Genetics of Heritable Thoracic Aortic Disease

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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.

aortopathy bicuspid aortic valve familial thoracic aneurysm Marfan syndrome Loeys–Dietz syndrome aortic dissection heritable thoracic aortic disease

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][4][5].

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 ≥2 that corresponds to a diameter ≥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 ≥2) and ectopia lentis or a systemic score ≥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 ≥1 of the following criteria: (a) ectopia lentis, (b) systemic score ≥7, (c) aortic root enlargement with Z-score ≥2 in patients >20 years and (d) Z score ≥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 ≥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 [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][19][20][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).

2.3. 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 [25], which updated the earlier nosology of Villefranche [26]. Men seem to have a poorer prognosis than women (median survival age of 46 ± 1.8 years vs. 54 ± 2.5 years) [27]. Surveillance may include periodic arterial screening.

Genetic testing is highly specific and sensitive for vEDS, revealing a genetic defect in 95% of cases [28]. Lethal arterial events in classic (nonvascular) Ehlers–Danlos syndrome (EDS) caused by *COL5A1* or *COL1A1* variants have also been reported [29]. Identification of a pathogenic variant establishes the diagnosis [26]. 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 [27][30][31][32]. Glycine substitutions, splice-site and in-frame insertions/deletions bear the poorer prognosis leading to earlier complications [33].

Although aortic dissection can occur at normal aortic sizes in up to 33% of patients [34], 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 [35]. 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 [32][36].

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 [37].

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 [38]. 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 [39]. 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 [40][41]. 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 [40].

3. Nonsyndromic HTAD

3.1. 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% [42]. Although BAV can be part of the phenotype in some cases of sHTAD such as MFS or LDS [43], there is also mounting evidence of familial clustering in up to 6–9% of first-degree relatives of nonsyndromic BAV [44][45]. An autosomal dominant inheritance pattern with variable expressivity and typically incomplete penetrance is recognized [43][45]. Up to 75% of patients with BAV might develop aortic dilatation [46], although this typically occurs later than other syndromic or nonsyndromic HTAD and at relatively slower growth rates (average of 0.19 cm/year) [47].

Variants in the *NOTCH1* gene have been described in approximately 1% of sporadic BAV cases and in up to 7% of familial BAV cases [43][48][49] and are typically associated with prominent valve calcification [50]. Recently, loss-of-function *SMAD6* variants have been found in up to 11% of nsHTAD patients with BAV [51][52]. *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 [53][54].

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 [49].

3.2. 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 [55]. 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][41]. Common single nucleotide polymorphisms at the 15q21.1 locus of the *FBN1* gene have been shown to be associated with sporadic nsHTAD [56] 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%) [57]. 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 [58][59][60] and are associated with a malignant aortic phenotype. Pathogenic variants in the *MYLK* gene [61][62][63], with missense pathogenic variants showing an earlier onset aortic event, and variants in the *MYH11* [64] and *PRKG1* genes [65] 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][58][66].

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