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

Thais Faggion Vinholo, MSc1 Adam J. Brownstein, MD2 Bulat A. Ziganshin, MD, PhD1,3 Mohammad A. Zafar, MD1 Helena Kuivaniemi, MD, PhD4 Simon C. Body, MD, MPH5 Allen E. Bale, MD6 John A. Elefteriades, MD, PhD (hon)1

1 Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut
2 Department of Medicine, Johns Hopkins Hospital and Johns Hopkins School of Medicine, Baltimore, Maryland
3 Department of Cardiovascular and Endovascular Surgery, Kazan State Medical University, Kazan, Russia
4 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
5 Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
6 Department of Genetics, Yale School of Medicine, New Haven, Connecticut

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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, TAs 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
| Gene   | Protein                                                                 | 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) | Mode of inheritance | Associated clinical characteristics of the vasculature | Ascending aorta size (cm) for surgical intervention | OMIM | Associated disease/syndrome | Associated vascular characteristics |
|--------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------------------|--------------------------------------------------|------|-----------------------------|-----------------------------------|
| ACTA2  | Smooth muscle α-actin                                                    | YES20                                                                                                                                            | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 4.5–5.0b, 7.5–8.5a | 611788, 6613834, 614042 | Multisystemic smooth muscle dysfunction | TAAD, early aortic dissectiont, CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV21,22 |
| ARH1   | Ariadne RBR E3 ubiquitin protein ligase 1                               | No                                                                                                                                             | Partially AD       | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0–5.5b, 7.5–8.5a | 610561, 229320 | Cutis laxa, AR Type Ib | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| COL1A2 | Collagen 1 α2 chain                                                     | Partially AD                                                                                                                                   | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.025, 7.5–8.5a | 130060 | EDS, arthrochalasia Type (VIIb) | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| COL3A1 | Collagen 3 α1 chain                                                     | Yes29, 30                                                                                                                                       | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b–5.5a, 7.5–8.5a | 130050 | EDS, vascular Type (IV) | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| COL5A1 | Collagen 5 α1 chain                                                     | No                                                                                                                                              | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 130000 | EDS, classic Type I | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| COL5A2 | Collagen 5 α2 chain                                                     | Partially AD                                                                                                                                   | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 130000 | EDS, classic Type II | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| EFEMP2 | Fibulin-4                                                               | Yes38, 39                                                                                                                                     | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 3.0b, 7.5–8.5a | 614437 | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| ELN    | Elastin                                                                 | No                                                                                                                                             | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.025, 7.5–8.5a | 130000 | Cutis laxa, AR Type Ib | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| EMILIN1| Elastin microfibril interfacer 1                                       | No                                                                                                                                              | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | Unassigned | CTSD and peripheral neuropathy | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| FBN1   | Fibrillin-1                                                             | Yes45, 49                                                                                                                                     | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.025, 7.5–8.5a | 154700 | Marfan syndrome | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| FBN2   | Fibrillin-2                                                             | No                                                                                                                                              | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.025, 7.5–8.5a | 121050 | Contractural arachnodactyly | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| FLNA   | Filamin A                                                               | Yes53, 54                                                                                                                                     | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 300049 | Periventricular nodular heterotopia and otopalato-digital syndrome | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| FOXE3  | Forkhead box 1                                                         | No                                                                                                                                              | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.025, 7.5–8.5a | 617349 | AAT11 | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| HCN4   | Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 | No                                                                                                                                             | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 163800 | Noncompaction cardiomyopathy, bradycardia, and mitral valve disease | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| LOX    | Lysyl oxidase                                                          | No26                                                                                                                                           | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 617168 | Dental anomalies and short stature | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| LTBP1  | Latent TGF-β binding protein   | Noi, 12                                                                                                                                       | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 150590 | AT10, AA, Aortic aneurysms and arterial aneurysms, pulmonary artery dilatation, BAV, CAD, and aortic dissection, SI, BAV, MAV, BAV1, BAV2, and cutaneous vascular disease | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| LTBP3  | Latent TGF-β binding protein   | Yesi, 12                                                                                                                                     | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 602099 | AAT9 | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| MAT2A  | Methionine adenosyltransferase II-α                                     | No                                                                | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 616166 | Contractural arachnodactyly | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |
| MFAP5  | Microfibril-associated glycoprotein 2                                   | Partially                               | AD                  | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 | 5.0b, 7.5–8.5a | 616166 | Partially AD | Ascending and descending aortic aneurysms, aortic dissection, thoracic aortic aneurysm, and BAV21,22 |

**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).
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                               | −              | +                | AAT4                        | TAAD, early aortic dissection, PDA, CAD, peripheral vascular occlusive disease, carotid IA   | 4.5–5.6⁴,³⁰       | AD   | 132900 |
| MYLK    | Myosin light chain kinase              | No⁴                                        | −              | +                | AAT7                        | TAAD, early aortic dissection                        | 4.5–5.0³,⁲³,⁴⁸     | AD   | 613780 |
| NOTCH1  | NOTCH1                                 | Partially                               | −              | +                | AOVD1                       | BAV/TAAD                                              | Standard           | AD   | 109730 |
| PRAG1   | Type I CFP-dependent protein kinase    | No                                        | −              | +                | AAT8                        | TAAD, early aortic dissection, AAA, coronary artery aneurysm/disse tion, aortic tortuosity, small vessel CVD | 4.5–5.8³³         | AD   | 615436 |
| ROBO4   | Roundabout guidance receptor 4         | Yes                                      | −              | +                | BAV                         | BAV/TAAD                                              | Standard           | AD   | 607528 |
| SKI     | Sloan Kettering proto-oncoprotein      | No⁶                                        | +              | −                | Shprintzen-Goldberg syndrome | ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysms     | Standard           | AD   | 182212 |
| SLC2A10 | Glucose transporter 10                 | No⁶                                        | +              | −                | Arterial tortuosity syndrome | ARD, ascending aortic aneurysms, 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/cerebral arterial aneurysms/dissections, AAA, IA | AD                | Unassigned |
| SMAD3   | SMAD3                                  | Partially                               | +              | +                | LDS Type III                | ARD, TAAD, early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissections, IA, BAV⁹,³⁵ | 4.0–4.2⁴,³¹       | AD   | 613795 |
| SMAD4   | SMAD4                                  | Yes⁸¹                                    | +              | −                | JP/HHT syndrome             | ARD, TAAD, AVMs, IA⁸²,⁸³                              | Standard           | AD   | 175050 |
| SMAD6   | SMAD6                                  | No⁷                                      | −              | +                | AOVD2                      | BAV/TAAD                                              | Standard           | AD   | 602931 |
| TGFBR1  | TGF-β receptor type I                  | Yes⁸⁹                                    | +              | −                | AOVD                       | BAV/TAAD                                              | Standard           | XLD  | 188826 |
| TGFBR2  | TGF-β receptor type II                 | Yes⁸¹,⁸⁹                                | +              | −                | AOVD                       | BAV/TAAD                                              | Standard           | XLD  | 305370 |
| TGFBR3  | TGF-β                                  | Yes⁸³                                    | +              | +                | LDS Type IV                 | ARD, TAAD, arterial tortuosity, other arterial aneurysms, BAV³⁰,³⁶                            | 4.5–5.0³,⁴⁷        | AD   | 614816 |
| TGFBR3  | TGF-β                                  | No⁷                                      | −              | +                | LDS Type V                  | ARD, TAAD, AAA/dissection, other arterial aneurysms, IA/dissection⁶⁸                       | Standard           | AD   | 615582 |
| TGFBR1  | TGF-β receptor type I                  | Yes⁸⁹                                    | +              | +                | LDS Type I + AAT5           | TAAD, early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV³⁰ | 4.0–4.5³⁰,⁵¹,⁵³,⁹⁸ | AD   | 609192 |
| TGFBR2  | TGF-β receptor type II                 | Yes⁸¹,⁸⁹                                | +              | +                | LDS Type II + AAT3          | TAAD, early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV³⁰ | 4.0–4.5³⁰,⁵¹,⁵³,⁹⁸ | 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; AVH, arteriovenous malformation; BAV, bicuspid aortic valve; CAD, coronary artery disease; CTD, connective tissue disease; CVD, cerebrovascular disease; EDS, Ehlers-Danlos syndrome; FTAAD, familial thoracic aortic aneurysm; FTAA, familial thoracic aortic aneurysm and/or dissection; HHT, hereditary hemorrhagic telangiectasia; IA, intracranial aneurysms; JP, juvenile polyposis; LDS, Loeys-Dietz syndrome; MYMY, moyamoya 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.
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 dissection = dissection at aortic diameters < 5.0 cm.

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

There 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. 92

There 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.

Current 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

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

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

Todorovic et al 98 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

Guo et al showed that the knockout mice have larger aortic roots and ascending aortas than wild type, however, no aneurysms or dissections were reported. 99

Guo et al found that the knockdown of MAT2A in zebrafish led to defective aortic arch development. 93

Combs 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. 80 While Kuang et al reported that a mouse knock-in model (Myh11R247C/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 necroscopy 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).

Wang et al demonstrated that SMC-specific knockdown of Mylk in mice led to histopathological changes (increased pools of proteoglycans) and altered gene expression consistent with medial degeneration of the aorta, though no aneurysm formation was observed. 88

Koenig 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. 88

Doyle et al found that knockdown of paralogs of mammalian SKI in zebrafish led to craniofacial and cardiac anomalies, including failure of cardiac looping and malformations of the outflow tract. 76 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

Mice 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

Tan et al demonstrated that SMAD3 knockout mice only developed aortic aneurysms with angiotensin II-induced vascular inflammation, though the knockout mice did have medial dissections evident on histological analysis of their aortas and exhibited aortic dilation relative to wild type mice prior to angiotensin II infusion. 78

Gahinet 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

TGFβ3 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
These genes encode proteins of the extracellular matrix, vascular smooth muscle cell contractile unit, or transforming growth factor β (TGF-β)-signaling pathways 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 al 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. 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. ROBO4 is well expressed in vascular endothelial cells and plays a role in endothelial barrier function. In this study, its expression was found to be diminished in the resected aorta sample of an affected individual with AscAA. 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.

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. LTBP1, in particular, can bind to fibrillin-1 and inactivate TGF-β. 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. 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. 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.

Rare mutations in the Parkin-like E3 ubiquitin ligase Ariadne-1 (ARIH1) have been observed in patients with early-onset or familial TAAD. ARIH1 encodes a protein of the LINC (linker of nucleoskeleton and cytoskeleton), a protein complex essential for anchoring myocyte nuclei to the cytoskeleton. 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 al.\(^\text{16}\) demonstrated that Turner syndrome patients with putatively-deleterious mutations in \textit{TIMP3} are associated with a greater incidence of BAV and TAA than the patients without \textit{TIMP3} variants. Hemizygosity for coincident \textit{TIMP1} / \textit{TIMP3} variants, synergistically increased the risk for BAV and TAA,\(^\text{16}\) due to \textit{TIMP1}\’s functional redundancy with \textit{TIMP3}.

Numerous mutations of the myosin light chain kinase (\textit{MYLK}) gene have been associated with TAAD. Shalata et al. have identified an additional \textit{MYLK} missense mutation in a single pedigree.\(^\text{17}\) 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 al.\(^\text{18}\) 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.\(^\text{18}\) SmgGDS is encoded by the \textit{RAP1GDS1} gene and known to be involved in the contraction of vascular smooth muscle cell (VSMC).\(^\text{18}\) Using a heterozygous SmgGDS\(^{+/−}\) mouse model, since the complete knockout (SmgGDS\(^{−/−}\)) was embryologically lethal, they observed that the downregulation of SmgGDS was causing \textit{“pathological phenotype changes in VSMC” via the angiotensin-II pathway}.\(^\text{18}\) 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 report\(^\text{2}\) 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.

**Conflict of Interest**

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

**Acknowledgment**

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, Loeyrs 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; 2017:461–480
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: 2016:49–79
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: Patient’s True Stories and the Innovations that Saved Their Lives. Milan, Italy: Edi.Ernes; 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. Quijones-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. Takeeda 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-[beta] binding protein (LTBP)-3-null mice indicate a role for Ltbp-3 in modulating TGF-[beta] bioavailability. J Cell Biol 2002;156(02):227–232
15. Tan KL, Haelterman NA, Kwiatler 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.
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 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
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 COL3A1 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’ondt S, Guillemyn 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 SE, 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 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
40 Loeys B, De Paepe A, Urban Z. EFEMP2-related cutis laxa. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews®. Seattle, WA1993
41 Jelsig AM, Urban Z, Huchtagower 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, Huchtagower 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, 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
45 Pereira I, Andrikopoulos K, Tian J, et al. Targeting of the gene encoding fibrillin-1 recapitates the vascular aspect of Marfan syndrome. Nat Genet 1997;17(02):218–222
46 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
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 Fn1 expression. PLoS One 2010;5(11):e14136
50 Morris SA, Orbach DB, Geva T, Singh MN, Gauvreau K, Laco 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/ATS/ACS/SCA/SCAI/SIR/ST/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 contractual 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 filament A is a major determinant of conduit artery structure and function at the adult stage. Pflugers Arch 2016;468(07):1151–1160.

54 Perfetti C, 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, Frenz T, 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 ascends 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. Microfilibril-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. MAFAP5 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/R247T) mutations increase thoracic aorta vulnerability to intramural damage despite a general biomechanical adaptivity. J Biomech 2015;48(01):113–122.

67 Faggion Vinholo et al. 2019 Update on the Genetics of TAAD, 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.

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, Stattn 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. Permutation 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 Go Exome Sequencing Project; Mibava Leducq Consortium. MAT2A mutations predispose to thoracic aortic aneurysms and dissections. Am J Hum Genet 2015;92(03):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-osteoarthriti 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 TGFβ2 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. TGFβ2 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 TGFBR2. Int J Cardiol 2013;165(03):584–587
88 Bertoli-Avellà AM, Gillis E, Morisaki H, et al. Mutations in a TGF-β ligand, TGFBR3, 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 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