

# New insights into the molecular diagnosis and management of heritable thoracic aortic aneurysms and dissections

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## KEY WORDS

aneurysm syndrome, molecular genetic testing, thoracic aortic aneurysms and dissections

## ABSTRACT

Since the identification of the fibrillin-1 gene as the causal gene for Marfan syndrome, our knowledge of molecular genetics and the applicability of genetic testing for heritable thoracic aneurysms and dissections (H-TAD) in clinical practice have increased substantially. Several new syndromes related to H-TAD have been described and the list of mutated genes in syndromal and nonsyndromal H-TAD is rapidly expanding. This knowledge has led to a significant improvement of our insight into the underlying pathophysiology of H-TAD resulting in new opportunities for targeted treatment, as well as in improved risk stratification. Clinicians involved in the care for H-TAD patients require a basic knowledge of the disease entities and need to be correctly informed on the applicability of genetic testing in their patients and families. Gene-tailored treatment and management should now be considered as part of good clinical practice. We provide a systematic overview of genetic H-TAD entities and practical recommendations for genetic testing and patient management.

**Introduction** Our understanding of the pathogenesis of heritable thoracic aneurysms and dissections (H-TAD) has significantly improved over the past decade, which is largely attributable to better insights into underlying genetic defects. This has enabled us to optimize risk stratification and medical guidance of patients and their families. Strategies for molecular genetic testing have reached a hinge point with the introduction in routine diagnostics of high-throughput, next generation sequencing based techniques. Therefore, it is important that clinicians in the field know the indications and limitations of molecular genetic testing. These will be reviewed in this manuscript.

**Etiology and classification** The etiology of H-TAD is complex and heterogeneous. Degenerative aortic disease related to classic cardiovascular risk factors, such as smoking, arterial hypertension, and hyperlipidemia, are the main cause of H-TAD in older patients. In younger patients with no risk factors, other causes, including genetic disease,

should be considered. Genetic aneurismal disease can be categorized in 2 main groups depending on the presence or absence of manifestations in other organ systems, namely, syndromic and nonsyndromic H-TAD and account for less than 5% and 20% of all H-TAD cases, respectively (TABLE 1). Among the known causes of syndromic H-TAD are Marfan syndrome (MFS), Loeys–Dietz syndrome (LDS), and aneurysm–osteoarthritis syndrome (AOS).<sup>1–3</sup> In some patients/families with nonsyndromic H-TAD associated cardiovascular lesions may occur, depending on the underlying gene such as bicuspid aortic valve and/or cerebrovascular disease in case of *ACTA2* mutations, patent ductus arteriosus in case of *MYH11* mutations, or gastro-intestinal disease in case of *MYLK* mutations (TABLE 1).<sup>4–7</sup>

The prototype for syndromic H-TAD is MFS, caused by mutations in the fibrillin-1 (*FBN1*) gene. The diagnosis of MFS is based on the identification of clinical manifestations and may be supplemented with *FBN1* gene sequencing. Cardinal manifestations include dilatation of the aortic

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**TABLE 1** Schematic overview of syndromic and nonsyndromic hereditary thoracic aneurysms and dissections

Disorder	Gene(s)	Main cardiovascular features	Additional clinical features
<b>syndromic H-TAD</b>			
MFS <sup>1,29,30</sup>	<i>FBN1</i>	<b>aortic root aneurysm</b> , aortic dissection, mitral valve prolapse, main pulmonary artery dilatation, ventricular dysfunction	<b>lens luxation</b> , skeletal features (arachnodactyilia, pectus deformity, scoliosis, flat feet, increased armspan, dolichocephalia)
TGFβ-related vasculopathies	LDS <sup>2,14</sup>	<b>aortic root aneurysm</b> , aortic dissection, arterial aneurysms and dissections, <b>arterial tortuosity</b> , mitral valve prolapse, congenital cardiac malformations	<b>bifid uvula/cleft palate, hypertelorism</b> , pectus abnormalities, scoliosis, club feet
	AOS <sup>3,15, 16</sup>	<b>aortic root aneurysm</b> , aortic dissection, arterial aneurysms and dissections, <b>arterial tortuosity</b> , mitral valve prolapse, congenital cardiac malformations	<b>osteoarthritis</b> , soft skin, flat feet, scoliosis, recurrent hernia's, hypertelorism, pectus abnormalities
	<i>TGFβ2</i> <sup>17-19</sup>	<b>aortic root aneurysm</b> , aortic dissection, arterial aneurysms and dissections, <b>arterial tortuosity, mitral valve prolapse</b> , congenital cardiac malformations	club feet, soft translucent skin
	SGS <sup>21,22</sup>	<b>mild aortic root dilatation</b> , mitral valve prolapse	craniosynostosis, distinctive craniofacial features, skeletal changes, neurologic abnormalities, mild-to-moderate intellectual disability
<b>nonsyndromic H-TAD</b> <sup>4,6,7,17,18,24-28,31,32</sup>			
	<i>TGFBR1/2</i> (3%–5%)	<b>thoracic aortic aneurysm/dissection</b>	lack of syndromal features
	<i>ACTA2</i> (10%–14%)	<b>thoracic aortic aneurysm/dissection, BAV</b> cerebrovascular disease, coronary artery disease	lack of marfanoid skeletal features, <b>livedo reticularis, iris flocculi, coronary artery/cerebrovascular disease)</b>
	<i>MYLK</i>	<b>thoracic aortic aneurysm/dissection</b>	gastrointestinal abnormalities
	<i>SMAD3</i> (2%)	intracranial and other arterial aneurysms	
	<i>TGFβ2</i>	<b>mitral valve prolapse</b>	
	<i>PRKG1</i>	<b>thoracic aortic aneurysm/dissection</b> , arterial aneurysms and dissections, arterial tortuosity	
	<i>MYH11</i>	<b>patent ductus arteriosus</b>	

Discriminative features are indicated in bold.

Abbreviations: AOS – aneurysm–osteoarthritis syndrome, BAV – bicuspid aortic valve, H-TAD – hereditary thoracic aneurysms and dissections, LDS – Loeys–Dietz syndrome, MFS – Marfan syndrome, SGS – Shprintzen–Goldberg syndrome

sinus, lens luxation and a combination of additional features defined by the “systemic score”. Dilatation in more distal parts of the aorta occurs in a minority of MFS patients<sup>8-10</sup>; patients with previous type B aortic dissection seem to be at a particularly increased risk, often necessitating recurrent surgery.<sup>11</sup> A recent study from Mimoun et al.<sup>12</sup> demonstrated that dissection in the descending part of the aorta may occur whatever the diameter of the ascending aorta.

In 2004, Mizuguchi et al.<sup>13</sup> identified mutations in the transforming growth factor beta receptor 2 gene (*TGFBR2*) in a large family and 4 additional probands presenting with aortic dilatation and variable additional clinical features reminiscent of a connective tissue disorder, referred to as MFS type 2. In 2005, Loeys et al.<sup>14</sup> published their findings on a large series of patients presenting widespread aggressive aortic disease with rapid growth and early dissections. They observed an increased prevalence of dysmorphic features including hypertelorism and cleft palate/bifid uvula. Patients harbored mutations in either the *TGFBR1* or

*TGFBR2* gene and the disorder was named after the authors (LDS). Patients with LDS may also present arterial tortuosity/aneurysms/dissections outside the aorta necessitating extensive vascular imaging at regular time intervals (TABLE 3).

With the identification of mutations in genes involved in the transforming growth factor β (*TGFβ*) pathway, a new era with regards to our understanding of the pathophysiology and treatment of H-TAD emerged. Mutations in other genes involved in the *TGFβ* pathway (see below) have been identified including *SMAD3* causing AOS, *SMAD4*, the *TGFβ2* ligand *TGFβ2*, and the *TGFβ* repressor *SKI* causing Shprintzen–Goldberg syndrome (SGS).<sup>15-22</sup> In view of the important clinical overlap between these disorders, the term “*TGFβ*-associated vasculopathies” may be preferred over individual syndrome names.

The genetic background of nonsyndromic H-TAD is complex and heterogeneous. Genes involved in syndromic forms may also be encountered in patients with isolated aortic disease,<sup>23-25</sup> emphasizing the fact that the clinical

**TABLE 2** Overview of hereditary thoracic aortic aneurysms and dissections panels available at the Centre for Medical Genetics, Ghent, Belgium

panel 1	<i>FBN1, TGFBR1, TGFBR2, SMAD3, TGFβ2, ACTA2, COL3A1, MYH11, SKI</i>
panel 2	<i>MYLK, SLC2A10, NOTCH1, FBN2, ADAMTS10, FBLN4, FLNA, ELN</i>

spectrum of these disorders is very broad. Other genes involved in nonsyndromic H-TAD include genes encoding the contractile cytoskeletal proteins, smooth muscle  $\alpha$ -actin (*ACTA2*), and myosin heavy chain 11 (*MYH11*), and genes encoding enzymes regulating smooth muscle cell contraction, including *MYLK* (myosin light chain kinase) and *PRKG1* (type I cGMP-dependent protein kinase).<sup>4,7,26-28</sup>

Establishing a correct diagnosis of H-TAD in an individual patient primarily requires detailed clinical evaluation of the proband and family members (see below). Additional molecular genetic testing may be helpful and sometimes even required for confirmation of the specific diagnosis (TABLE 1).

#### Strategy for clinical evaluation and genetic testing

**Clinical evaluation** The absolute prerogative for further clinical/genetic investigations in H-TAD patients is a correct diagnosis of the aneurysm itself, based on careful measurement of the diameter of the aorta, according to appropriate guidelines, with correction for age and body surface area of the patient.<sup>29</sup> Aortic dilatation and aneurysm are defined as a measured diameter of respectively 2 and 3 standard deviations above the predicted diameter for a certain patient and is reported as z-score >2 and z-score >3. In children, growth needs to be taken into account and z-scores >3 have been suggested.<sup>33</sup>

Further investigations will depend on the age and cardiovascular risk profile of the patient.

As mentioned above, consideration of a genetic entity is especially of interest in young subjects with no additional risk factors.

Detailed family history taking, including pedigree drawing and clinical assessment of first-degree relatives, is required to differentiate between familial and isolated forms of H-TAD. Next, careful multidisciplinary clinical evaluation of the proband is undertaken, which will help us in the identification of specific syndromes as reported in TABLE 1.

As H-TAD is a genetically heterogeneous disease with important clinical overlap between known genetic entities, simultaneous testing of multiple genes is often indicated. Until recently, strategies for genetic testing were limited as only sequential analyses of genes was possible and both the time required as the costs for screening of multiple genes were substantial. The need for high-throughput techniques enabling simultaneous testing of several genes was met by the recent development and progress made in the field of the next generation sequencing. Previously, our center reported a mutation detection strategy using parallel sequencing of the *FBN1*, and

*TGFBR-1* and *-2* for the molecular diagnosis of MFS and LDS.<sup>34</sup> In a next stage, we implemented a novel screening strategy allowing simultaneous sequencing of 17 H-TAD-associated genes.

To this purpose, 2 complementary panels of genes were designed (TABLE 2), of which all coding regions and flanking sequences of each of the 17 genes are polymerase-chain reaction amplified in a fully automated fashion under identical reaction conditions in a high-throughput workflow. In the next step, all products are pooled and next generation sequencing using the Nextera protocol (Illumina) is performed on an Illumina MiSeq sequencer. The vast amount of sequence data is then processed by a bioinformatic pipeline including the CLC bio Workbench 6.0 followed by an in-house developed software package for variant interpretation. An in silico analysis of variants is done using Alamut, Polyphen, and SIFT software. The first gene panel comprises *FBN1, TGFBR1/2, SMAD3, TGFβ2, ACTA2, COL3A1, MYH11*, and *SKI*. The second gene panel comprises *MYLK, SLC2A10, NOTCH1, FBN2, ADAMTS10, FBLN4, FLNA*, and *ELN*. It is clear that the development and implementation of these new technologies in the diagnostics of H-TAD leads to a more cost-effective and much more efficient strategy to identify disease causing mutations.

Correct interpretation of the results obtained by molecular genetic testing requires basic knowledge of these different genes and clinical entities – all the more since medical and surgical management may differ according to the underlying diagnosis.

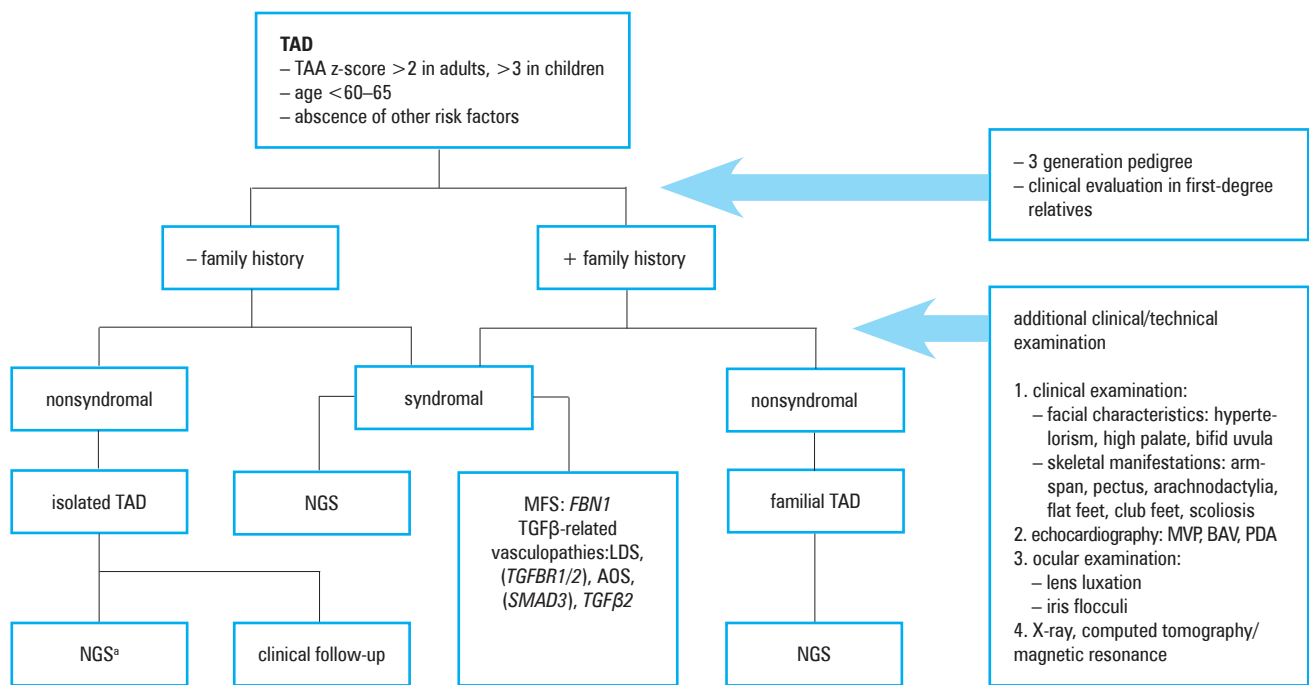
Importantly, the simultaneous sequencing of multiple H-TAD-associated genes is not always justified. In patients presenting with a thoracic aortic aneurysm in combination with lens luxation for instance, MFS is very likely and molecular genetics can be restricted to the *FBN1* gene.

A flow chart illustrating the diagnostic process (clinical and genetic evaluation) of H-TAD patients is provided in FIGURE 1.

**Genes and pathogenesis** In addition to its usefulness in a diagnostic setting, molecular genetics have been very useful in unravelling the complex pathogenesis of thoracic aortic aneurysm formation.

One of the most inspiring findings over the recent years was the observation of the involvement of the TGF $\beta$  pathway in several aortic/arterial aneurysm disorders. The TGF $\beta$  superfamily consists of a number of cytokines that regulate diverse cellular functions, including proliferation, differentiation, and synthesis of a wide array of gene products.

The first heritable connective tissue disorder linked to the TGF $\beta$  pathway was MFS. The underlying pathogenesis of aneurysm formation in MFS was initially considered to be a consequence of inherent structural weakness of the tissues due to structurally abnormal fibrillin-1 fibers.



**FIGURE 1** Flow chart illustrating the diagnostic process (clinical and genetic evaluation) of patients with thoracic aortic aneurysm. Abbreviations: MVP – mitral valve prolapse, NGS – next generation sequencing, PDA – persistent ductus arteriosus, TAA – thoracic aortic aneurysm, TAD – thoracic aneurysms and dissections, TGF $\beta$  – transforming growth factor  $\beta$ , others – see **TABLE 1 a** for isolated TAD it has to be evaluated case per case whether NGS is indicated

Recent developments have changed this insight and it is now recognized that fibrillin-1 containing microfibrils also play an important functional role in the complex TGF $\beta$  pathway (**FIGURE 2**). TGF $\beta$  is secreted from cells as part of a large latent complex (TGF $\beta$  bound to its latency associated peptide and latent TGF $\beta$  binding protein [LTBP]) that binds to extracellular matrix proteins including fibrillin-1. In the past, it was assumed that fibrillin-1 deficiency diminishes TGF $\beta$  sequestration in the matrix, thereby leading to upregulation of TGF $\beta$  signaling. However, recent studies in a specific mouse model – the H1 $\Delta$  MFS model, in which the LTBP binding region is deleted, assuming to yield excessive latent TGF $\beta$  activation – showed none of the clinical features of MFS.<sup>35</sup> Consequently, it was hypothesized that mesenchymal cells, such as fibroblasts or smooth muscle cells, can detect the defective extracellular matrix, generate active TGF $\beta$  and produce the required activators of latent TGF $\beta$  in order to repair the extracellular matrix.<sup>36</sup> Upon activation, TGF $\beta$  stimulates its cell surface receptors, TGF $\beta$  receptor type 1 and type 2 with subsequent activation of the downstream effectors (**FIGURE 2**).

Additional evidence for the involvement of the TGF $\beta$  pathway in aneurysmal disease came from the findings that mutations in several genes that encode different components of the pathway result in aneurysm conditions that have undeniable clinical overlap with MFS. As previously mentioned, these conditions can be grouped under the term “TGF $\beta$ -related vasculopathies”. First, mutations in the TGF $\beta$  receptor 1 and 2 genes (*TGFBR1* and *TGFBR2*) were identified in LDS. In 2011, mutations in the *SMAD3* gene were identified in patients with a very similar phenotype, but also presenting osteoarthritis, hence the name “aneurysm–osteoarthritis syndrome”. Soon thereafter, a family with juvenile polyposis associated with aortopathy and mitral valve disease caused

by *SMAD4* mutations was reported,<sup>20</sup> and mutations in the TGF $\beta$ 2 ligand were identified in several families displaying a very similar phenotype.<sup>17-19</sup> Finally, very recently mutations in the TGF $\beta$  repressor *SKI* were identified as the genetic cause for Shprintzen–Goldberg syndrome (SGS).<sup>21,22</sup>

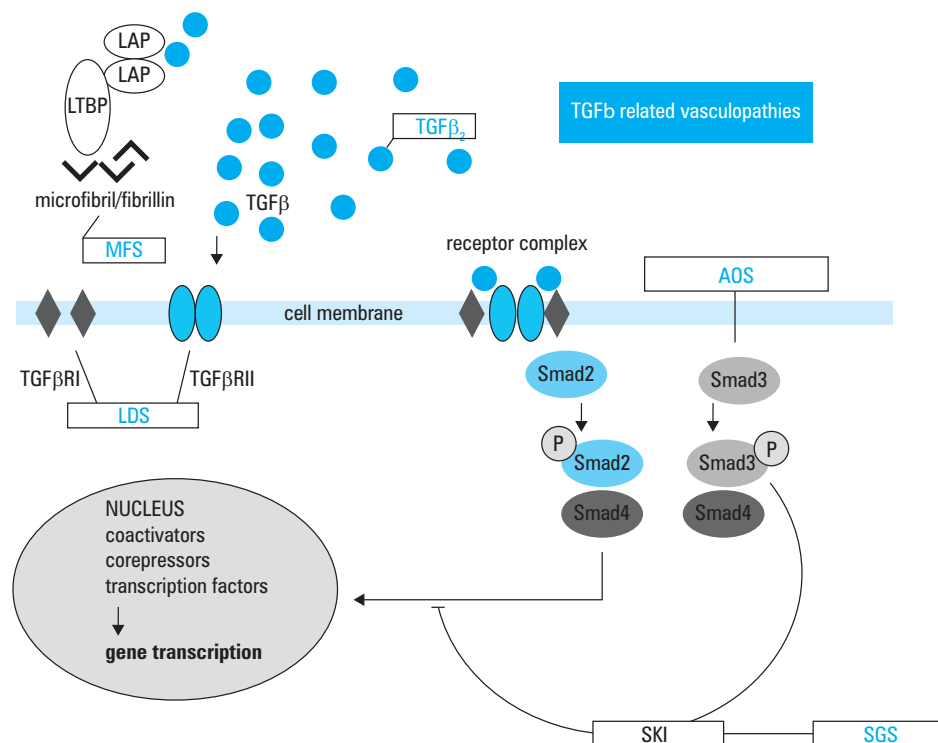
In human aortic specimens of patients with nonsyndromic H-TAD, caused by mutations in *ACTA2* and *MYH11* (encoding components of the smooth muscle cell apparatus), increased TGF $\beta$  signaling has also been reported. For *MYLK* and *PRKG1* (encoding proteins regulating smooth muscle cell contraction), this association still needs to be investigated. Evidence exists that the TGF $\beta$  signaling pathway, including the TGF $\beta$  receptors and downstream effectors, controls the contractile cytoskeleton.<sup>37,38</sup> However, further research is warranted to explore the exact mechanisms.

#### Gene-tailored follow-up and management in H-TAD

A schematic overview of the medical management is provided in **TABLE 3**.

**Imaging studies** Confirmation of the exact diagnosis in the proband facilitates the set-up of a personalized strategy for follow-up and treatment in the patient and his/her family (**TABLE 3**). Since the clinical manifestation of the disease is age dependent and may progress subclinically until later in life, lifelong follow-up is required in all mutation-carriers, even if aortic diameters are normal upon repeated measurements. Importantly, clinical monitoring and follow-up with cardiovascular imaging is also warranted in family members of H-TAD patients in whom no causal mutation was identified since familial clustering is observed in more than 20% of H-TAD cases.<sup>39,40</sup>

Echocardiography is the primary imaging tool for evaluation and follow-up of the diameters of



**FIGURE 2** The TGF $\beta$  pathway and related vasculopathies. Schematic and abbreviated overview of the TGF $\beta$  signalling pathway with indication of aneurismal diseases linked to it. Following its release from the extracellular matrix, TGF $\beta$  binds to its type II cell surface receptor (TGF $\beta$ RII), which recruits and phosphorylates the type I receptor (TGF $\beta$ RI). TGF $\beta$ RI then recruits and phosphorylates Smad2 and/or Smad3. These P-Smads then bind to the common Smad (co-Smad) Smad4 to form a heterodimeric complex. This complex enters the cell nucleus where it acts as a transcription factor for various TGF $\beta$ -dependent genes, such as connective tissue growth factor, plasminogen activator inhibitor-1, and multiple collagens. *SKI* inhibits the TGF $\beta$  pathway at several levels. Abbreviations: LAP – latency associated peptide, LTBP – latent TGF $\beta$ -binding protein, P – phosphorylated, others – see TABLE 1 and FIGURE 1

the aortic root and ascending aorta. Computed tomography (CT) or magnetic resonance angiography (MRA) can be used in case of insufficient visualization of the ascending aorta by echocardiography. The imaging study should be repeated in all patients 6 months after the initial diagnosis to assess evolutionary changes. Further follow-up is guided by the diameter, evolution, underlying diagnosis, and family history. Stable diameters <45mm in patients with MFS or isolated thoracic aortic aneurysm and no family history for dissection require yearly follow-up. Bi-annual controls are recommended in all other cases (TABLE 3).

Upon initial diagnosis, imaging of the entire aorta and side branches (“head-to-pelvis” study) should be performed in order to detect aneurysms at other sites and/or arterial tortuosity. Regular extensive vascular imaging from head to pelvis is recommended in patients with a *TGFBR1/2*, *SMAD3* and *TGF $\beta$ 2* mutation. Evaluation for coronary artery- and cerebrovascular disease can be considered in patients with an *ACTA2* mutation.<sup>41</sup>

**Medical treatment** The initial medical approach of H-TAD patients should include reduction of cardiovascular risk factors, such as blood pressure control, smoking cessation and optimization of the lipid profile. Central stimulating drugs,

such as cocaine, amphetamine and derivatives are known triggers for aortic dissection and should therefore be avoided.<sup>42,43</sup>

Medical treatment with a  $\beta$ -blocking agent in MFS reduces the progression of aortic dilatation in most patients through reduction of wall shear stress in the aorta and is used as a standard therapy in MFS patients.<sup>44</sup> As mentioned above, it has been demonstrated that the TGF $\beta$  pathway plays an important role in aneurismal disease. This knowledge has led to the search for strategies interfering with TGF $\beta$  signalization. From studies in nephrology, it was documented that losartan, an angiotensin receptor blocking agent, inhibits TGF $\beta$  signaling. Treatment with losartan in MFS mice showed significant reduction of aortic root aneurysm progression as well as rescue of the aortic wall architecture compared to treatment with either placebo or propranolol.<sup>45</sup> Several studies demonstrated a more beneficial effect of the combined treatment with losartan and a  $\beta$ -blocking agent on aortic root dilatation rate compared to a  $\beta$ -blocking agent alone.<sup>46-48</sup> Furthermore, losartan in monotherapy also seems to decrease indexed aortic diameters and aortic root z-scores as demonstrated in a small pediatric population.<sup>49</sup> Prior to changing treatment guidelines the results of these studies need to be confirmed

**TABLE 3** Overview of suggested treatment and follow-up in hereditary thoracic aortic aneurysm and dissections

Disorder/gene(s)	Treatment	Follow-up
<b>syndromic H-TAD</b>		
MFS <sup>1,29,30</sup>	$\beta$ -blocking agents, losartan surgery when AoD >50mm or >45 mm in case of familial history of dissection or rapid growth (>2 mm/y) or severe AR or MR	echocardiography q1y when diameter <45 mm q6m in all other cases MRAq5y when aortic diameters outside the sinuses of Valsalva are normal, MRAq1y in all other cases
TGF $\beta$ -related vasculopathies	LDS <sup>2,14</sup>	no trials yet – adopt medical treatment from MFS for LDS surgery when AoD >42–45 mm
	aneurysm–osteoarthritis syndrome <sup>3,15,16</sup>	
	TGF $\beta$ 2 <sup>17–19</sup>	
<b>nonsyndromic H-TAD</b>		
TGFBR1/2, ACTA2, MYLK, SMAD3, TGF $\beta$ 2, PRKG1, MYH11 <sup>4,6,7,17,18,24–28,31,32</sup>	no trials yet – adopt from MFS	same as in MFS consider coronary/cerebrovascular imaging in ACTA2 mutation carriers

Abbreviations: AoD – aortic root diameter, AR – aortic regurgitation, MR – mitral regurgitation, MRA – magnetic resonance angiography, others – see **TABLE 1** and **FIGURE 1**

in large double-blind randomized controlled trials. A double-blind randomized controlled trial comparing the effect of atenolol therapy with that of losartan therapy on the rate of aortic root growth is currently underway.<sup>50</sup>

**Surgery** It is beyond any doubt that elective surgical aortic root replacement leads to better survival in patients with genetic aortic disease. If the function and anatomy of the aortic valve are acceptable, valve sparing replacement of the aortic root (David procedure) is preferred over a Bentall procedure (simultaneous replacement of the aortic valve and root).<sup>51</sup>

It has been demonstrated that the risk for dissection or rupture for thoracic aortic aneurysms of nondegenerative origin rises at lower diameters when compared to degenerative aortic disease. Accordingly, the threshold for surgery of the aortic root is lower than the conventional 55 mm. Indeed, the conventional surgical indication for aortic root replacement in MFS according to the European Society of Cardiology guidelines on Grown-up Congenital Heart Disease and on Valvular Heart Disease, is an aortic diameter-measured at the sinuses of Valsalva – of 50 mm or more. This threshold is reduced to 45–46 mm in case of a positive family history of aortic dissection, in case of a rapid growth of the aorta (>2 mm/y), severe aortic and/or mitral valve regurgitation and/or in case of desire of pregnancy.<sup>52,53</sup> In certain other syndromic and nonsyndromic H-TAD entities, aortic dissection may occur at even smaller diameters, which requires an adjusted treatment policy. Current guidelines of the American College of Cardiology recommend prophylactic surgery in patients with a mutation in *TGFBR1* or *TGFBR2* (as well as patients with LDS as nonsyndromic H-TAD), when the diameter of the ascending aorta reaches 42 mm measured by echocardiography or 44–46 mm on CT or MRA imaging.<sup>41,54</sup> Patients with a mutation in *ACTA2*, *MYH11*, *MYLK*, *TGF $\beta$ 2* and *SMAD3* can dissect

at a diameter <50 mm.<sup>4,6,7,15,18,25,27,41,54</sup> There are no clear guidelines concerning the indications for prophylactic surgery in these patients. Prophylactic surgery may be considered if the diameter is above 45 mm in nonsyndromic H-TAD patients with a familial history of aortic dissection at minimal dilatation of the thoracic aorta (<50 mm), in case of rapid growth of the aorta, and in patients who need surgery for aortic valve repair or replacement.<sup>41,53,54</sup>

**Conclusion** In the current era of improved availability of high-throughput molecular genetic techniques, knowledge of the indications and limitations for these tests in daily clinical practice is increasingly important. In the case of H-TAD, additional genetic testing may be helpful for confirmation of the correct diagnosis. Since follow-up and treatment of patients may be adapted according to the underlying condition, clinicians dealing with these patients should acquire this knowledge. Close collaboration between cardiovascular surgeons, cardiologists and clinical geneticists is strongly recommended in the care of these patients and families. In view of the rarity of hereditary H-TAD current guidelines are often based on small studies and expert opinions. Pooling of clinical and molecular data is required in order to develop evidence based guidelines.

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# Postępy diagnostyki molekularnej i leczenia dziedzicznych tętniaków i rozwarstwień aorty piersiowej

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## SŁOWA KLUCZOWE

molekularne testy genetyczne, tętniaki i rozwarstwienia aorty piersiowej, zespół tętniaka

## STRESZCZENIE

Od czasu zidentyfikowania genu fibryliny-1 jako odpowiedzialnego za wystąpienie zespołu Marfana znaczącemu poszerzeniu uległa wiedza o genetyce molekularnej dziedzicznych tętniaków i rozwarstwień aorty piersiowej (*heritable thoracic aneurysms and dissections* – H-TAD), jak również wskazania do badań genetycznych w praktyce klinicznej. Opisano kilka nowych zespołów związanych z H-TAD, a lista zmutowanych genów w postaci zespołowej i niezespołowej H-TAD szybko rośnie. Ta wiedza doprowadziła do lepszego zrozumienia patofizjologii H-TAD, a co za tym idzie – do nowych możliwości leczenia celowanego i do lepszej stratyfikacji ryzyka. Lekarze opiekujący się chorymi z H-TAD potrzebują podstawowej wiedzy o jednostkach chorobowych oraz ścisłych informacji o zastosowaniu badań genetycznych u pacjentów i ich rodzin. Za część dobrej praktyki klinicznej należy obecnie uważać leczenie i postępowanie dopasowane do podłoża genetycznego. W niniejszej pracy przedstawiono systematyczny opis poszczególnych postaci H-TAD oraz praktyczne zalecenia dotyczące badań genetycznych i postępowania z chorymi.

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