SPANDIDOS PUBLICATIONS

MOLECULAR MEDICINE REPORTS 34: 232, 2026

Genetic and molecular mechanisms of hereditary thoracic aortic aneurysm and dissection (Review)

XIAOKANG WANG[1,2*], QIWEN TAN[1,2*], JINGCHENG XU[1,2*], YUNLIN YANG[2],
HAOYUE HUANG[2], XIAOMEI TENG[2] and WEIHUA WU[1]

[1]Center of Clinical Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, P.R. China;
[2]Department of Cardiovascular Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, P.R. China

Received October 9, 2025; Accepted May 20, 2026

DOI: 10.3892/mmr.2026.13942

Abstract. Thoracic aortic aneurysm and dissection (TAAD) is a life-threatening disease with an insidious onset and a largely elusive pathogenesis. Hereditary TAAD (HTAD) can be classified into syndromic forms, including Marfan syndrome, Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome and non-syndromic forms, including familial TAAD and bicuspid aortic valve-associated TAAD. Current evidence suggests that HTAD development shares several core mechanisms, including extracellular matrix disruption, dysregulated transforming growth factor-β signaling, vascular smooth muscle cell dysfunction and, in the case of bicuspid aortic valve, abnormal hemodynamic stress. The present review summarizes the major genes and molecular pathways involved in HTAD and discusses their contributions to disease progression. Elucidating the underlying mechanisms associated with HTAD may facilitate risk assessment and the development of targeted therapies.

Contents

1. Introduction

Thoracic aortic aneurysm and dissection (TAFAD) is a life-threatening condition associated with a high risk of aortic rupture and substantial mortality. Approximately 30% of TAAD cases demonstrate familial aggregation or carry pathogenic genetic variants, and are collectively classified as hereditary TAAD (HTAD) (1-3). Compared with sporadic cases, HTAD often manifests at a younger age and may progress to dissection at aortic diameters below conventional intervention thresholds (4-7). These features underscore the clinical importance of early recognition, genetic evaluation, individualized surveillance and refined risk stratification.

Over the last decade, advances in genetic sequencing technology and disease modeling have provided new insights into the molecular pathogenesis and altered signaling pathways of TAAD. Core pathogenic processes include extracellular matrix (ECM) disorganization, dysregulated signaling networks, phenotypic and contractile dysfunctions of vascular smooth muscle cells (vSMCs) and altered biomechanical stress, with transforming growth factor-β (TGF-β)-associated signaling occupying a central, but complex position in numerous HTAD subtypes. Importantly, these mechanisms do not stand as independent linear pathways. Rather, genetic defects, cellular dysfunction, ECM instability and hemodynamic forces interact dynamically within the aortic wall (8-10).

Correspondence to: Dr Weihua Wu, Center of Clinical Laboratory, The First Affiliated Hospital of Soochow University, 899 Pinghai Road, Suzhou, Jiangsu 215006, P.R. China
E-mail: wwh.1216@163.com

Dr Xiaomei Teng, Department of Cardiovascular Surgery, The First Affiliated Hospital of Soochow University, 899 Pinghai Road, Suzhou, Jiangsu 215006, P.R. China
E-mail: txm_2020@126.com

[*]Contributed equally

Abbreviations: BAV, bicuspid aortic valve; ECM, extracellular matrix; ERK1/2, extracellular signal-regulated kinase 1 and 2; FTAAD, familial thoracic aortic aneurysm dissection; HTAD, hereditary thoracic aortic aneurysm and dissection; JNK, Jun N-terminal kinases; LAP, latency-associated peptide; LDS, Loeys-Dietz syndrome; LOX, lysyl oxidase; M2K6, mitogen-activated protein kinase kinase 6; MFS, Marfan syndrome; MLCK, myosin light chain kinase; MMP, matrix metalloproteinase; PKG-I, cGMP-dependent protein kinase I; RLC, regulatory light chains; TAAD, thoracic aortic aneurysm dissection; TF, transcription factors; TGF-β, transforming growth factor-β; vEDS, vascular Ehlers-Danlos syndrome; vSMCs, vascular smooth muscle cells; WSS, wall shear stress

Key words: thoracic aortic aneurysm dissection, pathogenesis, transforming growth factor-β, vascular smooth muscle cell

Although several recent reviews have summarized the genetic architecture of HTAD, a comprehensive framework integrating shared molecular pathways with subtype-specific mechanisms is still lacking (2,11,12). Given the marked genetic heterogeneity of HTAD, distinguishing pathogenic mechanisms from mutation- or syndrome-specific processes may help to explain phenotypic variability, improve genotype-informed risk assessment and facilitate the development of mechanism-based therapeutic strategies.

The present review therefore aims to synthesize different strands of our current knowledge regarding the molecular pathogenesis of HTAD, placing an emphasis on both common disease pathways and subtype-specific features. Additionally, unresolved controversies, gaps in the evidence and emerging research directions were discussed, also proposing a conceptual framework for integrating genetic findings, molecular mechanisms, biomechanical influences and translational therapy in HTAD.

2. Classification of HTAD

As mentioned above, HTAD is a clinically and genetically heterogeneous group of disorders and its classification has important implications for diagnosis, risk stratification and clinical management. Traditionally, HTAD has been categorized into syndromic and non-syndromic forms, based on the presence or absence of extra-aortic systemic manifestations (Fig. 1).

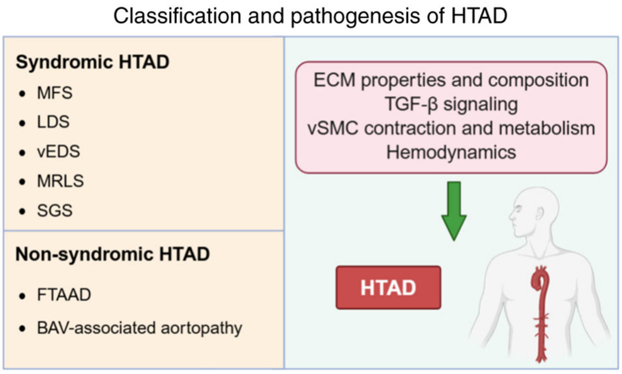

Figure 1. Classification and pathogenesis of HTAD. HTAD is classified into syndromic and non-syndromic forms. These forms share common pathogenic mechanisms involving ECM integrity and composition, dysregulation of TGF-β signaling, and altered SMC contraction and metabolism. BAV, bicuspid aortic valve; ECM, extracellular matrix; FTAAD, familial thoracic aortic aneurysm and dissection; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; MRLS, Meester-Loeys syndrome; SGS, Shprintzen-Goldberg syndrome; SMC, smooth muscle cell; TAAD, thoracic aortic aneurysm and dissection; HTAD, hereditary TAAD; vEDS, vascular Ehlers-Danlos syndrome.

Syndromic HTAD is most commonly associated with Mendelian connective tissue disorders and typically involves multisystem abnormalities affecting the skin, skeleton, eyes, craniofacial structures and vasculature (13). Major syndromic forms include Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS) and vascular Ehlers-Danlos syndrome (vEDS). By contrast, non-syndromic HTAD is characterized predominantly by cardiovascular involvement, and includes conditions such as familial thoracic aortic aneurysm and dissection (FTAAD) and bicuspid aortic valve (BAV)-associated aortopathy (BAV is the most frequent congenital heart disease, where the aortic valve only has two leaflets instead of the normal three) (14).

However, this distinction is not absolute. An increasing recognition of phenotypic overlap and convergent genetic mechanisms has blurred the boundaries between syndromic and non-syndromic HTAD. Taken together, these observations suggest that HTAD is better viewed as a spectrum of associated disorders, rather than as two entirely discrete categories.

3. Shared molecular mechanisms in HTAD

Despite the clinical and genetic heterogeneity of HTAD, accumulating evidence suggests that diverse subtypes focus on several core pathogenic mechanisms that drive aortic wall degeneration and disease progression (Table I). These processes are highly interconnected and collectively contribute to progressive aortic wall degeneration.

Changes in ECM properties and composition. The aortic ECM, composed predominantly of elastin and collagen, provides elasticity, tensile strength and structural support to the aortic wall (15). Disruption of ECM homeostasis weakens the aortic wall, thereby predisposing it to aneurysm formation and dissection. In addition, pathogenic variants in genes such as fibrillin-1 (*FBN1*) and type III collagen α1 chain (*COL3A1*), disrupt collagen maturation and deposition, thereby compromising the structural integrity of the aortic wall and increasing susceptibility to aortic disease (16,17). Although ECM dysfunction is strongly supported by genetic and experimental evidence, the events that link primary matrix defects to cellular and signaling abnormalities have yet to be completely elucidated.

Dysregulation of signaling pathways. The TGF-β signaling pathway is a key pathway that is implicated in HTAD due to its role in vascular development, ECM regulation and cellular homeostasis. Pathogenic variants affecting TGF-β pathway components are associated with thoracic aortic disease of varying severity (18-20). In mechanistic terms, these alterations may disturb the balance between canonical Smad-dependent signaling and non-canonical pathways. In particular, the downstream activation of extracellular signal-regulated kinases ½ (ERK1/2), c-Jun N-terminal kinase (JNK) and PI3K/Akt has been implicated in maladaptive aortic remodeling (21,22).

However, the precise contributions made by TGF-β signaling events remains controversial, since both increased and decreased pathway activity has been reported in the literature, suggesting the existence of subtype-specific, stage-dependent and compensatory effects.

Contractile and metabolic abnormalities of vSMCs. vSMCs are essential for maintaining aortic wall integrity, vascular tone and adaptive responses to mechanical stress. Pathogenic variants in genes such as smooth muscle cell-specific myosin heavy chain (*MYH*)*11* and actin α2, smooth muscle (*ACTA2*) impair the contractile function of vSMCs and ECM synthesis, leading to a reduction in the mechanical strength of the vascular wall (23,24). As a result, these mutations

Table I. Classification and causative genes of HTAD.

A, Syndromic TAAD

Disease/subtype	Related genes	OMIM number	Mechanism of action
Marfan syndrome signaling	*FBN1*	#154700	ECM properties and composition; TGF-β
Loeys-Dietz syndrome type I	*TGFBR1*	#609192	TGF-β signaling
Loeys-Dietz syndrome type II	*TGFBR2*	#610168	
Loeys-Dietz syndrome type III	*SMAD3*	#613795	
Loeys-Dietz syndrome type IV	*TGFB2*	#614816	
Loeys-Dietz syndrome type V	*TGFB3*	#615582	
Loeys-Dietz syndrome type VI	*SMAD2*	#619656	
Loeys-Dietz syndrome type VII	*IPO8*	#605600	
Vascular Ehlers-Danlos syndrome	*COL3A1*	#130050	ECM properties and composition
Meester-Loeys syndrome	*BGN*	#301870	ECM properties and composition
Shprintzen-Goldberg syndrome	*SKI*	#182212	TGF-β signaling

B, Non-syndromic TAAD

Disease/subtype	Related genes	OMIM number	Mechanism of action
Familial thoracic aortic aneurysm dissection	*LOX*	#617168	ECM properties and composition
	ACTA2	#613834	vSMC contraction and metabolism
	MYH11	#132900	
	MYLK	#613780	
	PRKG1	#615436	
Bicuspid aortic valve	*NOTCH1*	#109730	Hemodynamics; ECM properties and composition; vSMC contraction and metabolism
	GATA4	#600576	
	GATA5	#611496	
	GATA6	#601656	
	SMAD6	#614823	
	LOX	#617168	
	ROBO4	#618496	
	ACTA2	*#611788*	

ACTA2, actin alpha 2, smooth muscle; ECM, extracellular matrix; *LOX*, lysyl oxidase; *MYH11*, myosin heavy chain 11; OMIM, Online Mendelian Inheritance in Man; *PRKG1*, protein kinase cGMP-dependent 1; *ROBO4*, roundabout guidance receptor 4; TAAD, thoracic aortic aneurysm dissection; TGF-β, transforming growth factor-β; vSMCs, vascular smooth muscle cells.

hinder vSMCs from appropriately sensing and responding to hemodynamic stresses, which accelerates the degradation and dilation of the aortic wall (25-27). In particular, increased rates of vSMC apoptosis have been implicated in both the initiation and progression of HTAD, further undermining aortic wall stability (28). Nevertheless, the precise contributions made by distinct vSMC phenotypes across genetic subtypes have yet to be fully elucidated.

Hemodynamic influences. Hemodynamic stress contributes to aortic remodeling, particularly in BAV-associated aortopathy. Valvular abnormalities may lead to the generation of disturbed flow, aortic regurgitation and increased wall shear stress (WSS), all of which may promote aortic dilation (29-31). The BAV exhibits a significant genetic predisposition, with variants in genes including members of the *NOTCH1* and *GATA* families being implicated in non-syndromic disease (32). These variants may be predisposed not only to valve malformation, but also to intrinsic aortic wall weakness, thereby amplifying the effects of abnormal flow. Therefore, mechanistically speaking, hemodynamic stress probably acts in concert with genetic susceptibility, rather than as an isolated driver.

Considered altogether, ECM disruption, vSMC dysfunction, dysregulated signaling and abnormal hemodynamic stress form an interconnected pathogenic network in HTAD. Matrix defects may alter mechanotransduction and growth factor bioavailability; signaling abnormalities may affect vSMC phenotype and ECM remodeling; and abnormal flow may further aggravate wall degeneration in genetically susceptible aortas. In view of these defects, defining the relative contribution and hierarchy of these mechanisms will be essential in terms of improving risk prediction and developing mechanism-based therapies.

4. Syndromic HTAD

MFS. MFS, an autosomal dominant connective tissue disorder with aortic dissection represents a major life-threatening complication. The primary causative gene, *FBN1*, encodes fibrillin-1, the major structural component of extracellular microfibrils distributed throughout multiple tissues and organs (33). FBN1 is composed of multiple epidermal growth factor (EGF)-like domains, the majority of which are calcium-binding (cb)EGF-like domains. These motifs bind extracellular calcium ions, thereby stabilizing FBN-1 and protecting it from proteolytic degradation (34,35).

In various MFS mouse models, different degrees of FBN1 deficiency have been observed, frequently accompanied by aortic aneurysm formation, dissection and premature death (34). In patients with Marfan syndrome, distinct histopathological alterations have been identified across different affected aortic segments, which also exhibit segment-specific patterns of ECM remodeling (36). At the molecular level, mutations in FBN1 alter the secondary structure of EGF-like domains, leading to protein misfolding and impaired microfibril assembly and stability. Furthermore, structural abnormalities in cbEGF-like motifs increase the susceptibility of FBN1 to proteolytic degradation (37). Collectively, these abnormalities in microfibril architecture and the reduction in FBN1 levels compromise aortic wall integrity and promote the development of TAAD.

Beyond these structural abnormalities, studies conducted on MFS models and patient tissues have revealed the critical yet complex role of TGF-β in the progression of TAAD. Accumulating evidence indicates that enhanced TGF-β signaling, particularly through the non-canonical (Smad-independent) pathway, is a major driver of aortic disease. Inhibition of TGF-β signaling in myeloid cells attenuates aortic aneurysm formation in MFS mouse models, whereas TGFB1 expression has been reported to be elevated in patients with MFS (38,39). Studies suggest that FBN1 plays an essential role in sequestering active TGF-β via latency-associated peptide through its interaction with potential TGF-β binding proteins, thereby limiting TGF-β activation (Fig. 2A) (40,41). The loss of FBN1 integrity may therefore increase TGF-β activity, consequently resulting in excessive TGF-β activation and overactivation of multiple downstream non-canonical signaling cascades, including the ERK1/2 and JNK1 pathways (Fig. 2B). Losartan, an angiotensin II (AngII) type 1 receptor blocker, has been shown to exert protective effects against aneurysm formation by suppressing non-canonical ERK1/2 signaling (42). Collectively, dysregulation of the TGF-β signaling pathway and aberrant ERK1/2 activation are considered key contributors to aortic aneurysm development in MFS.

LDS. LDS is an autosomal dominant aortic aneurysm syndrome characterized by arterial aneurysms and tortuosity, craniofacial abnormalities, skeletal features and cutaneous manifestations. Although its clinical manifestations are similar to those of MFS, typical distinguishing features of LDS include a bifid uvula, arterial tortuosity and wide-set eyes. The current gene-based classification acknowledges seven LDS subtypes (43). The two most common forms, LDS1 and LDS2, are caused by pathogenic variants in TGF-β receptor 1 (*TGFBR1*) and *TGFBR2*, respectively, whereas variants in the genes *SMAD*3, *TGFB2*, *TGFB3*, *SMAD2* and importin 8 have also been identified in affected individuals (44-46). Collectively, these genes encode ligands, receptors or intracellular mediators of the TGF-β signaling pathway, thereby rendering TGF-β dysregulation the central pathogenic feature of LDS.

Clinical studies have consistently shown enhanced TGF-β signaling in LDS aortic tissue across subtypes, including increased levels of TGF-β expression, SMAD2 phosphorylation and TGF-β target gene expression (19,46). However, these findings were paradoxical, as the majority of the reported *TGFBR1* and *TGFBR2* mutations have been shown to reduce receptor serine/threonine kinase activity (18). Notably, increased levels of phosphorylated SMAD2 have been observed both in LDS patient aortic tissue with loss-of-function *TGFBR1* variants and in LDS mouse models (47,48).

Taken together, these observations suggest that cell-autonomous defects in canonical TGF-β signaling may trigger the compensatory upregulation of TGF-β ligand production, which, in turn, both promotes the paracrine activation of neighboring cells and enhances non-canonical signaling, thereby amplifying maladaptive aortic wall remodeling (49). Therefore, LDS-associated mutations may attenuate canonical TGF-β signaling while driving the compensatory activation of non-canonical pathways, and the uncovering of this mechanism helps to explain the paradoxical increases in TGF-β expression that are observed in LDS, underscoring the complex role of TGF-β pathway dysregulation in the pathogenesis of HTAD (Fig. 2C).

vEDS. vEDS is one of the most severe forms of EDS and is caused by heterozygous pathogenic variants in the gene *COL3A1*. Arterial dissection or rupture, including aortic rupture, is the leading cause of mortality in affected individuals (50). *COL3A1* encodes the α1 chain of type III collagen. Of note, three of these chains assemble into homotrimeric type III collagen molecules, which are characterized by a repeating Gly-X-Y amino acid sequence. Type III collagen is abundant in blood vessels and hollow organs, where it provides tensile strength and tissue flexibility (51).

The majority of pathogenic *COL3A1* variants in vEDS involve glycine substitutions within the collagen triple-helical domain, which results in the disruption of trimer formation and the destabilization of type III collagen. In addition to this structural mechanism, however, recent studies have suggested that altered stress-activated signaling may modify the severity of the disease (52-54). In vEDS modeled mice, genetic ablation of the signaling protein mitogen-activated protein kinase kinase 6 (Map2k6), a p38-activating kinase, was found to increase the risk of aortic rupture, and this was associated with reduced activation of p38 and enhanced protein kinase C/ERK phosphorylation (53). Taken together, these findings suggested that maladaptive crosstalk between ERK and MAP2K6/p38 signaling may exacerbate matrix-driven vascular fragility.

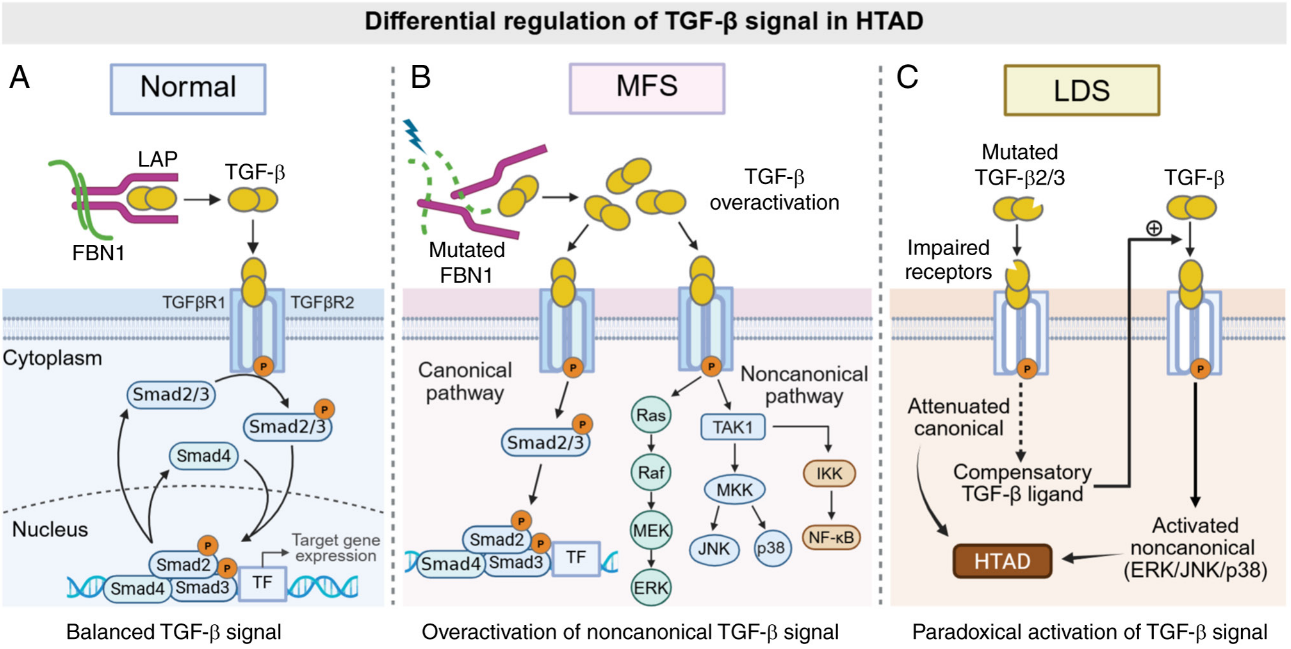

Figure 2. Differential regulation of TGF-β signaling in HTAD subtypes. (A) Under physiological conditions, fibrillin-1 sequesters the latent TGF-β complex, maintaining signaling homeostasis. (B) In MFS, pathogenic variants in FBN1 lead to increased availability of active TGF-β and the overactivation of noncanonical pathways, such as ERK and JNK. (C) In LDS, mutations in TGF-β receptors impair canonical signaling; however, this induces a compensatory upregulation of TGF-β ligands, resulting in the paradoxical activation of downstream pathways. These mechanisms highlight both shared and distinct features of TGF-β dysregulation across HTAD subtypes. ERK, extracellular signal-regulated kinase; FBN1, fibrillin-1; HTAD, hereditary thoracic aortic aneurysm and dissection; IKK, inhibitor of nuclear factor κB kinase; JNK, c-Jun N-terminal kinase; LAP, latency-associated peptide; LDS, Loeys-Dietz syndrome; MEK, MAPK/ERK kinase; MFS, Marfan syndrome; MKK, MAP kinase kinase; TAK1, transforming growth factor-β-activated kinase 1; TF, transcription factor.

In conclusion, vEDS is primarily driven by COL3A1-mediated type III collagen instability, which results in profound arterial and visceral fragility. Emerging evidence has demonstrated that signaling modifiers may further influence rupture susceptibility, thereby linking ECM defects to broader stress-response pathways in syndromic HTAD.

5. Non-syndromic HTAD

FTAAD. Approximately 20% of cases of non-syndromic TAAD have exhibited familial aggregation, and this condition, which is typically inherited in an autosomal dominant manner, is termed FTAAD (55). Compared with sporadic disease, FTAAD generally presents at an earlier stage and is associated with more rapid aneurysm growth. The most significant FTAAD-associated genes include *ACTA2*, *MYH11*, *MYLK*, protein kinase cGMP-dependent 1 (*PRKG1*) and lysyl oxidase (*LOX*) (3,56-59). With the exception of *LOX*, these genes mainly affect the vSMC contractile apparatus, leading to impaired contraction, defective mechanosensing and phenotypic remodeling, whereas *LOX* variants are primarily responsible for compromising ECM crosslinking and biomechanical strength.

Mutations affecting the vSMC contractile apparatus. The contractile apparatus of vSMCs consists of two myosin heavy chains, two essential light chains and two regulatory light chains (RLC) (25,60). Concerning the genes involved in these processes (and as mentioned above), the SMC-specific filament, α-actin, is encoded by *ACTA2*, whereas the myosin heavy chain is encoded by *MYH11*. During vSMC contraction, intracellular Ca^{2+} levels increase, and Ca^{2+} binding to calmodulin activates MYLK, which subsequently phosphorylates RLC, resulting in the contractile force of vSMCs (60). By contrast, during relaxation, x cGMP-dependent protein kinase I (PKG-I), encoded by *PRKG1*, activates myosin light chain phosphatase, leading to RLC dephosphorylation and vSMC relaxation. Notably, *MYLK* and *PRKG1* encode key kinases involved in the regulation of smooth muscle contraction and relaxation, respectively.

Among these genes, *ACTA2* is the most common mutation associated with FTAAD. Mutations that disrupt arginine 179 (p.R179H) and arginine 258 (p.R258C) have been shown to correlate with aortic events (61). In the *ACTA2* knockout mouse model, aortic α-SMA expression was reduced, accompanied by more severe aortic dilatation, which was associated with increased levels of reactive oxygen species and enhanced NF-κB signaling in vSMCs, as well as increased sensitivity to exogenous AngII (62,63). Concurrently, downregulation of α-SMA reduces the expression of integrins involved in cell-matrix adhesion and impairs the interaction between vSMCs and the ECM, thereby weakening aortic wall contractility (64,65).

Mutations in *MYH11* are less common, but likewise impair vSMC function. vSMC phenotypic switching from a contractile to a synthetic state has been observed in the aortas of patients with TAAD carrying mutations in both *ACTA2* and *MYH11* (24,26,66). This phenotypic transition is considered an important mechanism contributing to TAAD pathogenesis. Furthermore, histological staining of aortic sections from patients carrying *MYH11* mutations revealed enhanced TGF-β signaling, which may be associated with the pathogenesis of their TAAD. By contrast, the upregulation of TGF-β in *ACTA2* mutations exhibited a less pronounced effect on TAAD (67).

Pathogenic variants in *MYLK* and *PRKG1* are relatively rare; however, both have been associated with severe TAAD by disrupting vSMC contractile function (68). Insufficient *MYLK* activity reduces phosphorylation of RLC proteins, thereby impairing vSMCs' contractile function. A recent study has further shown that *MYLK* overexpression can reverse the transition of vSMC from a contractile phenotype to a secretory phenotype, and suppress the TGF-β signaling, ultimately attenuating TAAD progression (69). In addition, the p.Arg177Gln mutation in *PRKG1* alters the structure of its protein PKG-I, leading to its overactivation, which results in reduced phosphorylation of RLC in vSMC. This ultimately leads to a reduction in vSMC contractility, thereby predisposing to aneurysm and dissection (70).

Mutations affecting the ECM. *LOX* encodes a copper-dependent LOX, which catalyzes the oxidative deamination of lysine and hydroxylysine residues. In the ECM, LOX facilitates the formation of covalent crosslinking between collagen and elastin, as well as the precipitation of an insoluble matrix, making it an indispensable component of tissue development and pathological repair (71-73). Both missense and loss-of-function *LOX* variants have been associated with extensive aortic and arterial aneurysmal disease, which is accompanied by connective tissue manifestations (74,75). Reduced LOX activity, along with a reduction in elastin within the ECM, is hypothesized to impair the elasticity and tensile strength of the aorta, thereby inducing the occurrence of TAAD.

Other ECM-associated genes affecting the ECM have also been implicated in FTAAD, including *COL3A1* and microfibril-associated glycoprotein 5 (*MFAP5*), encoding a protein involved in the interaction within FBN1 in the ECM. Loss-of-function variants in *MFAP5* may likewise represent a potential cause for the development of FTAAD (76).

BAV-associated TAAD. A BAV is the most common congenital valvular heart defect, with aortic stenosis and regurgitation as its most common complications. The incidence of Stanford type A proximal aortic dilatation TAAD is significantly increased in patients with a BAV, indicating a strong association between valve morphology and aortic disease (77). BAV-related TAAD can be attributed to various factors, including genetic predispositions, alterations in the ECM of the vascular wall and hemodynamic changes.

The primary aortopathy hypothesis. The primary aortopathy hypothesis proposes that BAV-associated aortic dilation arises, at least in part, as an intrinsic developmental or genetic abnormality of the aortic wall. *NOTCH1* variants have been shown to hinder the endothelial-mesenchymal transition of blood vessels during embryonic development, impairing the aorta's ability to respond to pulse pressure (29,78). GATA binding protein 4 (*GATA4*), *GATA5* and *GATA6*, members of transcription factor family, are expressed in the mesoderm during early heart development. Variants in these genes can disrupt transcription factor activity, leading to BAV, although their direct contribution to TAAD remains less well defined (32). Additionally, variants in other genes, including *LOX*, roundabout guidance receptor 4 and *ACTA2*, may also contribute to aortic dilation through affecting ECM integrity, endothelial stability or vSMC contractile function.

The hemodynamic hypothesis. The hemodynamic hypothesis holds that the BAV significantly alters the direction of blood flow and shear stress in the ascending aorta, resulting in structural changes in the aortic wall. Four-dimensional flow cardiovascular magnetic resonance imaging has revealed altered blood flow patterns and increased WSS in the aorta of patients diagnosed with a BAV (79-81). Computational models likewise have shown such features as a reduced valve opening area, eccentric flow and elevated WSS compared with tricuspid aortic valves (30,82). Collectively, these findings support a mechanistic role for abnormal hemodynamic stress in BAV-associated aortopathy; furthermore, a greater extent of elevated WSS has been associated with faster aortic dilation, suggesting that WSS may serve as a marker of disease progression (83).

However, TAAD progression may persist in certain patients with BAV even after aortic valve replacement, suggesting that both the primary aortopathy and hemodynamics hypotheses likely play a role (84). Increasing evidence suggests that their relative contribution may vary according to the aortic segment, with aortic root dilation being more strongly influenced by intrinsic genetic factors, and ascending aortic dilation being more susceptible to hemodynamic stress (85). However, definitive separation of these effects remains challenging, since most of the studies in the literature, to date, have lacked integrated genetic and flow imaging data. Future studies combining genomic profiling with advanced hemodynamic phenotyping will be essential, both to clarify their respective roles and to improve risk stratification in BAV-associated TAAD.

6. Gene-environment interactions in HTAD

Although HTAD is primarily genetically determined, environmental and acquired factors have also been shown to modulate disease onset and progression. Rather than acting independently, these influences interact with the underlying genetic susceptibility, and may contribute to variability in clinical presentation and severity.

Hypertension is among the most established risk factors, as chronic hypertension increases the mechanical stress on the aortic wall, leading to damage and aneurysmal dilatation. Patients diagnosed with HTAD are advised to regularly take antihypertensive medications, even if their blood pressure remains within normal limits (86).

Inflammation has been shown to facilitate the development of aneurysmal dilatation and entrapment by disrupting the structural integrity of the aortic wall (2,87). In BAV-associated TAAD, elevated levels of aortic matrix metalloproteinase (MMP)-2 and MMP-9 and increased rates of apoptosis have been found to disrupt elastic fibers, to weaken aortic wall strength and to promote disease progression (88-90). However, whether inflammation is a primary driver of, or only a secondary response to, aortic injury remains elusive.

Unhealthy lifestyles, including smoking, having a high-fat diet and physical inactivity, may further exacerbate disease progression of TAAD by promoting atherosclerosis and hyperlipidemia (14). However, evidence currently available in support of their direct role in HTAD progression is relatively limited compared with that for sporadic aortic disease.

Overall, these observations support a gene-environment interaction model in HTAD in which genetic mutations establish baseline susceptibility, whereas environmental and acquired factors modulate disease penetrance and progression. Future studies integrating genetic profiling with longitudinal clinical and environmental data will be essential in order to clarify these interactions and to improve risk stratification.

7. Therapeutic strategies for HTAD

ECM disruption, TGF-β dysregulation, vSMC dysfunction and abnormal hemodynamic stress all provide potential therapeutic targets in HTAD; however, current treatment methods mainly aim to reduce aortic wall stress and slow disease progression.

Current clinical pharmacotherapy. In MFS, β-blockers, including atenolol and propranolol, remain the standard treatment, although losartan may also be administered to slow aortic dilation in certain patients, with the efficacy of the treatment being influenced by the FBN1 genotype (84,91).

In LDS, pharmacologic management mainly relies on angiotensin receptor blockers and β-blockers to reduce blood pressure and aortic wall stress (92-94). Comparative data have suggested that losartan may be more effective at reducing pulse wave velocity and arterial stiffness, whereas atenolol may be more effective at lowering cardiac output and in the treatment of stroke, supporting individualized drug selection (95). No LDS-specific targeted therapy has yet been approved.

Because vEDS has a distinct pathogenic basis, therapies effective in other forms of HTAD may not be equally beneficial. The selective β1-blocker celiprolol appears to improve vascular integrity in vEDS animal models and is currently the preferred preventive medication, whereas losartan has been shown to have limited benefits in experimental models (96,97).

For FTAAD and BAV-associated TAAD, no etiology-specific drug therapies are available at present; their management therefore depends on antihypertensive treatment, imaging surveillance and prophylactic surgery (98,99).

Emerging experimental strategies. Several mechanism-based approaches have shown promise in preclinical studies. Given the central role of TGF-β signaling in MFS and LDS, TGF-β type I receptor (TβRI/ALK5) kinase inhibitors have been shown to be beneficial in animal models and may represent a future targeted strategy (100,101). RNA-based therapies, including allele-specific silencing or correction of pathogenic variants such as *MYH11*, are also currently being investigated, although efficient vascular delivery, specificity and long-term safety remain major challenges.

Other experimental targets include inducible nitric oxide synthase 2, the inhibition of which has also been shown to reverse aortic dilation and medial degeneration in MFS animal models (102). In BAV-associated TAAD, epigenetic regulation and microRNA-based mechanisms are currently being explored as possible therapeutic targets (103-105).

Advances that are being made in disease modeling and biomarker development may further accelerate therapeutic discovery. For example, patient-derived smooth muscle cell organ-on-a-chip models can recapitulate cyclic biomechanical strain in the aortic wall, thereby providing a platform for mechanistic studies and drug screening (106). In parallel, standardized biomarker validation frameworks may facilitate the clinical application of circulating markers associated with disease progression or treatment response (107-109).

8. Summary and future prospects

In the present review, HTAD has been classified into syndromic and non-syndromic forms based on clinical phenotype. Despite substantial genetic heterogeneity, the implicated genes largely converge on several key processes, including ECM homeostasis, TGF-β signaling, vSMC contraction and metabolism, and abnormal hemodynamic stress. Across most forms of HTAD, three shared mechanisms are prominent: ECM disruption, dysregulated TGF-β signaling and impaired vSMC contractility.

Multiple signaling pathways have been shown to contribute to HTAD pathogenesis. TGF-β signaling is central to aortic homeostasis via both canonical and non-canonical pathways (20). The PI3K/Akt signaling pathway regulates cell survival, growth and metabolism, and has been implicated in aortic aneurysm formation (110,111). On the other hand, NF-κB activation promotes inflammation and ECM degradation in TAAD, and experimental evidence suggests that targeting either PI3K/Akt or NF-κB signaling may attenuate disease progression (112,113). Crosstalk among these pathways further supports their potential as therapeutic targets (114).

Subtype-specific mechanisms further refine this framework. In MFS, *FBN1* mutations promote excessive non-canonical TGF-β signaling, whereas in LDS, variants in TGF-β receptors or SMADs reduce canonical signaling, while enhancing compensatory non-canonical activation. In vEDS, *COL3A1* mutations have been shown to primarily destabilize type III collagen and to weaken the vascular wall, with a less prominent role identified for TGF-β. In FTAAD, pathogenic variants mainly affect the vSMC contractile apparatus, particularly *ACTA2* and *MYH11*, and this is often accompanied by secondary TGF-β activation. Finally, in BAV-associated TAAD, genetic susceptibility interacts with abnormal wall shear stress to drive aortic remodeling.

Overall, HTAD can be viewed as a gene-driven disorder in which modifier genes, hemodynamic forces and environmental factors shape disease penetrance, progression and severity. Future studies should focus on four major priorities: First, large genotype-phenotype registries should be set up to improve risk stratification; secondly, patient-derived induced pluripotent stem cells and CRISPR-engineered models should be established to investigate disease mechanisms and therapeutic responses; thirdly, experiments should be devised with targeted genetic interventions, including allele-specific silencing and gene replacement, paying particular attention to vascular delivery and long-term safety; and fourthly and finally, polygenic and molecular modifiers should be identified that may reveal new therapeutic targets for both HTAD and sporadic TAAD. These efforts will help both to refine disease prediction and to promote precision therapies for HTAD.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 82370478) and the Social Development Project from the Key Research and Development Plan of Jiangsu Province (grant no. BE2022731).

Availability of data and materials

Not applicable.

Authors' contributions

XW conducted the literature review and drafted the manuscript. QT screened the articles identified through database searches and revised the manuscript. JX organized the reviewed literature and prepared the tables. YY contributed to the literature review and revision of the manuscript. XT conceived and designed the study and revised the manuscript. HH revised the manuscript. WW edited the manuscript and supervised the project. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Huang T and Yang B: Heritable thoracic aortic aneurysms and dissections. Tech Vasc Interv Radiol 24: 100747, 2021.
2. Rodrigues Bento J, Meester J, Luyckx I, Peeters S, Verstraeten A and Loeys B: The genetics and typical traits of thoracic aortic aneurysm and dissection. Annu Rev Genomics Hum Genet 23: 223-253, 2022.
3. Wallace SE, Regalado ES, Gong L, Janda AL, Guo DC, Russo CF, Kulmacz RJ, Hanna N, Jondeau G, Boileau C, *et al*: MYLK pathogenic variants aortic disease presentation, pregnancy risk, and characterization of pathogenic missense variants. Genet Med 21: 144-151, 2019.
4. Duan Y, Xiong J, Lai Z, Zhong Y, Tian C, Du Z, Luo Z, Yu J, Li W, Xu W, *et al*: Analysis of the genetic contribution to thoracic aortic aneurysm or dissection in a prospective cohort of patients with familial and sporadic cases in East China. Orphanet J Rare Dis 18: 251, 2023.
5. Milleron O, Arnoult F, Delorme G, Detaint D, Pellenc Q, Raffoul R, Tchitchinadze M, Langeois M, Guien C, Beroud C, *et al*: Pathogenic FBN1 genetic variation and aortic dissection in patients with marfan syndrome. J Am Coll Cardiol 75: 843-853, 2020.
6. Ostberg NP, Zafar MA, Ziganshin BA and Elefteriades JA: The genetics of thoracic aortic aneurysms and dissection: A clinical perspective. Biomolecules 10: 182, 2020.
7. Isselbacher EM, Preventza O, Hamilton Black J III, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, *et al*: 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: A report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 80: e223-e393, 2022.
8. Chakraborty A, Li Y, Zhang C, Li Y, Rebello KR, Li S, Xu S, Vasquez HG, Zhang L, Luo W, *et al*: Epigenetic induction of smooth muscle cell phenotypic alterations in aortic aneurysms and dissections. Circulation 148: 959-977, 2023.
9. Deng H, Min E, Baeyens N, Coon BG, Hu R, Zhuang ZW, Chen M, Huang B, Afolabi T, Zarkada G, *et al*: Activation of Smad2/3 signaling by low fluid shear stress mediates artery inward remodeling. Proc Natl Acad Sci USA 118: e2105339118, 2021.
10. Qin H, Ishiwata T, Wang R, Kudo M, Yokoyama M, Naito Z and Asano G: Effects of extracellular matrix on phenotype modulation and MAPK transduction of rat aortic smooth muscle cells in vitro. Exp Mol Pathol 69: 79-90, 2000.
11. Isselbacher EM, Lino Cardenas CL and Lindsay ME: Hereditary influence in thoracic aortic aneurysm and dissection. Circulation 133: 2516-2528, 2016.
12. Rylski B, Schilling O and Czerny M: Acute aortic dissection: Evidence, uncertainties, and future therapies. Eur Heart J 44: 813-821, 2023.
13. Asta L, D'Angelo GA, Marinelli D and Benedetto U: Genetic basis, new diagnostic approaches, and updated therapeutic strategies of the syndromic aortic diseases: Marfan, loeys-dietz, and vascular ehlers-danlos syndrome. Int J Environ Res Public Health 20: 6615, 2023.
14. Senser EM, Misra S and Henkin S: Thoracic aortic aneurysm: A clinical review. Cardiol Clin 39: 505-515, 2021.
15. Kemberi M, Salmasi Y and Santamaria S: The role of ADAMTS proteoglycanases in thoracic aortic disease. Int J Mol Sci 24: 12135, 2023.
16. Asano K, Cantalupo A, Sedes L and Ramirez F: Pathophysiology and therapeutics of thoracic aortic aneurysm in marfan syndrome. Biomolecules 12: 128, 2022.
17. Kuivaniemi H and Tromp G: Type III collagen (COL3A1): Gene and protein structure, tissue distribution, and associated diseases. Gene 707: 151-171, 2019.
18. Velchev JD, Van Laer L, Luyckx I, Dietz H and Loeys B: Loeys-dietz syndrome. Adv Exp Med Biol 1348: 251-264, 2021.
19. Schepers D, Tortora G, Morisaki H, MacCarrick G, Lindsay M, Liang D, Mehta SG, Hague J, Verhagen J, van de Laar I, *et al*: A mutation update on the LDS-associated genes TGFB2/3 and SMAD2/3. Hum Mutat 39: 621-634, 2018.
20. Perrotta S, Carnevale D and Lembo G: TGF-β signalling: The Dr Jekyll and Mr Hyde of the aortic aneurysms. Cardiovasc Res 120: 2160-2162, 2024.
21. Wang C, Chang Q, Sun X, Qian X, Liu P, Pei H, Guo X and Liu W: Angiotensin II induces an increase in matrix metalloproteinase 2 expression in aortic smooth muscle cells of ascending thoracic aortic aneurysms through JNK, ERK1/2, and p38 MAPK activation. J Cardiovasc Pharmacol 66: 285-293, 2015.
22. Da X, Li Z, Huang X, He Z, Yu Y, Tian T, Xu C, Yao Y and Wang QK: AGGF1 therapy inhibits thoracic aortic aneurysms by enhancing integrin α7-mediated inhibition of TGF-β1 maturation and ERK1/2 signaling. Nat Commun 14: 2265, 2023.
23. Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, Avidan N, Bourgeois S, Estrera AL, Safi HJ, Sparks E, *et al*: Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet 39: 1488-1493, 2007.
24. Kuang SQ, Kwartler CS, Byanova KL, Pham J, Gong L, Prakash SK, Huang J, Kamm KE, Stull JT, Sweeney HL and Milewicz DM: 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 110: 1411-1422, 2012.
25. Rombouts KB, van Merrienboer TAR, Ket JCF, Bogunovic N, van der Velden J and Yeung KK: The role of vascular smooth muscle cells in the development of aortic aneurysms and dissections. Eur J Clin Invest 52: e13697, 2022.
26. Cao G, Xuan X, Hu J, Zhang R, Jin H and Dong H: How vascular smooth muscle cell phenotype switching contributes to vascular disease. Cell Commun Signal 20: 180, 2022.
27. Chen PY, Qin L, Li G, Malagon-Lopez J, Wang Z, Bergaya S, Gujja S, Caulk AW, Murtada SI, Zhang X, *et al*: Smooth muscle cell reprogramming in aortic aneurysms. Cell Stem Cell 26: 542-557.e11, 2020.
28. Song W, Fu G, Li Q, Huo C, Xiao L, Liu M, Zhang X, Sun H, Shen K, Shi L, *et al*: BMAL1 insufficiency increases the risk of thoracic aortic aneurysm and dissection. Cardiovasc Res 122: 146-161, 2025.
29. Rashed ER, Dembar A, Riasat M and Zaidi AN: Bicuspid aortic valves: An Up-to-date review on genetics, natural history, and management. Curr Cardiol Rep 24: 1021-1030, 2022.

30. Hou Q, Tao K, Du T, Wei H, Zhang H, Chen S, Pan Y and Qiao A: A computational analysis of potential aortic dilation induced by the hemodynamic effects of bicuspid aortic valve phenotypes. Comput Methods Programs Biomed 220: 106811, 2022.
31. Soulat G, Scott MB, Allen BD, Avery R, Bonow RO, Malaisrie SC, McCarthy P, Fedak PWM, Barker AJ and Markl M: Association of regional wall shear stress and progressive ascending aorta dilation in bicuspid aortic valve. JACC Cardiovasc Imaging 15: 33-42, 2022.
32. Bravo-Jaimes K and Prakash SK: Genetics in bicuspid aortic valve disease: Where are we? Prog Cardiovasc Dis 63: 398-406, 2020.
33. Connolly HM, Niaz T and Bowen JM: What is marfan syndrome? JAMA 329: 1618, 2023.
34. Zeigler SM, Sloan B and Jones JA: Pathophysiology and Pathogenesis of Marfan Syndrome. In: Progress in Heritable Soft Connective Tissue Diseases. Halper J (ed.). Springer International Publishing, Cham, pp185-206, 2021.
35. Takeda N and Komuro I: Genetic basis of hereditary thoracic aortic aneurysms and dissections. J Cardiol 74: 136-143, 2019.
36. Doukas P, Hruschka B, Bassett C, Buhl EM, Simon F, Saraber P, Jacobs MJ, Uhl C, Schurgers LJ and Gombert A: Distribution and maturity of medial collagen fibers in thoracoabdominal Post-dissection aortic aneurysms: A comparative study of marfan and non-marfan patients. Int J Mol Sci 26: 14, 2024.
37. Haller SJ, Roitberg AE and Dudley AT: Steered molecular dynamic simulations reveal Marfan syndrome mutations disrupt fibrillin-1 cbEGF domain mechanosensitive calcium binding. Sci Rep 10: 16844, 2020.
38. Dawson A, Li Y, Li Y, Ren P, Vasquez HG, Zhang C, Rebello KR, Ageedi W, Azares AR, Mattar AB, *et al*: Single-cell analysis of aneurysmal aortic tissue in patients with marfan syndrome reveals dysfunctional TGF-β signaling. Genes 13: 95, 2021.
39. Holm TM, Habashi JP, Doyle JJ, Bedja D, Chen Y, van Erp C, Lindsay ME, Kim D, Schoenhoff F, Cohn RD, *et al*: Noncanonical TGFβ signaling contributes to aortic aneurysm progression in Marfan syndrome mice. Science 332: 358-361, 2011.
40. Lockhart-Cairns MP, Cain SA, Dajani R, Steer R, Thomson J, Alanazi YF, Kielty CM and Baldock C: Latent TGFβ complexes are transglutaminase cross-linked to fibrillin to facilitate TGFβ activation. Matrix Biol 107: 24-39, 2022.
41. Du Q, Zhang D, Zhuang Y, Xia Q, Wen T and Jia H: The molecular genetics of marfan syndrome. Int J Med Sci 18: 2752-2766, 2021.
42. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, Myers L, Klein EC, Liu G, Calvi C, *et al*: Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 312: 117-121, 2006.
43. Loeys BL and Dietz HC: Loeys-Dietz Syndrome. In: GeneReviews(®). Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE and Amemiya A (eds.). University of Washington, Seattle Copyright © 1993-2026, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved., Seattle (WA), 1993.
44. van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, Hoedemaekers YM, Willemsen R, Severijnen LA, Venselaar H, *et al*: Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 43: 121-126, 2011.
45. Boileau C, Guo DC, Hanna N, Regalado ES, Detaint D, Gong L, Varret M, Prakash SK, Li AH, d'Indy H, *et al*: TGFB2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nat Genet 44: 916-921, 2012.
46. Bertoli-Avella AM, Gillis E, Morisaki H, Verhagen JMA, de Graaf BM, van de Beek G, Gallo E, Kruithof BPT, Venselaar H, Myers LA, *et al*: Mutations in a TGF-β ligand, TGFB3, cause syndromic aortic aneurysms and dissections. J Am Coll Cardiol 65: 1324-1336, 2015.
47. Hara H, Takeda N, Fujiwara T, Yagi H, Maemura S, Kanaya T, Nawata K, Morita H and Komuro I: Activation of TGF-β signaling in an aortic aneurysm in a patient with Loeys-Dietz syndrome caused by a novel loss-of-function variant of TGFBR1. Hum Genome Var 6: 6, 2019.
48. Gallo EM, Loch DC, Habashi JP, Calderon JF, Chen Y, Bedja D, van Erp C, Gerber EE, Parker SJ, Sauls K, *et al*: Angiotensin II-dependent TGF-β signaling contributes to Loeys-Dietz syndrome vascular pathogenesis. J Clin Invest 124: 448-460, 2014.
49. Bramel EE, Espinoza Camejo WA, Creamer TJ, Restrepo L, Saqib M, Bagirzadeh R, Zeng A, Mitchell JT, Stein-O'Brien GL, Pedroza AJ, *et al*: Intrinsic GATA4 expression sensitizes the aortic root to dilation in a Loeys-Dietz syndrome mouse model. Nat Cardiovasc Res 3: 1468-1481, 2024.
50. Malfait F, Castori M, Francomano CA, Giunta C, Kosho T and Byers PH: The Ehlers-Danlos syndromes. Nat Rev Dis Primers 6: 64, 2020.
51. Omar R, Malfait F and Van Agtmael T: Four decades in the making: Collagen III and mechanisms of vascular Ehlers Danlos Syndrome. Matrix Biol Plus 12: 100090, 2021.
52. Micale L, Di Muro E, De Cegli R, Tumaini B, Capuozzo A, Bernardi P, Morlino S, Fusco C, Nardella G, Mormone E, *et al*: Multi-OMICs analysis on tridimensional fibroblast spheroids to model vascular Ehlers-Danlos syndrome pathogenesis. Biochim Biophys Acta Mol Basis Dis 1871: 167896, 2025.
53. Bowen CJ, Sorber R, Calderón Giadrosic JF, Doyle JJ, Rykiel G, Burger Z, Zhang X, Espinoza Camejo WA, Anderson N, Sabnis S, *et al*: Map2k6 is a potent genetic modifier of arterial rupture in vascular Ehlers-Danlos syndrome mice. JCI Insight 10: e187315, 2025.
54. Chiarelli N, Cinquina V, Martini P, Bertini V, Zoppi N, Venturini M, Ritelli M and Colombi M: Deciphering disease signatures and molecular targets in vascular Ehlers-Danlos syndrome through transcriptome and miRNome sequencing of dermal fibroblasts. Biochim Biophys Acta Mol Basis Dis 1870: 166915, 2024.
55. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, Rizzo JA and Elefteriades JA: Familial thoracic aortic aneurysms and Dissections-incidence, modes of inheritance, and phenotypic patterns. Ann Thorac Surg 82: 1400-1405, 2006.
56. Lu H, Fagnant PM, Bookwalter CS, Joel P and Trybus KM: Vascular disease-causing mutation R258C in ACTA2 disrupts actin dynamics and interaction with myosin. Proc Natl Acad Sci USA 112: E4168-E4177, 2015.
57. Negishi K, Aizawa K, Shindo T, Suzuki T, Sakurai T, Saito Y, Miyakawa T, Tanokura M, Kataoka Y, Maeda M, *et al*: An Myh11 single lysine deletion causes aortic dissection by reducing aortic structural integrity and contractility. Sci Rep 12: 8844, 2022.
58. Gago-Díaz M, Blanco-Verea A, Teixidó G, Huguet F, Gut M, Laurie S, Gut I, Carracedo Á, Evangelista A and Brion M: PRKG1 and genetic diagnosis of early-onset thoracic aortic disease. Eur J Clin Invest 46: 787-794, 2016.
59. Guo DC, Regalado ES, Gong L, Duan X, Santos-Cortez RL, Arnaud P, Ren Z, Cai B, Hostetler EM, Moran R, *et al*: LOX mutations predispose to thoracic aortic aneurysms and dissections. Circ Res 118: 928-934, 2016.
60. Fang X, Bogdanov V, Davis JP and Kekenes-Huskey PM: Molecular insights into the MLCK Activation by CaM. J Chem Inf Model 63: 7487-7498, 2023.
61. Regalado ES, Guo DC, Prakash S, Bensend TA, Flynn K, Estrera A, Safi H, Liang D, Hyland J, Child A, *et al*: Aortic disease presentation and outcome associated with ACTA2 mutations. Circ Cardiovasc Genet 8: 457-464, 2015.
62. Chen J, Peters A, Papke CL, Villamizar C, Ringuette LJ, Cao J, Wang S, Ma S, Gong L, Byanova KL, *et al*: Loss of smooth muscle α-Actin leads to NF-κB-dependent increased sensitivity to Angiotensin II in smooth muscle cells and aortic enlargement. Circ Res 120: 1903-1915, 2017.
63. Cheng J, Zhou X, Jiang X and Sun T: Deletion of ACTA2 in mice promotes angiotensin II induced pathogenesis of thoracic aortic aneurysms and dissections. J Thorac Dis 10: 4733-4740, 2018.
64. Massett MP, Bywaters BC, Gibbs HC, Trzeciakowski JP, Padgham S, Chen J, Rivera G, Yeh AT, Milewicz DM and Trache A: Loss of smooth muscle α-actin effects on mechanosensing and cell-matrix adhesions. Exp Biol Med (Maywood) 245: 374-384, 2020.
65. Ojha KR, Kim H, Padgham S, Hopkins L, Zamen RJ, Chattopadhyay A, Han G, Milewicz DM, Massett MP and Trache A: Smooth Muscle-Alpha actin R149C pathogenic variant downregulates integrin recruitment at Cell-matrix adhesions and decreases cellular contractility. Int J Mol Sci 24: 9616, 2023.
66. Lu H, Du W, Ren L, Hamblin MH, Becker RC, Chen YE and Fan Y: Vascular smooth muscle cells in aortic aneurysm: From genetics to mechanisms. J Am Heart Assoc 10: e023601, 2021.
67. Renard M, Callewaert B, Baetens M, Campens L, MacDermot K, Fryns JP, Bonduelle M, Dietz HC, Gaspar IM, Cavaco D, *et al*: Novel MYH11 and ACTA2 mutations reveal a role for enhanced TGFβ signaling in FTAAD. Int J Cardiol 165: 314-321, 2013.

68. Regalado ES, Morris SA, Braverman AC, Hostetler EM, De Backer J, Li R, Pyeritz RE, Yetman AT, Cervi E, Shalhub S, *et al*: Comparative risks of initial aortic events associated with genetic thoracic aortic disease. J Am Coll Cardiol 80: 857-869, 2022.
69. Liu ZL, Li Y, Lin YJ, Shi MM, Fu MX, Li ZQ, Ning DS, Zeng XM, Liu X, Cui QH, *et al*: Aging aggravates aortic aneurysm and dissection via miR-1204-MYLK signaling axis in mice. Nat Commun 15: 5985, 2024.
70. Guo DC, Regalado E, Casteel DE, Santos-Cortez RL, Gong L, Kim JJ, Dyack S, Horne SG, Chang G, Jondeau G, *et al*: Recurrent gain-of-function mutation in PRKG1 causes thoracic aortic aneurysms and acute aortic dissections. Am J Hum Genet 93: 398-404, 2013.
71. Laczko R and Csiszar K: Lysyl oxidase (LOX): Functional contributions to signaling pathways. Biomolecules 10: 1093, 2020.
72. Umana-Diaz C, Pichol-Thievend C, Marchand MF, Atlas Y, Salza R, Malbouyres M, Barret A, Teillon J, Ardidie-Robouant C, Ruggiero F, *et al*: Scavenger Receptor cysteine-rich domains of Lysyl Oxidase-Like2 regulate endothelial ECM and angiogenesis through non-catalytic scaffolding mechanisms. Matrix Biol 88: 33-52, 2020.
73. Yi X, Zhou Y, Chen Y, Feng X, Liu C, Jiang DS, Geng J, Li X, Jiang X and Fang ZM: The expression patterns and roles of lysyl oxidases in aortic dissection. Front Cardiovasc Med 8: 692856, 2021.
74. Cirnu A, Kolokotronis K, Walz K, Kilinç A, Janz A, Williams T, Busch A, Rost S and Gerull B: Novel mutation in LOX associates with a complex aneurysmal vascular and cardiac phenotype. Circ Genom Precis Med 14: e003217, 2021.
75. Van Gucht I, Krebsova A, Diness BR, Laga S, Adlam D, Kempers M, Samani NJ, Webb TR, Baranowska AA, Van Den Heuvel L, *et al*: Novel LOX variants in five families with Aortic/Arterial aneurysm and dissection with variable connective tissue findings. Int J Mol Scie 22: 7111, 2021.
76. Barbier M, Gross MS, Aubart M, Hanna N, Kessler K, Guo DC, Tosolini L, Ho-Tin-Noe B, Regalado E, Varret M, *et al*: MFAP5 loss-of-function mutations underscore the involvement of matrix alteration in the pathogenesis of familial thoracic aortic aneurysms and dissections. Am J Hum Genet 95: 736-743, 2014.
77. Verma R, Cohen G, Colbert J and Fedak PWM: Bicuspid aortic valve associated aortopathy: 2022 guideline update. Curr Opin Cardiol 38: 61-67, 2023.
78. Liu T, Xie M, Lv Q, Li Y, Fang L, Zhang L, Deng W and Wang J: Bicuspid aortic valve: An update in morphology, genetics, biomarker, complications, imaging diagnosis and treatment. Front Physiol 9: 1921, 2018.
79. Rodríguez-Palomares JF, Dux-Santoy L, Guala A, Kale R, Maldonado G, Teixidó-Turà G, Galian L, Huguet M, Valente F, Gutiérrez L, *et al*: Aortic flow patterns and wall shear stress maps by 4D-flow cardiovascular magnetic resonance in the assessment of aortic dilatation in bicuspid aortic valve disease. J Cardiovasc Magn Reson 20: 28, 2018.
80. Bissell MM, Hess AT, Biasiolli L, Glaze SJ, Loudon M, Pitcher A, Davis A, Prendergast B, Markl M, Barker AJ, *et al*: Aortic dilation in bicuspid aortic valve disease: Flow pattern is a major contributor and differs with valve fusion type. Circ Cardiovasc Imaging 6: 499-507, 2013.
81. Barker AJ, Markl M, Bürk J, Lorenz R, Bock J, Bauer S, Schulz-Menger J and von Knobelsdorff-Brenkenhoff F: Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. Circ Cardiovasc Imaging 5: 457-466, 2012.
82. Sundström E and Tretter JT: Impact of variation in commissural angle between fused leaflets in the functionally bicuspid aortic valve on hemodynamics and tissue biomechanics. Bioengineering (Basel) 10: 1219, 2023.
83. Tessler I, Albuisson J, Piñeiro-Sabarís R, Verstraeten A, Kamber Kaya HE, Siguero-Álvarez M, Goudot G, MacGrogan D, Luyckx I, Shpitzen S, *et al*: Novel Association of the NOTCH pathway regulator MIB1 gene with the development of bicuspid aortic valve. JAMA Cardiol 8: 721-731, 2023.
84. Yang M, Nie Z, Yue H, Liang W and Wu Z: Aortopathy associated with bicuspid aortic valve: Advances in clinical and hemodynamics research. Front Physiol 16: 1576072, 2025.
85. Yassine NM, Shahram JT and Body SC: Pathogenic mechanisms of bicuspid aortic valve aortopathy. Front Physiol 8: 687, 2017.
86. Rabkin SW and Janusz MT: Aortic wall stress in hypertension and ascending thoracic aortic aneurysms: Implications for antihypertensive therapy. High Blood Press Cardiovasc Prev 20: 265-271, 2013.
87. Zhou Z, Liu Y, Zhu X, Tang X, Wang Y, Wang J, Xu C, Wang D, Du J and Zhou Q: Exaggerated autophagy in stanford type A aortic dissection: A Transcriptome Pilot Analysis of Human Ascending Aortic Tissues. Genes (Basel) 11: 1187, 2020.
88. Haunschild J, Schellinger IN, Barnard SJ, von Aspern K, Davierwala P, Misfeld M, Petroff D, Borger MA and Etz CD: Bicuspid aortic valve patients show specific epigenetic tissue signature increasing extracellular matrix destruction. Interact Cardiovasc Thorac Surg 29: 937-943, 2019.
89. Balistreri CR, Pisano C, Candore G, Maresi E, Codispoti M and Ruvolo G: Focus on the unique mechanisms involved in thoracic aortic aneurysm formation in bicuspid aortic valve versus tricuspid aortic valve patients: Clinical implications of a pilot study. Eur J Cardiothorac Surg 43: e180-e186, 2013.
90. Chung AW, Au Yeung K, Sandor GG, Judge DP, Dietz HC and van Breemen C: Loss of elastic fiber integrity and reduction of vascular smooth muscle contraction resulting from the upregulated activities of matrix metalloproteinase-2 and -9 in the thoracic aortic aneurysm in Marfan syndrome. Circ Res 101: 512-522, 2007.
91. Singh MN and Lacro RV: Recent clinical drug trials evidence in marfan syndrome and clinical implications. Can J Cardiol 32: 66-77, 2016.
92. Choo JT, Tan TH, Lai AH and Wong KY: Loeys-Dietz syndrome: A Marfan-like syndrome associated with aggressive vasculopathy. Singapore Med J 50: e353-e357, 2009.
93. Everitt MD, Pinto N, Hawkins JA, Mitchell MB, Kouretas PC and Yetman AT: Cardiovascular surgery in children with Marfan syndrome or Loeys-Dietz syndrome. J Thorac Cardiovasc Surg 137: 1327-1333, 2009.
94. Sayama S, Iriyama T, Takeda N, Yamauchi H, Toshimitsu M, Seyama T, Sone K, Kumasawa K, Nagamatsu T, Fujii T and Osuga Y: Proposed management policy for pregnant women with Loeys-Dietz syndrome following prophylactic aortic root replacement based on experience from a tertiary care center. Int Heart J 63: 176-179, 2022.
95. Sandor GG, Alghamdi MH, Raffin LA, Potts MT, Williams LD, Potts JE, Kiess M and van Breemen C: A randomized, double blind pilot study to assess the effects of losartan vs. atenolol on the biophysical properties of the aorta in patients with Marfan and Loeys-Dietz syndromes. Int J Cardiol 179: 470-475, 2015.
96. Dubacher N, Münger J, Gorosabel MC, Crabb J, Ksiazek AA, Caspar SM, Bakker ENTP, van Bavel E, Ziegler U, Carrel T, *et al*: Celiprolol but not losartan improves the biomechanical integrity of the aorta in a mouse model of vascular Ehlers-Danlos syndrome. Cardiovasc Res 116: 457-465, 2020.
97. Alqahtani M, Claudinot A, Gaudry M, Bartoli A, Barral PA, Vidal V, Boyer L, Busa T, Cadour F, Jacquier A, *et al*: Endovascular management of vascular complications in Ehlers-danlos syndrome type IV. J Clin Med 11: 6344, 2022.
98. Elendu C, Nzeako TR, Nwachukwu NO, Idahor CO, Nwevo C, Bob-Ume NC and Ezeh EC: Genetic factors and management strategies in aortic health: A literature review of inherited aortopathy. Ann Med Surg (Lond) 87: 598-615, 2024.
99. Atash A, Mees BME, Cramer MJ, Baas AF, Schurgers LJ, Doevendans PA and Stillitano F: MYH11 variants in thoracic aortic aneurysm pathophysiology: From bench to bedside. Eur J Clin Invest 56: e70196, 2026.
100. Rhodes SD, Wu X, He Y, Chen S, Yang H, Staser KW, Wang J, Zhang P, Jiang C, Yokota H, *et al*: Hyperactive transforming growth factor-β1 signaling potentiates skeletal defects in a neurofibromatosis type 1 mouse model. J Bone Miner Res 28: 2476-2489, 2013.
101. Dalal AR, Pedroza AJ, Kim JL, Gilles C, Gu W, Kusadokoro S, Shad R, Mitchel O, Jackson W, Hiesinger W, *et al*: Chemokine (C-C Motif) Ligand 2 expressing adventitial fibroblast expansion during Loeys-Dietz syndrome aortic aneurysm formation. Arterioscler Thromb Vasc Biol 45: 722-742, 2025.
102. Oller J, Méndez-Barbero N, Ruiz EJ, Villahoz S, Renard M, Canelas LI, Briones AM, Alberca R, Lozano-Vidal N, Hurlé MA, *et al*: Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome. Nat Med 23: 200-212, 2017.
103. Magouliotis DE, Sicouri S, Sicouri N, Baudo M, Cabrucci F, Yamashita Y and Ramlawi B: Epigenetic biomarkers in thoracic aortic aneurysm, dissection, and bicuspid aortopathy: A comprehensive review. Biomolecules 15: 568, 2025.
104. Pasipoularides A: Clinical-pathological correlations of BAV and the attendant thoracic aortopathies. Part 2: Pluridisciplinary perspective on their genetic and molecular origins. J Mol Cell Cardiol 133: 233-246, 2019.

105. Balistreri CR, Forte M, Greco E, Paneni F, Cavarretta E, Frati G and Sciarretta S: An overview of the molecular mechanisms underlying development and progression of bicuspid aortic valve disease. J Mol Cell Cardiol 132: 146-153, 2019.
106. Abudupataer M, Yin X, Xiang B, Chen N, Yan S, Zhu S, Ming Y, Liu G, Zhou X, Lai H, *et al*: Construction of a human aorta smooth muscle cell Organ-On-A-chip model for recapitulating biomechanical strain in the aortic wall. J Vis Exp Jul: 6, 2022 doi: 10.3791/64122.
107. Martin-Blazquez A, Martin-Lorenzo M, Santiago-Hernandez A, Heredero A, Donado A, Lopez JA, Anfaiha-Sanchez M, Ruiz-Jimenez R, Esteban V, Vazquez J, *et al*: Analysis of vascular smooth muscle cells from thoracic aortic aneurysms reveals DNA damage and cell cycle arrest as hallmarks in bicuspid aortic valve patients. J Proteome Res 23: 3012-3024, 2024.
108. Baratta M, Jian W, Hengel S, Kaur S, Cunliffe J, Boer J, Hughes N, Kar S, Kellie J, Kim YJ, *et al*: 2023 White Paper on Recent Issues in Bioanalysis: Deuterated Drugs; LNP; Tumor/FFPE Biopsy; Targeted Proteomics; Small Molecule Covalent Inhibitors; Chiral Bioanalysis; Remote Regulatory Assessments; Sample Reconciliation/Chain of Custody (PART 1A-Recommendations on Mass Spectrometry, Chromatography, Sample Preparation Latest Developments, Challenges, and Solutions and BMV/Regulated Bioanalysis PART 1B-Regulatory Agencies' Inputs on Regulated Bioanalysis/BMV, Biomarkers/IVD/CDx/BAV, Immunogenicity, Gene & Cell Therapy and Vaccine). Bioanalysis 16: 307-364, 2024.
109. Fernández-Metzler C, Ackermann B, Garofolo F, Arnold ME, DeSilva B, Gu H, Laterza O, Mao Y, Rose M, Vazvaei-Smith F and Steenwyk R: Biomarker assay validation by mass spectrometry. AAPS J 24: 66, 2022.
110. Song W, Qin L, Chen Y, Chen J and Wei L: Single-cell transcriptome analysis identifies Versican(+) myofibroblast as a hallmark for thoracic aortic aneurysm marked by activation of PI3K-AKT signaling pathway. Biochem Biophys Res Commun 643: 175-185, 2023.
111. Zhang K, Li R, Matniyaz Y, Yu R, Pan J, Liu W and Wang D: Liraglutide attenuates angiotensin II-induced aortic dissection and aortic aneurysm via inhibiting M1 macrophage polarization in APOE-/-mice. Biochem Pharmacol 223: 116170, 2024.
112. Wang X, Zhang X, Qiu T, Yang Y, Li Q and Zhang X: Dexamethasone reduces the formation of thoracic aortic aneurysm and dissection in a murine model. Exp Cell Res 405: 112703, 2021.
113. Zhao K, Zhu H, He X, Du P, Liang T, Sun Y, Jing Z and Zhou J: Senkyunolide I ameliorates thoracic aortic aneurysm and dissection in mice via inhibiting the oxidative stress and apoptosis of endothelial cells. Biochim Biophys Acta Mol Basis Dis 1869: 166819, 2023.
114. Luo K: Signaling cross talk between TGF-β/Smad and other signaling pathways. Cold Spring Harb Perspect Biol 9: a022137, 2017.