2 at ascending aortic diameters of 4.0 to 4.2 cm.^{15,38} However, the European guidelines state that more clinical data are required.²² Patients with TGFBR2 mutations have similar outcomes to patients with FBNI mutations once their disease is diagnosed,⁷⁵ and the clinical course of LDS 1 and 2 does not appear to be as severe as originally reported.^{73,76,77} 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.¹¹ Individuals with TGFBR2 mutations are more likely to have aortic dissections at diameters < 5.0 cm than those with TGFBR1 mutations.^{73,77} 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.⁷³ 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.⁷³

^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.⁷⁸

^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.⁷⁹ 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.⁸⁰

^gGuo et al found that knockdown of mat2a in zebrafish led to defective aortic arch development.⁴⁹

^hCombs 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.

ⁱWhile Kuang et al reported that a mouse knock-in model (Myh11^{R247C/R247C}) does not lead to a severe vascular phenotype under normal conditions,⁸¹ 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).

^jWang 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.

^kKoenig 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.⁸²

^lDoyle 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.⁵⁷ 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.⁸³

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

ⁿTan 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.⁶¹

^oGalvin 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.⁸⁶

^pTgfb3 knockout mice die at birth from cleft palate⁷⁰, but minor differences in the position and curvature of the aortic arches of these mice compared with wild-type mice have been described.⁸⁷

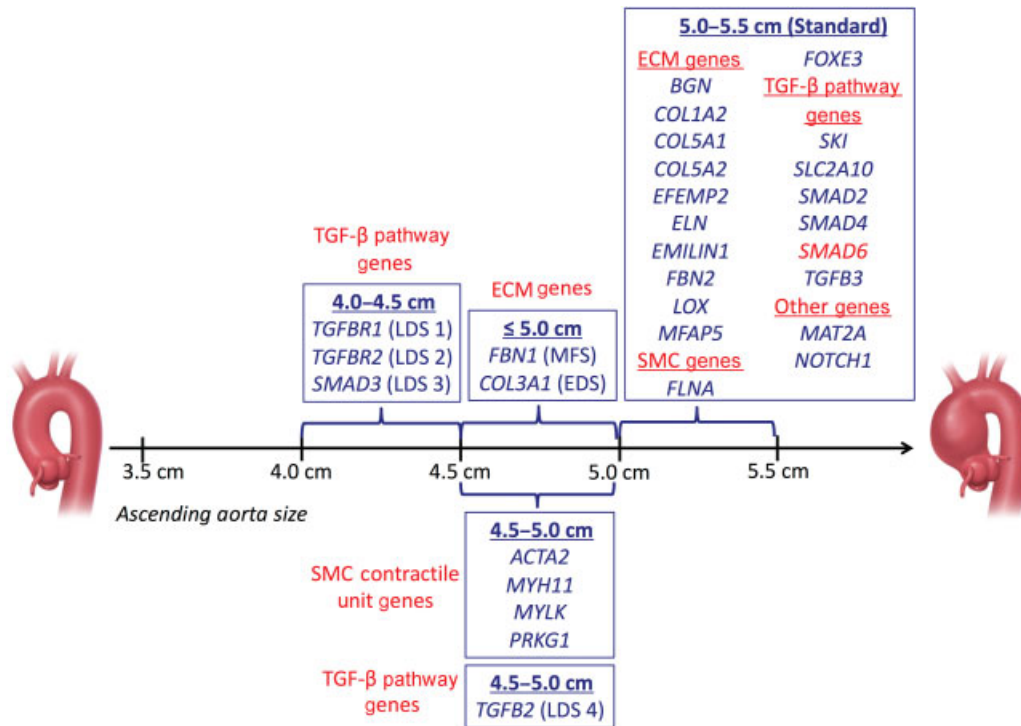


Fig. 1 Ascending aorta dimensions for prophylactic surgical intervention. (Data derived from ►Table 1 and modified with permission from Brownstein et al.¹) Any gene newly reported during the past year to be associated with TAAD is highlighted in red. Abbreviations: ECM, extracellular matrix; SMC, smooth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

genes.⁵ Mutations in these genes lead to a spectrum of risk and severity of type A and B aortic dissections,⁵ 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.⁵ Other genes listed in ►Table 1 are estimated to contribute to 1 to 2% each or less of familial nonsyndromic TAAD.⁵ 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.⁶ 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.⁷ 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.⁸ 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.⁹

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.

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References

- 1 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
- 2 Verstraeten A, Luyckx I, Loeys B. Aetiology and management of hereditary aortopathy. *Nat Rev Cardiol* 2017;14(04):197–208
- 3 Mody PS, Wang Y, Geirsson A, et al. Trends in aortic dissection hospitalizations, interventions, and outcomes among Medicare beneficiaries in the United States, 2000–2011. *Circ Cardiovasc Qual Outcomes* 2014;7(06):920–928
- 4 Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM; Oxford Vascular Study. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation* 2013;127(20):2031–2037
- 5 Milewicz DM, Regalado E. Heritable Thoracic Aortic Disease Overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., eds. Seattle, WA: GeneReviews(R); 1993
- 6 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
- 7 Landis BJ, Schubert JA, Lai D, et al. Exome sequencing identifies candidate genetic modifiers of syndromic and familial thoracic aortic aneurysm severity. *J Cardiovasc Transl Res* 2017;10(04):423–432
- 8 Franken R, Teixeira-Tura G, Brion M, et al. Relationship between fibrillin-1 genotype and severity of cardiovascular involvement in Marfan syndrome. *Heart* 2017;103(22):1795–1799
- 9 De Cario R, Sticchi E, Lucarini L, et al. Role of TGFBR1 and TGFBR2 genetic variants in Marfan syndrome. *J Vasc Surg* 2017;S0741-5214(17)31587-2. Article in Press
- 10 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
- 11 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
- 12 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
- 13 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
- 14 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
- 15 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
- 16 Heegaard AM, Corsi A, Danielsen CC, et al. Biglycan deficiency causes spontaneous aortic dissection and rupture in mice. *Circulation* 2007;115(21):2731–2738
- 17 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
- 18 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
- 19 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
- 20 De Paepe A, Malfait F. The Ehlers-Danlos syndrome, a disorder with many faces. *Clin Genet* 2012;82(01):1–11
- 21 Germain DP. Ehlers-Danlos syndrome type IV. *Orphanet J Rare Dis* 2007;2:32
- 22 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
- 23 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
- 24 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
- 25 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
- 26 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
- 27 Igoucheva 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
- 28 Jelsig 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
- 29 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
- 30 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
- 31 Capuano A, Bucciotti 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
- 32 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
- 33 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
- 34 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
- 35 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
- 36 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
- 37 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
- 38 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
- 39 Takeda N, Morita H, Fujita D, et al. Congenital contractual arachnodactyly complicated with aortic dilatation and dissection: case report and review of literature. *Am J Med Genet A* 2015;167A(10):2382–2387
 - 40 Retailliau 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
 - 41 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
 - 42 Reinstein E, Frenzt 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
 - 43 Lange M, Kasper B, Bohring A, et al. 47 patients with FLNA associated periventricular nodular heterotopia. *Orphanet J Rare Dis* 2015;10:134
 - 44 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
 - 45 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
 - 46 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
 - 47 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
 - 48 Ren W, Liu Y, Wang X, et al. β -Aminopropionitrile monofumarate induces thoracic aortic dissection in C57BL/6 mice. *Sci Rep* 2016;6:28149
 - 49 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
 - 50 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
 - 51 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
 - 52 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
 - 53 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
 - 54 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
 - 55 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
 - 56 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
 - 57 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
 - 58 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
 - 59 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
 - 60 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
 - 61 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
 - 62 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
 - 63 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
 - 64 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
 - 65 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
 - 66 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
 - 67 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
 - 68 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
 - 69 Renard M, Callewaert B, Malfait F, et al. Thoracic aortic-aneurysm and dissection in association with significant mitral valve disease caused by mutations in *TGFB2*. *Int J Cardiol* 2013;165(03):584–587
 - 70 Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF- β ligand, *TGFB3*, cause syndromic aortic aneurysms and dissections. *J Am Coll Cardiol* 2015;65(13):1324–1336
 - 71 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
 - 72 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
 - 73 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

- 74 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
- 75 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
- 76 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
- 77 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
- 78 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
- 79 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
- 80 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
- 81 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
- 82 Koenig SN, LaHaye S, Feller JD, et al. Notch1 haploinsufficiency causes ascending aortic aneurysms in mice. *JCI Insight* 2017;2(21):91353
- 83 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
- 84 Zoppi N, Chiarelli N, Cinquina V, Ritelli M, Colombi M. GLUT10 deficiency leads to oxidative stress and non-canonical $\alpha\beta3$ integrin-mediated TGF β signalling associated with extracellular matrix disarray in arterial tortuosity syndrome skin fibroblasts. *Hum Mol Genet* 2015;24(23):6769–6787
- 85 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
- 86 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
- 87 Azhar M, Schultz JJ, Grupp I, et al. Transforming growth factor beta in cardiovascular development and function. *Cytokine Growth Factor Rev* 2003;14(05):391–407