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

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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 genes.
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, \( ^{11,12} \) CAD, stroke ( moyamoya disease), PDA, pulmonary artery dilation, BAV \( ^{11,12} \) | 4.5−5.0^{13−15}                                  | AD                  | 611788 613834 614042 |
| BGN        | Biglycan                                     | Yes^{16}                                  | +              | −                 | Meesteer-Loeys syndrome                                                                    | ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity \( ^{17} \)                                               | Standard \( ^{17} \)                                | X-linked            | 300989 |
| COL1A2     | Collagen 1 α2 chain                          | No                                        | +              | −                 | EDS, arthrochalasia type (VII) + cardiac valvular type                                     | Borderline aortic root enlargement \( ^{12,18} \)                                                                         | Standard \( ^{12,18} \)                               | AD + AR             | 130060 225320 |
| COL3A1     | Collagen 3 α1 chain                          | Yes^{19}                                  | +              | −                 | EDS, vascular type (IV)                                                                    | TAAD, early aortic dissection, \( ^{11,12} \) visceral arterial dissection, vessel fragility, IA \( ^{10−22} \) | 5.0^{10−22}                                             | AD                  | 130050 |
| COL5A1     | Collagen 5 α1 chain                          | No^{8}                                    | +              | −                 | EDS, classic type 1                                                                      | ARD, rupture/dissection of medium sized arteries \( ^{13−15} \)                                                        | Standard \( ^{13−15} \)                               | AD                  | 130000 |
| COL5A2     | Collagen 5 α2 chain                          | Partially^{6}                             | +              | −                 | EDS, classic type 2                                                                      | ARD                                                                                                                     | Standard \( ^{26} \)                                 | AD                  | 130000 |
| EFEMP2     | Fibulin-4                                    | Yes^{26,27}                               | +              | −                 | Cutis laxa, AR type Ib                                                                   | Ascending aortic aneurysms, other arterial aneurysms, arterial tortuosity and stenosis                                  | Standard \( ^{26} \)                                 | AR                  | 614437 |
| ELN        | Elastin                                      | No                                        | +              | −                 | Cutis laxa, AD                                                                            | ARD, ascending aortic aneurysm and dissection, BAV, IA possibly associated with SVAS \( ^{28−30} \)                  | Standard \( ^{28−30} \)                               | AD                  | 123700 185500 |
| EMILIN1    | Elasin microfibril interacter 1              | No                                        | +              | −                 | Unidentified CTD                                                                        | Ascending and descending aortic aneurysm \( ^{11} \)                                                                  | Standard \( ^{11} \)                                 | AD                  | Unassigned |
| FBNI       | Fibrillin-1                                  | Yes^{32−36}                               | +              | +                 | Marfan syndrome                                                                          | ARD, TAAD, AAA, other arterial aneurysms, pulmonary artery dilatation, arterial tortuosity \( ^{37} \)               | 5.0^{15,38}                                             | AD                  | 154700 |
| FBN2       | Fibrillin-2                                  | No                                        | +              | −                 | Contractual arachnodactyly                                                                | Rare ARD and aortic dissection, \( ^{39} \) BAV, PDA                                                                 | Standard \( ^{39} \)                                 | AD                  | 121050 |
| FLNA       | Filamin A                                    | Yes^{40,41}                               | +              | −                 | Per/ventricular nodular heterotopia                                                      | Aortic dilatation/aneurysms, \( ^{42} \) peripheral arterial dilatation, PDA, IA, BAV                                     | Standard \( ^{42} \)                                 | XLD                 | 300049 |
| FOXE3      | Forkhead box 3                               | Yes^{44}                                  | −              | +                 | AAT11                                                                                     | TAAD (primarily Type A dissection)\( ^{44} \)                                                                          | Standard \( ^{44} \)                                 | AD                  | 617349 |
| LOX        | Lysyl oxidase                                | Yes^{45−48}                               | −              | +                 | AAT10                                                                                     | TAAD, AAA, hepatic artery aneurysm, BAV, CAD                                                                              | Standard \( ^{45−48} \)                              | AD                  | 617168 |
| MAT2A      | Methionine adenosyltransferase II α          | No^{49}                                   | −              | +                 | FTAA                                                                                      | Thoracic aortic aneurysms, BAV \( ^{49} \)                                                                               | Standard \( ^{49} \)                                 | AD                  | Unassigned |
| MFAP5      | Microfibril-associated glycoprotein 2       | Partially^{50}                            | −              | +                 | AAT9                                                                                      | ARD, TAAD                                                                                                                | Standard \( ^{50} \)                                 | AD                  | 616166 |
| Gene     | Protein                      | Mode of Inheritance | OMIM               | Associated clinical characteristics of the vasculature                                                                 | Associated disease/syndrome                                                                                   |
|----------|------------------------------|---------------------|--------------------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| MYH11    | Smooth muscle myosin heavy chain | Partially            | 613790             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| MYLK     | Myosin light chain kinase     | Partially            | 6109720            | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| NOTCH1   | Type 1 GMP-dependent protein kinase | Partially            | 613795             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| NKCC1    | Sodium-glucose cotransporter 10 | Partially            | 615316             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| SKI      | Sloan Kettering proto-oncoprotein | No                   | 613795             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| SLC2A10  | Glucose transporter           | Partially            | 609192             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| SMAD2    | Smad-2                       | Yes                 | 61582              | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| SMAD3    | Smad-3                       | Partially            | 614816             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| SMAD4    | Smad-4                       | Yes                 | 615582             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |
| SMAD6    | Smad-6                       | No                  | 610568             | TAAD, early aortic dissection, PDA, coronary artery disease, carotid artery dilation, other arterial aneurysms and dissections | Unidentified CTD with arterial aneurysms and dissections                                                    |

Abbreviations: AAA, abdominal aortic aneurysm; AAT, aortic aneurysm, familial thoracic; AD, autosomal dominant; AR, autosomal recessive; ARD, aortic root dilatation; AV, aortic valve disease; CAD, coronary artery disease; CTD, connective tissue disease; CVD, cerebrovascular disease; EDS, Ehlers-Danlos syndrome; FA, familial aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and/or dissection; HHT, hereditary hemorrhagic telangiectasia; IA, intracranial aneurysm; JP/HHT, juvenile polyposis/HHT syndrome; LDS, Loeys-Dietz syndrome; MO, moyamoya; PDA, patent ductus arteriosus; TGF, transforming growth factor; TAAD, thoracic aortic aneurysm and dissection; TAV, thoracic aortic valve; THM, thoracic hemangioma; AORTA Vol. 6 No. 1/2018 Brownstein et al.
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 There are no data to set threshold diameters for the surgical intervention for LSS 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 There are limited data concerning the timing of surgical intervention for LSS type IV. 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.

"bCurrent US guidelines recommend prophylactic surgery for LSS 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.72 Patients with TGFBR2 mutations have similar outcomes to patients with FBN1 mutations once their disease is diagnosed,75 and the clinical course of LSS 1 and 2 does not appear to be as severe as originally reported.73,76,77 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 LSS 1 and 2 patients to avoid unnecessary surgery at small aortic diameters.73 Therefore, in LSS 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

"cWensstrup et al found that mice heterozygous for an inactivating mutation in Col5a1 exhibit decreased aortic compliance and strength relative to wild-type mice.78

"dPark et al recently reported that Col5a2 haploinsufficiency increased the incidence and severity of AAA and led to aortic arch ruptures and dissections in an angiotensin II-induced atherosclerosis 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 Guo et al found that knockdown of mat2aa in zebrafish led to defective aortic arch development.49 Combs et al demonstrated that Mfap2 and Mfap5 double knockout (Mfap2/C0/C0/C0/Mfap5/C0/C0) mice exhibit age-dependent aortic dilation, though this is not the case with Mfap5 single knockout mice.81 While Kuo et al reported that a mouse knock-in model (Myh11R247C/R247C) does not lead to a severe vascular phenotype under normal conditions,82 Bellini et al demonstrated that induced hypertension in this mouse model led to intramuscular and intramural dissections (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).83 Wang et al demonstrated that SMCSpecific knockdown of Myl5 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.

"eKoenig et al recently found that Notch 1 haploinsufficiency exacerbates the aneurysmal aortic root dilation in a mouse model of Marfan syndrome and that Notch 1 heterozygous mice exhibited aortic root dilation, abnormal smooth muscle cell morphology, and reduced elastic laminae.84 Doyle et al found that knockdown of paralogs of mammalian SMK 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.85

"fMice 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

"gTan et al demonstrated that Smad5 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 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.86

"hTgfbr3 knockout mice die at birth from cleft palate80, but minor differences in the position and curvature of the aortic arches of these mice compared with wild-type mice have been described.87
Mutations in these genes lead to a spectrum of risk and severity of type A and B aortic dissections, 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. Other genes listed in Table 1 are estimated to contribute to 1 to 2% each or less of familial nonsyndromic TAAD.

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 affected individuals, adding to the growing list of genes associated with TAAD. 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. 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. Similarly, De Cario 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.

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, Kuivanemi 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, Loeyes 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, Teixido-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;50(04):5214(17)31587-2. Article in Press

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 Disabelli E, Grasso M, Gambarini FL, 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, Panhu 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, Loeyes 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 Erdel 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, Huchagowder 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, Huchagowder 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, Buccoiti 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 I, 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 I, 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 many faces. Circ Res 2010;106(03):583–592
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;
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

Proost D, Vandeweyger M, 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

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

Doyle AJ, Doyle JJ, Bessling SL, et al. Mutations in the TGF-β repressor SKI cause Shprintzen-Goldberg syndrome with aortic aneurysms. Nat Genet 2012;44(11):1249–1254

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

Micha D, Guo DC, Hillhorst-Hofstee Y, et al. SMAD2 mutations are associated with arterial aneurysms and dissections. Hum Mutat 2015;36(12):1145–1149

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

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

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

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

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

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 2012;160(05):1758–1762

Wain KE, Ellinson 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

Lindsay ME, Schepers D, Bolar NA, et al. Loss-of-function mutations in TGFBR2 cause a syndromic presentation of thoracic aortic aneurysm. Nat Genet 2012;44(08):922–927

Boileau C, Guo DC, Hanna N, et al; National Heart, Lung, and Blood Institute (NHLBI) Go Exome Sequencing Project. TGFBR2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nat Genet 2012;44(08):916–921

Renard M, Callewaert B, Malfait F, et al. Thoracic aortic-aneurysm and dissection in association with significant mitral valve disease caused by mutations in TGFBR2. Int J Cardiol 2013;165(03):584–587

Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF-β ligand, TGFBR3, cause syndromic aortic aneurysms and dissec-
tions. J Am Coll Cardiol 2015;65(13):1324–1336

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

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

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 αvβ3 integrin-mediated TGFβ 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