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*Review*

# Genetics of Heritable Thoracic Aortic Disease

**Efstathios Papatheodorou [1,2,3], Dimitrios Degiannis [3,4] and Aris Anastasakis [1,3,*]**

1 Unit of Inherited and Rare Cardiovascular Diseases, Onassis Cardiac Surgery Center, Siggrou Avenue 356, Kallithea, 17674 Athens, Greece; stathis.pap2@gmail.com
2 Molecular and Clinical Sciences Research Institute, St George's University of London, London SW17 0RE, UK
3 Greek National Network for Precision Medicine in Cardiology and Prevention of Sudden Cardiac Death in the Young, 17674 Kallithea, Greece
4 Molecular Immunopathology and Histocompatibility Unit, Division of Genetics, Onassis Cardiac Surgery Center, 17674 Athens, Greece; degianis@ocsc.gr
* Correspondence: anastasakisaris@gmail.com; Tel.: +(30)-2109493862

**Abstract:** Genetic testing plays an increasing diagnostic and prognostic role in the management of patients with heritable thoracic aortic disease (HTAD). The identification of a specific variant can establish or confirm the diagnosis of syndromic HTAD, dictate extensive evaluation of the arterial tree in HTAD with known distal vasculature involvement and justify closer follow-up and earlier surgical intervention in HTAD with high risk of dissection of minimal or normal aortic size. Evolving phenotype–genotype correlations lead us towards more precise and individualized management and treatment of patients with HTAD. In this review, we present the latest evidence regarding the role of genetics in patients with HTAD.

**Keywords:** aortopathy; bicuspid aortic valve; familial thoracic aneurysm; Marfan syndrome; Loeys–Dietz syndrome; aortic dissection; heritable thoracic aortic disease



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## 1. Introduction

Over the last two decades, genetic developments have significantly improved our understanding of heritable thoracic aortic disease (HTAD). The identification of new syndromes [1] and novel candidate genes [2] has changed the paradigm in the diagnostic evaluation of these patients. Specific genotype–phenotype correlations continue to emerge, promising a more precise and effective approach in the treatment of HTAD [3–5]. The goal of this review is to inform clinicians about the value and effect of genetics in the diagnosis, management, surveillance, risk stratification and familial evaluation of patients with HTAD.

### *1.1. Classification*

The presence of syndromic systemic features and a positive family history of aortic aneurysm or dissection are the key elements that determine the classification and thus the management of patients with HTAD. Thoracic aortic disease at a younger age occurs more often in the context of a genetic syndrome.

Syndromic HTAD (sHTAD) typically exhibits a multiorgan phenotype and is caused by genetic variants that are involved in the transforming growth factor-β (TGF-β) pathway and genes encoding extracellular matrix proteins [2]. Nonsyndromic HTAD (nsHTAD) is typically characterized by isolated thoracic aortic aneurysm or dissection, without any recognizable systemic features, and can be familial in up to 20–25% of cases. A genetic defect, mainly in genes of the contractile apparatus, may be identified in up to 20% of familial nsHTAD [6].

### *1.2. Diagnostic Workup*

Only 5% of patients present with alarming symptoms before an acute aortic event [7]. Most patients are usually diagnosed following a major complication, e.g., an aortic dissection, as part of familial evaluation, or based on characteristic physical findings suggestive of a specific syndrome.

Physical examination and history are vital in the assessment of patients with HTAD. The physician should be able to recognize any systemic features such as specific facial characteristics, skin lesions or skeletal manifestations, which suggest the presence of sHTAD. A detailed personal history should be obtained including history of recurrent pneumothorax, history of eye operations or ocular conditions. Ophthalmology evaluation, including slit-lamp examination, should be offered in all patients with a suspicion of Marfan syndrome (MFS). The reduced penetrance or incomplete expression and the phenotypic overlap and variability of hereditary aortopathy consist of major challenges, which make essential a multidisciplinary diagnostic approach.

## 2. Syndromic HTAD

### *2.1. Marfan Syndrome*

Marfan syndrome (MFS; Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, USA OMIM #154700, Orphanet rare disease nomenclature, French National Institute for Health and Medical Research, Paris, France ORPHA:558) is the most common syndromic aortopathy. It is characterized by aortic dilatation, ectopia lentis and skeletal abnormalities. MFS is associated with variants in the *FBN1* gene, encoding the extracellular matrix protein called fibrillin-1 [8]. Other genes, typically not causing any ocular involvement, also can lead to a phenotype resembling MFS [2].

The diagnosis of MFS is based on the revised 2010 Ghent criteria [8]. A pathogenic *FBN1* variant, along with ectopia lentis or enlarged aortic root (Z score $\geq$2 that corresponds to a diameter $\geq$2 standard deviations above normal, according to established aortic nomograms [9]), establishes the diagnosis. In the absence of a pathogenic *FBN1* variant, the diagnosis can be made in patients with aortic dilatation (Z score $\geq$2) and ectopia lentis or a systemic score $\geq$7 (encompassing systemic features suggestive of MFS) [8]. In patients with a family history of MFS, the diagnosis can be made in the presence of $\geq$1 of the following criteria: (a) ectopia lentis, (b) systemic score $\geq$7, (c) aortic root enlargement with Z-score $\geq$2 in patients >20 years and (d) Z score $\geq$3 in patients <20 years [8].

Over half of MFS patients are diagnosed after adolescence (median age of diagnosis is 19 years) [10], and the first cardiovascular procedure occurs at average at the age of 36 years [11]. Aortic dilatation typically occurs at the level of the sinuses of Valsalva (SoV), but aortic dilatation or dissection can occur at every level of the aorta [12]. Most patients with MFS are diagnosed before severe cardiac complications occur. This is particularly relevant, as MFS patients appear to have better survival rates with appropriate medical management and when undergoing prophylactic elective surgery (complication rate of 1.5% vs. 11.7% of urgent procedures) [13]. Established clinical factors of high risk are: (a) aortic diameter at the SoV $\geq$5 cm, (b) rapid increase in aortic dilatation ($\geq$3 mm per year), (c) family history of aortic dissection at a low aortic size, (d) progressive aortic regurgitation, (e) personal history of spontaneous vascular dissection and (f) desire for pregnancy [14,15]. Therapy is based on optimal blood pressure control, and medical management includes beta-blockers or angiotensin-1 antagonists (losartan) [14,16,17].

Most *FBN1* variants are missense, having in most cases a dominant-negative effect (DN-*FBN1*), resulting in a disorganized extracellular matrix incorporating both mutated and nonmutated fibrillin-1 proteins. Haploinsufficient *FBN1* variants (HI-*FBN1*), leading to reduced production of normal fibrillin-1 protein, are also well documented in up to 35% of MFS patients [5]. It has been reported that patients with HI-*FBN1* are at increased risk of aortic dissection and death, have more rapid aortic root and ascending aorta dilation rates, manifest more severe cardiovascular complications and respond better to losartan

therapy than patients with DN-*FBN1* variants [5,18–21]. In a large cohort of MFS patients, premature termination codon variants leading to haploinsufficiency were associated with an 83% lifelong aortic event risk during life, shorter life expectancy, severe scoliosis and relatively lower rates of ectopia lentis surgery [22].

Specific DN-*FBN1* variants have been linked with a similarly severe phenotype compared to *HI-FBN1* variants. MFS patients with in-frame DN-*FBN1* variants leading to a cysteine loss at the level of fibrillin-1 showed 73% lifelong risk of aortic dissection or surgery, high rates of severe scoliosis and ectopia lentis surgery. In-frame variants leading to a neutral cysteine effect were associated with an intermediate phenotype (61% of lifelong aortic event risk). In-frame variants leading to cysteine gain were associated with a better cardiovascular profile (29% of lifelong aortic event risk) and lower rates of severe scoliosis but high risk for ectopia lentis surgery [22]. Takeda et al. identified deleterious high-risk variants among DN-*FBN1* Japanese patients, in-specific variants affecting or creating cysteine residues and in-frame deletion variants in exons 25–36 and 43–49 [19].

Furthermore, despite a greater frequency of surgery and type B aortic dissections in MFS patients harboring HI-*FBN1* variants, all type A dissections that occurred at an aortic root diameter <50 mm were DN-*FBN1* variants in a cohort of 954 MFS patients followed for a mean 9.1 years [23].

### *2.2. Loeys–Dietz Syndrome*

Loeys–Dietz syndrome (LDS, ORPHA:60030) is characterized by the combination of arterial tortuosity with ascending aortic aneurysm/dissection, also involving the distal aorta and branching arteries, hypertelorism and bifid uvula or cleft palate. It was first described in 2005 as a novel autosomal dominant syndromic aortopathy [1]. Since 2005, loss-of-function variants in six genes have been linked to LDS (*TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2* and *TGFB3*), all of which are involved in the TGF-β signaling pathway [4].

LDS has been originally associated with a very aggressive natural history, probably reflecting a selection bias in the first series of patients. Aortic dissection in young patients (mean age at death of 26 years), very high incidence of pregnancy-related complications and aortic dissections at only mildly increased or even much normal aortic dimensions have been reported [1]. Current American Heart Association/American College of Cardiology guidelines suggest an aggressive approach with prophylactic surgery in aortic size ≥42 mm in all patients with LDS [24]. Recent European Society of Cardiology (ESC) guidelines suggest surgery in patients with *TGFBR1* or *TGFBR2* pathogenic variants with maximal aortic sinus diameter ≥45 mm [15]. Although there is no scientific evidence published to date, drug treatment with beta-blockers and/or angiotensin blockade and optimal antihypertensive management is thought to improve prognosis in LDS patients in a similar fashion to MFS patients. Extensive and distal vascular involvement in LDS patients warrants regular and more extensive imaging of the arterial tree (from head to pelvis).

#### 2.2.1. LDS Caused by Pathogenic Variants in TGFBR1 (OMIM #609192) and in TGFBR2 (OMIM #610168)

Most recent data from the biggest cohort to date, consisting of 441 patients with *TGFBR1* and *TGFBR2* variants from 228 families, showed a relatively more favorable overall clinical profile than previously reported and provided very important genotype–phenotype information [4]. No differences in survival or prevalence of syndromic characteristics between *TGFBR1* and *TGFBR2* carriers were identified.

The investigators identified a subgroup of female patients with a *TGFBR2* variant, marked systemic features and low body surface area who exhibited aortic dissection in aortic sizes <45 mm. Hypertelorism, aortic tortuosity and wide scars were significantly associated with aortic dissection in this cohort and were present in all women with aortic dissection and minimal aortic enlargement or pregnancy-related dissections. In a considerable percentage of patients that had surgery for an aortic root aneurysm (10%), dissection of the ascending aorta occurred during follow-up. Therefore, in patients with *TGFBR1*

or *TGBR2* variants, replacement of both the aortic root and the ascending aorta when an indication for surgery exists should be considered.

#### 2.2.2. LDS Caused by Pathogenic Variants in SMAD3 (OMIM #613795)

Variants in *SMAD3* cause a type of LDS also known as aneurysm–osteoarthritis syndrome, which is characterized by arterial tortuosity, aneurysms and dissection, as well as early-onset osteoarthritis [25–27]. Aside from osteoarthritis-related symptoms, which often may be missed if there is no high clinical suspicion [6], patients with *SMAD3* variants present with fewer and milder syndromic features compared to the other types of LDS or MFS. This possibly leads to a belated diagnosis, with the majority of *SMAD3* variant carriers presenting with type A dissections.

In contrast to *TGFBR1* and *TGFBR2*, patients with *SMAD3* variants show a relatively later onset of dilatation or dissection. Aortic events are extremely rare in children or adolescents [3,28]. A recent study indicated that missense variants in the region encoding the MAD homology 2 (MH2) domain may lead to a lower median age of the first aortic event compared with patients with haploinsufficient variants [3]. Aortic dissections typically occur with prior aortic root enlargement. In the largest series of patients with *SMAD3* variants to date, dissections occurred at root diameter from 43 mm to 66 mm, with the majority of dissections or elective surgical repair happening in aortic root diameters of 50 mm or greater [3].

#### 2.2.3. LDS Caused by Pathogenic Variants in TGFB2 (OMIM #614816) and SMAD2 or TGFB3 (OMIM #615582)

These variants are found in 10–15% of LDS cases and typically show milder phenotypes and reduced penetrance [27,29]. Aortic dissection in lower-than-standard surgical thresholds of 50 mm has been reported in LDS patients with *TGFB2* variants [30], indicating a possible intermediate risk. A more conservative approach regarding aortic surgery following standard aortic size thresholds is reasonable in patients with *SMAD2* or *TGFB3* variants until new data emerge [2].

### *2.3. Rare Syndromic HTAD*

#### 2.3.1. Vascular Ehlers–Danlos Syndrome (vEDS; OMIM #130050)

It is a rare autosomal dominant syndromic HTAD caused by genetic defects in the *COL3A1* gene. Rarely, vEDS can be caused by specific arginine-to-cysteine substitution variants in the *COL1A1* gene. The syndrome is characterized by arterial, uterine or bowel ruptures, skin translucency with visible veins and easy bruising and characteristic facial features (thin pinched nose, prominent eyes and lobeless ears, lack of subcutaneous fat). Diagnosis is established using the 2017 International Classification of the Ehlers–Danlos syndrome [31], which updated the earlier nosology of Villefranche [32]. Men seem to have a poorer prognosis than women (median survival age of 46 $\pm$ 1.8 years vs. 54 $\pm$ 2.5 years) [33]. Surveillance may include periodic arterial screening.

Genetic testing is highly specific and sensitive for vEDS, revealing a genetic defect in 95% of cases [34]. Lethal arterial events in classic (nonvascular) Ehlers–Danlos syndrome (EDS) caused by *COL5A1* or *COL1A1* variants have also been reported [35]. Identification of a pathogenic variant establishes the diagnosis [32]. The clinical phenotype and prognosis of vEDS may be influenced by the type of *COL3A1* variant. Patients heterozygous for "null" *COL3A1* variants, leading to loss of the stable mRNA from one *COL3A1* allele, show late-onset disease, reduced penetrance, solely vascular events and longest survival compared to missense and splicing variants [33,36–38]. Glycine substitutions, splice-site and in-frame insertions/deletions bear the poorer prognosis leading to earlier complications [39].

Although aortic dissection can occur at normal aortic sizes in up to 33% of patients [40], aortic surgery is not usually recommended due to the high rate of intraoperative mortality caused by extreme fragility of the vessel walls. Surgery is usually performed urgently to treat potentially life-threatening complications. Endovascular repair with coil embolization

has shown promising results in selected cases of ruptured pseudoaneurysms, visceral aneurysms and carotid-cavernous fistulas. A multicenter, randomized and blinded open trial study showed significantly lower arterial events (rupture or dissection) in vEDS patients receiving celiprolol, a β(1)-adrenoceptor antagonist with a β(2)-adrenoceptor agonist action, compared to controls [41]. Encouraging reports from animal models and an observational study in favor of celiprolol have been published since; however, no randomized prospective trials exist to date [38,42].

#### 2.3.2. Meester–Loeys Syndrome (MRLS; OMIM #300989)

Loss-of-function variants in the X-linked biglycan gene *(BGN)* have been described in five families with syndromic features overlapping with those of LDS and MFS patients. It is characterized by early-onset aneurysms of the aortic root or ascending aorta (as early as age 1) and aortic dissection (earliest at the age of 15 at an aortic size of 45 mm at the SoV) in male probands. Distal aneurysms in the brain have been detected in one patient. Female patients showed a relatively milder phenotype [43].

#### 2.3.3. Filamin A-Related HTAD

Pathogenic variants in the X-linked *filamin A* (*FLNA*) gene, encoding an actin-binding protein that regulates the cytoskeleton and cell motility, cause the brain malformation periventricular heterotopia (PVNH; OMIM #300049, ORPHA:82004), which may also occur in association with EDS features [44]. Neurological symptoms include mainly seizures and dyslexia. Chen et al. reported on the largest series to date of 114 patients, with loss-of-function *FLNA* pathogenic variants and found aortic dilatation in 18.4% of the patients [45]. Aortic rupture occurred in a 41-year-old male patient at an aortic root size of 42 mm. Pulmonary artery dilatation and aneurysms of other vessels (in the subclavian, middle cerebral and internal carotid arteries, as well as in the abdominal aorta) were common.

#### 2.3.4. LOX-Related HTAD

Loss-of-function variants in the *LOX* gene, encoding a lysyl oxidase involved in the remodeling of the extracellular matrix, have been shown to predispose to aortic root and fusiform aneurysms, involving both the aortic root and ascending aorta [46,47]. These patients exhibit some overlapping syndromic MFS features, without, however, fulfilling the Ghent criteria. No cases of aortic dissection in minimal aortic dimensions have been reported to date. Presence of a bicuspid aortic valve (BAV) has been found in up to 15% of *LOX* carriers [46].

#### 2.3.5. Gorlin–Chaudhry–Moss Syndrome (GCMS; OMIM #612289, ORPHA:2095)

Recently, four case reports of aortic dilatation have been reported in patients with GCMS, including a 45-year-old female patient who presented with aortic dissection at an aortic size of 51 mm [48–50]. The syndrome is caused by variants in the *SLC25A24* gene and is characterized by craniofacial dysostosis, hypertrichosis, underdeveloped genitalia, ocular and dental anomalies.

#### 2.3.6. Shprintzen–Goldberg Craniosynostosis Syndrome (SGS; OMIM #182212, ORPHA:2462)

Pathogenic variants in the *SKI* gene, coding a protein that regulates the TGF-β signaling pathway, cause a hereditary syndromic aortopathy, phenotypically overlapping with MFS and LDS, characterized by craniosynostosis, marfanoid habitus, intellectual disability, camptodactyly and typical facial dysmorphism [51]. Infantile hypotonia, early developmental delay and intellectual disability are distinct features of the syndrome. Aortic dilatation is generally restricted to the aortic root, and a more benign course than MFS and LDS has been described [52].

#### 2.3.7. Arterial Tortuosity Syndrome (ATORS; OMIM #208050, ORPHA:3342)

Pathogenic variants in the *SLC2A10* gene, coding the protein GLUT10 that regulates the TGF-β signaling pathway, lead to ATORS. It is characterized by widespread arterial involvement with elongation, tortuosity and aneurysms of the large and middle-sized arteries along with craniofacial, skin and ocular manifestations [53]. Cardiovascular findings also include aortic coarctation, abnormal implantation of the aortic branches, pulmonary stenosis and aortic stenosis. Patients with ATORS are at higher risk of ischemic events. Aggressive aortic root aneurysm formation even in infancy and aortic dimensions up to 60 mm has been reported; however, there have been no reports of aortic dissection to date [54].

#### 2.3.8. LTBP3-Related HTAD

The *LTBP3* gene encodes an extracellular matrix protein regulating the TGF-β signaling pathway in a latent state. Homozygous loss-of-function pathogenic variants in the *LTBP3* gene have been associated with dental anomalies and short stature (DASS) syndrome (OMIM #601216). Guo et al. reported segregation of compound heterozygous or homozygous *LTBP3* variants in two families with DASS and thoracic aortic disease [55]. The affected individuals also manifested arterial involvement, including abdominal aortic aneurysms and multiple visceral and peripheral arterial aneurysms as well as mitral valve prolapse. Zhu et al. recently reported another compound heterozygous patient with DASS and aortic dissection at the age of 42 and an aortic sinus size of 53 mm [56].

Monoallelic *LTBP3* variants appear to be involved in nsHTAD [55,56]. Guo et al. showed that relatives with heterozygous *LTBP3* variants presented with late-onset aortic aneurysms and dissection without any systemic features. Additionally, heterozygous *LTBP3* variants were identified in 9 out of 338 patients, with thoracic aortic dissection at <56 years of age and no family history or syndromic features [55]. Zhu et al., investigating a cohort of 266 Asian patients with thoracic aortic dissection and/or aneurysm, detected 4 patients with heterozygous *LTBP3* variants who had experienced aortic dissections at 33–52 years of age.

#### 2.3.9. ACTA2-Related sHTAD

Pathogenic variants in the *ACTA2* gene, encoding the vascular isoform of the smooth muscle cell contractile protein alpha-actin, lead to diverse forms of syndromic and nonsyndromic HTAD [6,57,58]. Heterozygous missense *ACTA2* variants cause a form of HTAD commonly associated with persistent livedo reticularis (a purplish skin discoloration caused by constriction or occlusion of deep dermal capillaries), iris floccule [58], premature onset of coronary artery disease, premature ischemic strokes due to Moyamoya disease (MYMY5; OMIM #614042, ORPHA:2573) (stenosis or occlusion of the terminal portion of the internal carotid artery with the formation of an abnormal vascular network in the vicinity of the arterial occlusion) or fusiform cerebral aneurysms [59], and BAV. The penetrance of thoracic aortic disease in these patients was estimated to be 50–70% and did not appear to be age dependent. Type A dissections were more common than type B dissections [58,60].

Pathogenic *ACTA2* variants leading to arginine replacement by histidine, leucine or cysteine at position 179 (R179 variants) cause a distinct syndrome called multisystemic smooth muscle dysfunction syndrome (MSMDS, OMIM #613834, ORPHA:404463) characterized by congenital fixed pupils (mydriasis), large patent ductus arteriosus or aortopulmonary window, small vessel disease, urinary bladder dysfunction, intestinal malrotation, severe cerebrovascular disease and fully penetrant thoracic aortic disease by the age of 25 years [61–65].

The p.R179 and p.R258 *ACTA2* variants are characterized by a significantly increased risk for aortic events, very early presentation typically in childhood warranting early repair, whereas the p.R185Q and p.R118Q variants seem to bare a more benign course [60]. Larger cohorts are required before implementation of these genotype–phenotype correlations into clinical practice. Dissections have been reported at aortic aneurysm sizes of as low as

40 mm [64,66]; therefore, earlier surgical intervention is advised in patients with established *ACTA2* variants.

2.3.10. Importin-Related HTAD-VISS Syndrome (OMIM #619472)

Biallelic variants in the *IPO8* gene, encoding the nuclear import protein importin 8, lead to a form of sHTAD presenting with a LDS/SGS-like phenotype with early-onset aortic aneurysms (before 1 year of age in the youngest), marked arterial tortuosity, structural heart disease in involving atrial or ventricular septal defects and patent ductus arteriosus, facial and skeletal anomalies, developmental delay, umbilical and/or inguinal hernias, immune dysregulation and allergic diseases [67–69]. No aortic dissection has been reported in a total of 28 patients who have been identified so far, despite a severe aneurysm phenotype in most affected individuals.

Turner syndrome (TS; OMIM #300082, ORPHA:881). TS is characterized by short stature, premature loss of ovarian function, webbing of the neck, lymphoedema, kidney and skeletal abnormalities in women and girls with complete or partial absence of the second X chromosome. Aortic coarctation (reported prevalence 7–18%) and BAV (reported prevalence 12–30%) are the most common congenital heart disease detected [70]. Aortic dilatation and dissection usually occur in TS patients with BAV or coarctation. However, the onset of aortic complications in TS occurs at a much younger age (20s and 30s) than nonsyndromic BAV or coarctation cases, aortic dilatation and dissection in the presence of apparently normal aortic valve has been reported, TS is an independent risk factor for aortic dilation and dissection and cystic medial necrosis has been found in a considerable portion of TS patients with aortic dissection during histology, indicating an inherent abnormality of the aortic tissue [70–72]. Aortic dissection in the absence of coarctation, BAV or hypertension has been reported in up to 11% of TS patients [73].

## 3. Thoracic Aortic Disease in Metabolic Storage Disease

Although metabolic storage diseases are not typically classified as syndromic HTAD, there is evidence of thoracic aortic disease in these conditions. El-Gharbawy et al. reported dilatation of the ascending aorta and/or aortic arch in five female patients (12.5% of the cohort) with late-onset Pompe disease (OMIM #232300, caused by variants in the *GAA* gene, leading to a deficiency in the acid α-glucosidase enzyme), including a 42-year-old patient with concomitant BAV who presented with aortic dissection of the ascending aorta at an aortic size >50 mm [74]. Aneurysms of the aortic root and ascending aorta, developing by the fifth decade of life, have been reported in 9.6% of male and 1.9% of female normotensive patients with Fabry disease (FD; OMIM #301500), an X-linked recessive disorder that is caused by deficiency of the lysosomal enzyme α-galactosidase A (*GLA* gene) [75–77]. Although vertebral artery and carotid artery dissection are relatively common and lead to stroke in FD, no cases of aortic dissection or rupture have been reported to date [76]. Aortic root dilatation (in 35–39% of the patients) has also been described in mucopolysaccharidoses, a group of 11 different lysosomal storage disorders, characterized by enzymatic deficiency leading to attenuated degradation and increased storage of glycosaminoglycans. No cases of aortic dissection have been published, and absolute aortic root dimensions greater than 45 mm are uncommon [78,79]. Hyperplasia and glycogen deposition vascular of smooth muscle cells, as indicated in animal models, may explain the presence of thoracic aortic disease in lysosomal storage disease [80].

## 4. Nonsyndromic HTAD

### *4.1. Bicuspid Aortic Valve Related HTAD*

Bicuspid aortic valve (BAV; OMIM #109730, ORPHA:402075) is the most common congenital heart disease with an estimated prevalence of 0.5–0.8% [81]. Although BAV can be part of the phenotype in some cases of sHTAD such as MFS or LDS [82], there is also mounting evidence of familial clustering in up to 6–9% of first-degree relatives of nonsyndromic BAV [83,84]. An autosomal dominant inheritance pattern with variable

expressivity and typically incomplete penetrance is recognized [82,84]. Up to 75% of patients with BAV might develop aortic dilatation [85], although this typically occurs later than other syndromic or nonsyndromic HTAD and at relatively slower growth rates (average of 0.19 cm/year) [86].

Variants in the *NOTCH1* gene have been described in approximately 1% of sporadic BAV cases and in up to 7% of familial BAV cases [82,87,88] and are typically associated with prominent valve calcification [89]. Recently, loss-of-function *SMAD6* variants have been found in up to 11% of nsHTAD patients with BAV [90,91]. *ROBO4* variants, encoding a factor known to contribute to endothelial performance, and *TBX20* variants, a transcription factor involved in the regulation of heart development, were shown to contribute to aortic aneurysm formation in families with nonsyndromic BAV [92,93].

Echocardiography screening of first-degree relatives of patients with BAV should be offered especially in boys, athletes and if hypertension is present [24]. Families with multiple affected relatives, a combination of other left-sided congenital abnormalities and a particularly malignant clinical profile should be offered genetic testing for at least *ACTA2, SMAD6, TBX20, ROBO4* and *NOTCH1* genes. Multiple gene panels should be considered in selected cases, taking into consideration the variable and incomplete penetrance of sHTAD that might lead to a mild phenotype with minimal or no systemic features in some patients. No specific genotype–phenotype correlations currently exist that could possibly guide surgical interventions or provide specific prognostic information. Recently, Pileggi et al. indicated that specific *NOTCH1* variants could be associated with better prognosis and later-onset development of aortic stenosis [88].

### *4.2. Familial and Sporadic Nonsyndromic HTAD*

Based on the presence of familial disease or not, nsHTAD is further categorized into familial and sporadic nsHTAD. A positive family history of thoracic aortic disease is associated with an increased aortic growth rate, a bigger chance of gene identification and earlier phenotypic manifestation [94]. The genetic etiology of familial nsHTAD is highly heterogeneous and usually involves genes that regulate the smooth muscle cell contractile apparatus. The genetic substrate of sporadic nsHTAD is largely unknown and seems to differ from familial nsHTAD cases.

To date, over 10 genes and 2 linked loci have been involved in the pathogenesis of nsHTAD, including genes involved in the (TGF-β) pathway and genes encoding extracellular matrix proteins that are typically associated with syndromic aortopathies [2,6,47]. Common single nucleotide polymorphisms at the 15q21.1 locus of the *FBN1* gene have been shown to be associated with sporadic nsHTAD [95] without other systemic features of MFS. Arnaud et al. performed genetic screening in 226 consecutive nsHTAD, either sporadic in patients under 45 years of age or in documented familial cases, and identified an overall yield of pathogenic or likely pathogenic variants (*SMAD3, FBN1, TGFBR1, TGFBR2, TGFB2, ACTA2, MYLK, FLNA, FBN2, LOX, MFAP5 genes*) in 18% of the patients (11% in sporadic cases vs. 22% in familial cases), with almost two-thirds located in *SMAD3* and *FBN1* genes. Exclusively missense variants and no premature termination codon variants were identified in the *FBN1* gene in this cohort. More careful clinical evaluation after the genetic result revealed clinical findings consistent with LDS in approximately half of the cases with *SMAD3* variants and history of periventricular heterotopia in patients with the *FLNA* variant, reclassifying these cases as syndromic [6]. Weerakkody et al. investigated a cohort of 1025 unrelated HTAD cases, including many cases of sporadic HTAD, and reported a 4.9% yield of genetic testing for a 15-gene genetic panel. Patients with a family history of HTAD were four times more likely to carry a pathogenic or likely pathogenic variant than those without a family history (9.8 vs. 2.4%) [96]. Since clinical information (syndromic features or clinical diagnosis) was not available in a significant percentage of the cases, these cases cannot automatically be categorized as sporadic nsHTAD.

Overall, pathogenic *ACTA2* variants are the most frequently encountered, as they are detected in 1–21% of nsHTAD [57,97,98] and are associated with a malignant aortic

phenotype. Pathogenic variants in the *MYLK* gene [99–101], with missense pathogenic variants showing an earlier onset aortic event, and variants in the *MYH11* [102] and *PRKG1* genes [103] have also been recognized as relatively rare but aggressive causes of thoracic aortic dissection (~1% prevalence of each), in nsHTAD which are not always preceded by obvious aortic dilatation. There is no evidence to date that defects in the other genes identified (*LOX*, *MFAP5*, *FOXE3*, *MAT2A*, *SMAD2*, *SMAD4*, *NOTCH1*, *PLOD1*, *TGFB2*, *TGFBR2*, *FBN1*, *FBN2*) are linked to a more severe phenotype or earlier presentation of HTAD [6,57,58].

## 5. Genetic Testing and Surgical Intervention

Genetic testing of patients with established or suspected HTAD is an essential part of their assessment and should follow clinical evaluation and proper genetic counseling (Figure 1). Specific gene testing may be considered when the phenotype indicates a distinct syndromic aortopathy to aid clinical decisions and offer prognostic and diagnostic information. In most cases, however, a multigene panel should be used, consisting of at least of the 11 genes (MFS–*FBN1*, LDS–*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, vEDS–*COL3A1*, *ACTA2*, *MYLK*, *LOX*, *PRKG1*, *MYH11)* that have been identified to have a "definitive" or "strong" association with HTAD [104]. Specific criteria for genetic testing have been proposed by the Rare Disease Group of VASCERN, based on expert opinion (Table 1) adopted in the most recent European guidelines of the ESC and the European Society of Human Genetics [105]. Exome sequencing may be performed in cases with equivocal diagnosis, nonsyndromic HTAD or for research purposes [106]. Cascade genetic screening should be offered in all family members of patients with well-established pathogenic or likely pathogenic variants. Surgery should be offered in patients with a malignant genetic and/or clinical profile and mildly dilated aortas (Table 2).

**Table 1.** Criteria for genetic testing in patients with suspected heritable thoracic aortic disease.

| Patient's Age | Criteria for Genetic Testing [a] |
|---|---|
| All ages | Familial HTAD (≥2 relatives identified) |
| | Personal history of aortic dissection |
| | Aortic root diameter Z-score >3.5 |
| <18 years old | Aortic root diameter Z-score ≥3 |
| 18–60 years old | Aortic root diameter Z-score 2.5–3.5 |
| >60 | Aortic root diameter Z-score 2.5–3.5 without hypertension |

HTAD: Heritable thoracic aortic disease, [a] Based on expert opinion [105].

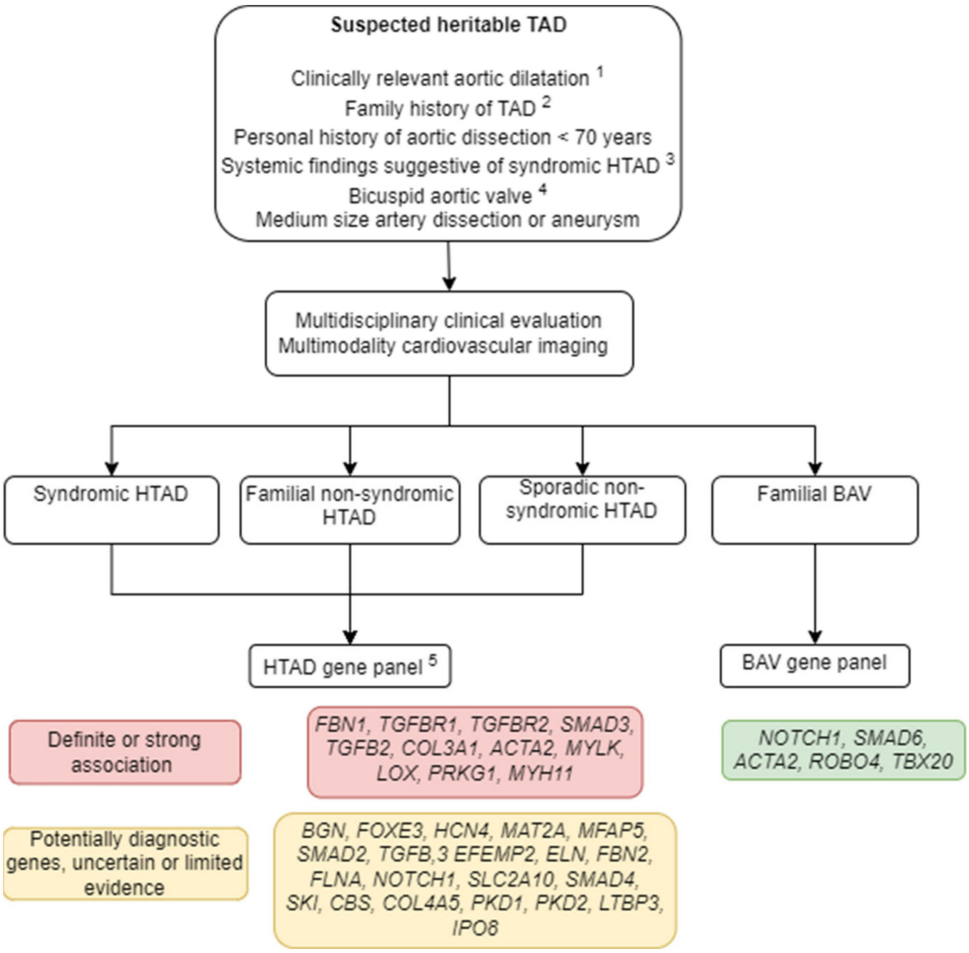


**Figure 1.** Clinical and genetic evaluation of suspected heritable thoracic aortic disease. HTAD: Heritable thoracic aortic disease; TAD: thoracic aortic disease, BAV: bicuspid aortic valve. [1] This includes one of the following: (a) Aortic root diameter Z-score >3.5 (b) Aortic root diameter Z-score ≥3 in patients <18 years (c) Aortic root diameter Z-score 2.5–3.5 in patients 18–60 years (d) Aortic root diameter Z-score 2.5–3.5 without hypertension in patients >60 years. [2] 1st- or 2nd-degree relative with aortic dissection or aneurysm aged <60 years or sudden cardiac death <45 years. [3] Ectopia lentis, hypertelorism, bifid uvula, premature and extensive osteoarthritis, club feet, cleft palate and other systemic features. [4] Familial cases, syndromic or extra phenotypic characteristics, young patients with severe disease. [5] In familial and/or syndromic cases consider exome sequencing, copy number variant testing if next-generation sequencing is negative and there is high clinical suspicion of HTAD or for research purposes.

**Table 2.** Genotype–phenotype correlations to be considered before aortic surgery in patients with heritable thoracic aortic disease.

| Aortopathy | *Genes* | Aortic Size to Consider Surgical Operation [a] | | | |
|---|---|---|---|---|---|
| | | ≥40–42 mm | ≥45 mm | ≥50 mm | ≥55 mm |
| Marfan syndrome | *FBN1* | | ≥1 high-risk factor [b] | No high-risk factors [b] | |
| Loeys–Dietz syndrome | *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2* | *TGFBR2* (females, severe phenotypic features, low body surface area) | *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2* | *SMAD2*, *TGFB3* | |
| Vascular Ehlers–Danlos syndrome | *COL3A1*, *COL1A1* | Surgical intervention not recommended due to high surgical risk; only as emergency treatment | | | |
| Meester–Loeys syndrome | *BGN (X–linked)* | Aortic dissection in a patient with aortic size of 45 mm has been reported; individualized expert assessment is needed | | | |
| Filamin-related HTAD | *FLNA (X-linked)* | Aortic rupture at aortic size of 42 mm has been reported; individualized expert assessment is needed | | | |
| *LOX*-related HTAD | *LOX* | | | Aortic dissection at aortic size >50 mm has been reported; individualized expert assessment is needed | |
| Gorlin–Chaudhry–Moss syndrome | *SLC25A24* | | | Aortic dissection at aortic size of 51 mm has been reported; individualized expert assessment is needed | |
| Shprintzen–Goldberg syndrome | *SKI* | | | Milder phenotype than Marfan syndrome or Loeys–Dietz syndrome; individualized expert assessment is needed | |
| Importin-related HTAD | *IPO8* (biallelic) | | | No aortic dissections have been reported | |
| *LTBP3*-related HTAD | *LTBP3* (biallelic) | | | Aortic dissection at aortic size >50 mm has been reported; individualized expert assessment is needed | |
| *ACTA2*-related HTAD | *ACTA2* (especially p.R179, p.R258) | Dissections have been reported at aortic aneurysm sizes of as low as 40 mm. More aggressive phenotype with p.R179 (multisystemic smooth muscle dysfunction syndrome) and p.R258 variants | | | |
| Arterial tortuosity syndrome | *SLC2A10* | | | No dissections reported; individualized expert assessment is needed | |
| Turner syndrome | Complete or partial X chromosome monosomy | ASI >25 mm/m$^2$, especially if ≥1 high-risk factor present [c] | | | |
| Pompe disease | *GAA (X-linked)* | | | Aortic dissection at aortic size >50 mm has been reported; individualized expert assessment is needed | |
| Fabry disease | *GLA (X-linked)* | | | | No aortic dissections have been reported |
| Mucopolysaccharidoses | *IDUA*, *IDS*, *SGSH*, *NAGLU*, *HGSNAT*, *GNS*, *GALNS*, *GLB1*, *ARSB*, *GUSB*, *HYAL1* | | | | No aortic dissections have been reported |
| Bicuspid aortic valve-related aortopathy | *NOTCH1*, *ACTA2*, *SMAD6*, *ROBO4*, *TBX20* | | | ≥1 high-risk factor present [d] | No high-risk factors present [d] |
| Nonsyndromic HTAD (familial or sporadic) | *MYLK*, *MYH11*, *PRKG1*, *ACTA2*, *LOX*, *MFAP5*, *FOXE3*, *MAT2A*, *SMAD2*, *SMAD4*, *NOTCH1*, *PLOD1*, *TGFB2*, *TGFBR2*, *FBN1*, *FBN2*, *LTBP3* | *MYLK*, *MYH11*, *PRKG1*, *ACTA2* (especially p.R179, p.R258) | All other genes; individualized expert assessment is needed | | |

HTAD: heritable thoracic aortic disease. [a] A lower threshold may be considered if there is a family history of aortic dissection, pregnancy or rapid aortic size increase on an individual basis; [b] High-risk factors for Marfan syndrome patients are: (a) aortic diameter at the sinuses of Valsalva ≥5 cm, (b) rapid increase in aortic dilatation (≥3 mm per year), (c) family history of aortic dissection at a low aortic size, (d) progressive aortic regurgitation, (e) personal history of spontaneous vascular dissection and (f) desire for pregnancy. [c] High-risk factors for Turner syndrome: (a) Bicuspid aortic valve, (b) elongation of the transverse aorta, (c) Aortic coarctation or (d) hypertension. [d] High-risk factors for bicuspid aortic valve: (a) Family history of dissection at a low diameter, (b) desire for pregnancy, (c) systemic hypertension, (d) increase >3 mm/year.

## 6. Conclusions

Genetic testing plays an increasing role in the management of patients with HTAD. The identification of a pathogenic variant can establish or confirm the diagnosis of syndromic HTAD, dictate extensive evaluation of the arterial tree in HTAD with known distal vasculature involvement and justify closer follow-up and earlier surgical intervention in HTAD with high risk of dissection of minimal or normal aortic size. Evolving phenotype–genotype correlations should soon allow for more precise and individualized management and treatment of patients with HTAD.

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