Genetic testing to modulate when to operate in thoracic aortic disease

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Abstract: Current classification of familial thoracic aortic aneurysm (TAA) includes two subtypes: syndromic, which is characterized by the involvement of multiple organs, and non-syndromic, where the damage is confined to the aortic tissue only. Positive family history for both syndromic and non-syndromic TAA suggests a connection between molecular genetics and TAA development. Multiple genes have been identified in TAA including those involved in the TGF-β signaling pathway, smooth muscle cell function and the structural integrity of the extracellular matrix. The knowledge about specific genes identified in TAA patients allows for the correlation between molecular profiling and the severity of the disease progression. More importantly, this information can be utilized to identify the most optimal surgical treatment options for TAA patients. This review discusses the current information regarding the TAA molecular genetics and surgical treatment options based on molecular profiling.

Keywords: Thoracic aortic aneurysm (TAA); molecular genetics; genes; surgery

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Introduction

Thoracic aortic aneurysm (TAA) can be fatal if it progresses asymptomatically until a later stage when dissection and rupture occur. Treatment methods for thoracic aortic aneurysm and dissection (TAAD) include both medical therapy and surgical repair. Medical therapy to prevent growth, rupture, and dissection of TAAs—including β-blockers and angiotensin receptor blockers (ARBs)—have been largely disappointing (1). Surgical repair is generally performed when the aortic diameter reaches 5.5 cm (2) but adjusted recommendations have been proposed based on clinical and molecular genetics. This monograph reviews the appropriate modulation of surgical criteria based on clinical and molecular genetics.

Categorization of TAAD

Family history, specifically the presence of an affected first-degree relative, is a crucial factor in the family history of the TAAs, as it suggests a strong genetic component in TAAD development. These studies show that a remarkably consistent 21% of patients with TAA have a family member with a known aneurysm somewhere in the body (3).

Familial TAA can be divided into two such categories: syndromic and non-syndromic. Syndromic aortic aneurysm connotes involvement of multiple organ systems and normally presents at an earlier age due to the severity of the phenotype. Patients with syndromic aneurysms are easier to identify based on the overt manifestations of genetic diseases with generalized defects in connective tissue.

Table 1 Aortic size at dissection and risk difference in female and male patients with LDS

Sex	Mutation	
	TGFBR1	*TGFBR2*
Male	Higher risk of aortic dissection	<4.5 cm aortic size at dissection
Female	Lower risk of aortic dissection	>4.5 cm aortic size at dissection

LDS, Loyez-Dietz syndrome.

Syndromic TAA disease includes Marfan syndrome (MFS), Loyez-Dietz syndrome (LDS), Ehlers-Danlos syndrome (EDS), and arterial tortuosity syndrome (ATS).

Non-syndromic TAAD is characterized by involvement of aortic tissue only. This can be divided into two subcategories: familial, which refers to more than one member of the family affected, and sporadic—without affected family members. Familial disease is usually clinically silent and difficult to detect until a later stage. Therefore, the ability to utilize genetic testing for detection, characterization and treatment recommendations of TAAD represents a major advance in patient care. We expect an increase in genetic testing and continued novel gene polymorphism identification as genetic understanding burgeons.

Syndromic TAAD

MFS

Hundreds of specific mutations in the *FBN1* gene have been found to cause MFS. Due to the virulence of this disease (potential for catastrophic aortic dissection), the current recommendation is to operate when the aneurysm reaches >5.0 or >4.5 cm for patients with familial history of aortic dissections. Rapid growth (more than 0.5 cm per year) as well as the presence of significant aortic valve regurgitation also encourage early operation (2). Specific recommendations for female MFS patients planning on pregnancy stipulate surgical repair of the aortic root and ascending aorta at the size of 4.0 cm (4). Moreover, if the patient is undergoing aortic valve replacement for aortic insufficiency, it is recommended to repair ascending aortic aneurysm if the diameter exceeds 4.5 cm (2). Similar guidelines are recommended for pediatric MFS patients, who should undergo aortic aneurysm repair if the aortic diameter is greater than 5.0 cm, if there is a rapid growth of 0.5 cm per year, or if aortic regurgitation is present (5).

LDS

LDS is another genetic connective tissue disease within the syndromic TAAD category. It is inherited in an autosomal dominant manner and can be distinguished from MFS by the presence of unique features such as bifid uvula, cleft palate and hypertelorism (6,7). This disease is primarily associated with heterozygous mutations in the transforming growth factor-β receptor 1 and 2 genes (*TGFBR1* and *TGFBR2*, respectively) and is characterized by a more severe vascular phenotype with dissections and ruptures happening at smaller aortic diameters (7). Although these two receptors contribute to the same TGF-β signaling pathway, they tend to affect the patient population in different ways. For instance, female patients with *TGFBR1* mutation tend to have lower risk of the aortic dissection than male patients with the same mutation, whereas those with *TGFBR2* mutation do not demonstrate the same sex preference (8). In addition to the risk difference, the aortic size at dissection also tends to be unequally distributed between the two sexes. Female patients with the *TFGBR2* mutations, but not *TGFBR1*, have had dissections with an aortic diameter of less than 4.5 cm. Men, on the other hand, did not generally experience dissections below 4.5 cm with *TGFBR1* or *TGFBR2* mutations (7) (*Table 1*).

Based on these observations, patients with these mutations should consider surgery when the aortic diameter is 4.5 cm, also women with the mutations in the *TGFBR2* gene should consider surgical repair when aortic size is 4.0 cm, especially if severe phenotypic features are present such as aortic tortuosity and hypertelorism. On the contrary, women with *TGFBR1* mutations can be subjected to less stringent criteria for surgery in the absence of familial history of aneurysm or drastic increase in the diameter of the aorta (7).

As more genes have been identified, the molecular profile of LDS has been expanded. Currently, this disease is subcategorized into six subtypes depending on the specific gene mutations identified. LDS type 1 patients are denoted by *TGFBR1* mutation, LDS type 2 presents with the *TGFBR2* mutations, LDS type 3 has mutations in the *SMAD3* gene, type 4—*TGFB2*, type 5—*TGFB3* and type 6—*SMAD2* (7) (*Table 2*). All of these genes contribute to the same TGF-β signaling pathway.

TGF-β is a cytokine recognized by the TGFBR receptor

Table 2 LDS types based on molecular profiling.

Type	Gene	% of cases	Diameter at which to operate (cm)
Type 1	*TGFBR1*	20–25	4.0–4.5
Type 2	*TGFBR2*	55–60	4.0–4.5
Type 3	*SMAD3*	5–10	4.0–4.2
Type 4	*TGFB2*	5–10	4.5–5.0
Type 5	*TGFB3*	1–5	5.5
Type 6	*SMAD2*	1–5	5.5

LDS, Loyez-Dietz syndrome.

and SMAD is a downstream effector molecule. Despite working through the common signaling pathway, these mutations have different prevalence rates among patient population. The majority of patients with LDS present with mutations in *TGFBR1* (subtype 1, 20–25% of cases) and *TGFBR2* (subtype 2, 55–60% of cases). This may be explained by a more drastic effect that the mutation of the upstream receptor may have on the overall signaling pathway.

The general surgical treatment recommendation for LDS patients is indicated surgery when the internal aortic diameter is >4.2–4.5 cm determined by the transesophageal echocardiogram or if external diameter is 4.4–4.6 cm shown by the computed tomographic imaging and/or MRI (2). As more knowledge has developed regarding molecular biology of the potential gene mutations involved in each individual subtype, more specific guidelines have been articulated. For instance, patients with LDS types 1, 2, 3 are known to have dissection when the diameter reaches 3.9–4.0 cm (6), whereas patients with LDS type 4 have dissection when the diameter is between 4 and 5 cm (9). Therefore, it is recommended to perform surgery for patients with LDS types 1 and 2 when the diameter is 4 cm (10). Patients with LDS type 3 and mutations in *SMAD3* gene should undergo surgical repair when the ascending aortic size is 4.0–4.2 cm (11). Patients with LDS type 4 are recommended surgery when the diameter is 4.5–5.0 cm (10), whereas patients with LDS types 5 and 6 should follow standard recommendations for surgical repair (*Table 2*).

Additionally, specific recommendations have been made for various LDS types in different age categories. For pediatric patients, the threshold of 4.0 cm should be used for children with a slowly growing aneurysm. Children with severe craniofacial malformations should undergo surgery when the aortic root z-score is >3.0 or if a growth rate greater than 0.5 cm per year is detected (11). However, surgery can be delayed until the size of the annulus is 1.8 cm, which would allow for a simultaneous placement of a valved graft that will accommodate rapid growth. Pediatric patients with mild craniofacial malformations should undergo surgery when the aortic root z-score is greater than 4 or if a growth rate greater than 0.5 cm per year is detected, or if there is significant aortic regurgitation (10,11). For adult patients with LDS types 1–3, surgery is recommended at >4.0 cm in ascending aortic aneurysm and aortic root aneurysm as well as if the aorta is rapidly expanding (0.5 cm over 1 year) (10). Moreover, since adult patients with the LDS type 4 develop dissection with the aortic diameter as low as 4.0 cm (10), monitoring should take place within the 4 cm range and patients should receive surgical repair at the size of 4.5–5.0 cm (12).

EDS

The vascular subtype of EDS is characterized by mutations in *COL3A1*, the gene that encodes collagen, a major component of the blood vessel wall. Since clinical presentation of patients with EDS is very similar to that of MFS and LDS, the precise diagnosis is usually confirmed by sequencing the *COL3A1* gene. Surgical repair recommendations in this case are stringent due the fragile nature of the aortic tissue which can, in some cases, be unworkable (2). However, surgery should be performed in the event of arterial rupture, unstable aneurysms, dissecting aneurysms that affect the aorta or iliac vessels, or when the aortic diameter reaches 4.5–5 cm range (13). Vessel friability is the key factor to be considered intraoperatively in order to decrease morbidity in EDS patients.

ATS

ATS is an autosomal recessive connective tissue disease characterized by mutations in the gene encoding glucose transporter SLC2A10 (14). Very few aortic mutations are recessive. The impaired transport of glucose, which is the main source of metabolic energy in the human body, leads to weakness of the blood vessel wall and causes aneurysmal dilation and focal stenosis (15). Additionally, recent studies in mice have demonstrated that mutations in this gene are associated with an increased production of the reactive oxygen species (ROS) that are known to cause oxidative damage to the aortic tissue (16). The ATS mortality rate is relatively high for younger patients: 40% for children under 5 years old. The severity of this condition is due to

vascular insufficiency that is caused by fragmentation of elastic membrane and fibers (17). A recent study examining phenotypic effects of SLC2A10 in three families implies that TAAD may not be a key feature of ATS as only 3 patients had developed aortic aneurysm and no dissections were reported (18). Despite rare occurrence of TAAD in ATS, surgery recommendations remain standard and repair should be performed when the aortic diameter reaches 5.5 cm (13).

Non-syndromic TAAD

As of now, 30 genes have been identified to contribute to TAAD development, mainly through their impact on the extracellular matrix modifications, TGF-β signaling pathway dysregulation and changes in smooth muscle contraction (*Table 3*) (12). Specific mutations contribute to the severity of TAAD and confer distinct recommendations regarding surgical intervention (*Figure 1*) (12).

TGF-β signaling: TGFBR1 and TGFBR2, TGF-β2 and SMAD3

In addition to their involvement in LDS pathogenicity, *TGFBR1* and *TGFBR2* also contribute to the development of the non-syndromic form of TAAD. Specifically, *TGFBR1* mutations are found in the familial thoracic aortic aneurysm-5 (AAT5) and *TGFBR2* mutation—in the familial thoracic aortic aneurysm-3 (AAT3). The molecular mechanism in both cases involve dysregulation of the TGF-β signaling pathway due to impaired receptor function. For patients with mutation in *TGFBR2*, surgery is recommended when the diameter reaches 4.2 cm. This recommendation applies to both for LDS and FTAAD patients with this mutation (2,19). Additionally, patients carrying mutations in the *TGFBR2* gene are more likely to develop aortic dissection in the absence of significant aortic enlargement as compared to the patients with the *TGFBR1* gene mutations (20).

Similar to TGFBR1 and 2, TGF-β2 and SMAD3, in addition to producing non-syndromic TAA, may also be present in syndromic TAA as part of LDS. They are also involved in the TGF-β signaling where the *TGF-β2* gene encodes the ligand for the TGFB receptor and *SMAD3* gene produces the downstream phosphorylation target for the TGFBR. Patients with these mutations are at high risk of dissection when the aortic diameter is less than 5.0 cm. Therefore, surgical intervention is recommended if the diameter is greater than 4.5 cm, especially if patients have a familial history of aortic dissection, rapid growth, or have been scheduled for aortic valve replacement surgery (20).

Smooth muscle contractile unit: MYH11, ACTA2, MYLK and PRKG1

This group of genes contribute to FTAAD pathogenesis by affecting structure or function of smooth muscle cells. The product of the *MYH11* gene is myosin heavy chain protein, which, together with another smooth muscle protein, actin, produces mechanical force for muscle contraction. Mutations in the *MYH11* gene tend to generate a dominant negative version of the protein and demonstrate an incomplete penetrance. Moreover, the presence of the *MYH11* mutation does not always correlate with the presence of the disease, which suggests that there could be other effectors contributing to the phenotype development, possibly in a synergistic manner (21). Current recommendation for intervention is to undergo surgery when the aortic diameter is between 4.5 and 5.0 cm (21,22).

The *ACTA2* gene encodes alpha smooth muscle actin protein, a transcriptional target of the TGF-β signaling pathway, which is also involved in smooth muscle contraction. To become functional, actin filaments must polymerize with each other via specific amino acid residues. Mutations within the ACTA2 locus that change those amino acids tend to produce a dominant negative protein that is unable to polymerize (23). Since patients with mutations in ACTA2 tend to have aortic dissection at diameter less than 5.0 cm, surgical intervention should be considered when the aortic diameter is between 4.5 and 5.0 cm (23,24).

The product of the *MYLK* gene is myosin light chain kinase, which activates myosin via phosphorylation, allowing for smooth muscle contraction. The disease-causing mutation in this gene produces a fully non-functional protein as it tends to destroy the binding site for calmodulin, a partner necessary for kinase phosphorylation activity (25). Similar to other smooth muscle contractile unit genes, patients with *MYLK* mutations have dissections at an aortic diameter less than 5.0 cm and should undergo surgical intervention when the size is between 4.5 and 5.0 cm (21). However, the fact that mutation in the *MYLK* gene can at times present with ascending aortic dissection with minimal enlargement of the aortic diameter should also be taken into consideration when making recommendations

Table 3 Genes associated with syndromic and non-syndromic thoracic aortic aneurysm and/or dissection, associated vascular characteristics, and size criteria for elective surgical intervention. Reproduced by permission from Brownstein AJ, Ziganshin BA, Kuivaniemi H, *et al.* [2017].

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Non-syndromic FTAAD	Associated disease/ syndrome	Associated clinical characteristics of the vasculature	Ascending aorta size (cm) for surgical intervention	Mode of inheritance	OMIM
ACTA2	Smooth muscle α-actin	Yes	+	+	AAT6 + multisystemic smooth muscle dysfunction + MYMY5	TAAD, early aortic dissection, CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV	4.5–5.0	AD	611788, 613834, 614042
BGN	Biglycan	Yes	+	–	Meester-Loeys syndrome	ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity	Standard	X-linked	300989
COL1A2	Collagen 1 α2 chain	No	+	–	EDS, arthrochalasia type (VIIb) + cardiac valvular type	Borderline aortic root enlargement	Standard	AD + AR	130060, 225320
COL3A1	Collagen 3 α1 chain	Yes	+	–	EDS, vascular type (IV)	TAAD, early aortic dissection, visceral arterial dissection, vessel fragility, IA	5.0	AD	130050
COL5A1	Collagen 5 α1 chain	No	+	–	EDS, classic type (I)	ARD, rupture/dissection of medium sized arteries	Standard	AD	130000
COL5A2	Collagen 5 α2 chain	Partially	+	–	EDS, classic type (II)	ARD	Standard	AD	130000
EFEMP2	Fibulin-4	Yes	+	–	Cutis laxa, AR type Ib	Ascending aortic aneurysms, other arterial aneurysms, arterial tortuosity and stenosis	Standard	AR	614437
ELN	Elastin	No	+	–	Cutis laxa, AD	ARD, ascending aortic aneurysm and dissection, BAV, IA possibly associated with SVAS	Standard	AD	123700, 185500
EMILIN1	Elastin microfibril interface 1	No	+	–	Unidentified CTD	Ascending and descending aortic aneurysm	Standard	AD	Unassigned
FBN1	Fibrillin-1	Yes	+	+	Marfan syndrome	ARD, TAAD, AAA, other arterial aneurysms, pulmonary artery dilatation, arterial tortuosity	5.0	AD	154700
FBN2	Fibrillin-2	No	+	–	Contractural arachnodactyly	Rare ARD and aortic dissection, BAV, PDA	Standard	AD	121050
FLNA	Filamin A	Yes	+	–	Periventricular nodular heterotopia	Aortic dilatation/aneurysms, peripheral arterial dilatation, PDA, IA, BAV	Standard	XLD	300049
FOXE3	Forkhead box 3	Yes	–	+	AAT11	TAAD (primarily type A dissection)	Standard	AD	617349
LOX	Lysyl oxidase	Yes	–	+	AAT10	TAAD, AAA, hepatic artery aneurysm, BAV, CAD	Standard	AD	617168
MAT2A	Methionine adenosyltransferase II alpha	No	–	+	FTAA	Thoracic aortic aneurysms, BAV	Standard	AD	Unassigned

Table 3 (*continued*)

Table 3 (*continued*)

Gene	Protein	Animal model leading to vascular phenotype?	Syndromic TAAD	Non-syndromic FTAAD	Associated disease/ syndrome	Associated clinical characteristics of the vasculature	Ascending aorta size (cm) for surgical intervention	Mode of inheritance	OMIM
MFAP5	Microfibril-associated glycoprotein 2	Partially	–	+	AAT9	ARD, TAAD	Standard	AD	616166
MYH11	Smooth muscle myosin heavy chain	Partially	–	+	AAT4	TAAD, early aortic dissection, PDA, CAD, peripheral vascular occlusive disease, carotid IA	4.5–5.0	AD	132900
MYLK	Myosin light chain kinase	No	–	+	AAT7	TAAD, early aortic dissections	4.5–5.0	AD	613780
NOTCH1	NOTCH1	Partially	–	+	AOVD1	BAV/TAAD	Standard	AD	109730
PRKG1	Type 1 cGMP-dependent protein kinase	No	–	+	AAT8	TAAD, early aortic dissection, AAA, coronary artery aneurysm/ dissection, aortic tortuosity, small vessel CVD	4.5–5.0	AD	615436
SKI	Sloan Kettering proto-oncoprotein	No	+	–	Shprintzen-Goldberg syndrome	ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysms	Standard	AD	182212
SLC2A10	Glucose transporter 10	No	+	–	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/carotid aneurysms and dissections, AAA	Standard	AD	Unassigned
SMAD3	SMAD3	Partially	+	+	LDS type 3	ARD, TAAD, early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissections, IA, BAV	4.0–4.2	AD	613795
SMAD4	SMAD4	Yes	+	–	JP/HHT syndrome	ARD, TAAD, AVMs, IA	Standard	AD	175050
SMAD6	SMAD6	No	–	+	AOV2	BAV/TAA	Standard	AD	602931
TGFB2	TGF-β2	Yes	+	+	LDS type 4	ARD, TAAD, arterial tortuosity, other arterial aneurysms, BAV	4.5–5.0	AD	614816
TGFB3	TGF-β3	No	+	–	LDS type 5	ARD, TAAD, AAA/dissection, other arterial aneurysms, IA/dissection	Standard	AD	615582
TGFBR1	TGF-β receptor type 1	Yes	+	+	LDS type 1 + AAT5	TAAD, early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV	4.0–4.5	AD	609192
TGFBR2	TGF-β receptor type 2	Yes	+	+	LDS type 2 + AAT3	TAAD, early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissection, IA, PDA, BAV	4.0–4.5	AD	610168

EDS, Ehlers-Danlos syndrome; LDS, Loyez-Dietz syndrome; TAAD, thoracic aortic aneurysm and dissection; AD, autosomal dominant; AR, autosomal recessive; CTD, connective tissue disease; JP, juvenile polyposis; HHT, hereditary hemorrhagic telangiectasia; PDA, patent ductus arteriosus; CAD, coronary artery disease; BAV, bicuspid aortic valve; ARD, aortic root dilatation; SVAS, supravalvular aortic stenosis; AAA, abdominal aortic aneurysm; OMIM, Online Mendelian Inheritance in Man.

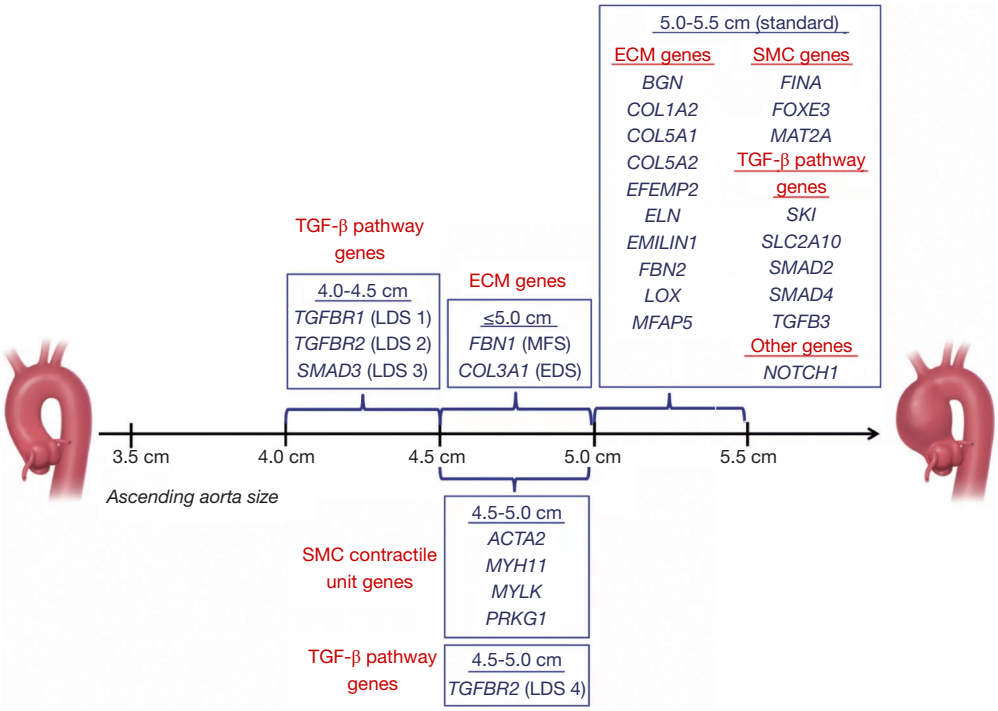

Figure 1 Ascending aorta dimensions for prophylactic surgical intervention. Reproduced by permission from Brownstein AJ, Ziganshin BA, Kuivaniemi H, *et al.* [2017].

for surgical repair (26).

Another gene contributing to non-syndromic TAAD via altering smooth muscle cell contraction is *PRKG1*. This gene encodes the type 1 cGMP-dependent protein kinase that is involved in the process of the smooth muscle relaxation and works by altering smooth muscle contraction (26). Heterozygous mutations in this gene locus are associated with familial thoracic aortic aneurysm-8 (AAT8) and contribute to the loss and fragmentation of elastic fibers, decreased amount of smooth muscle cells, and invasion of the vasa vasorum into the medial layer (26). Surgical repair for patients with the mutations in this gene is normally recommended when the ascending aortic size is 4.5–5.0 cm.

Conclusions

Genetic mutations involving TGF-β signaling pathway, smooth muscle cell function and the structural integrity of the extracellular matrix contribute to TAAD development and progression. The connection between the TAAD heterogeneous molecular genetic profile and the different levels of TAAD severity strongly supports the use of gene sequencing in patient care. We and others have expended on and reported large clinical experience with exome sequencing in thoracic aortic care. Genetic testing should indeed modulate when to operate in thoracic aortic disease. Such testing permits focused, precise, truly personalized thoracic aortic care.

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