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Heritable Thoracic Aortic Disease: A Literature Review on Genetic Aortopathies and Current Surgical Management

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Abbreviations:
AAA = Abdominal aortic aneurysm
ARB = Angiotensin II type I receptor antagonist
BAV = Bicuspid aortic valve
FTAAD = Familial thoracic aortic aneurysms and dissections
HTAD = Heritable thoracic aortic disease
TAA = Thoracic aortic aneurysm
TGF-β = Transforming growth factor-beta
TTE = Transthoracic echocardiography

Abstract
Heritable thoracic aortic disease puts patients at risk for aortic aneurysms, rupture, and dissections. The diagnosis and management of this heterogenous patient population continues to evolve. Last year, the American Heart Association/American College of Cardiology Joint Committee published diagnosis and management guidelines for aortic disease, which included those with genetic aortopathies. Additionally, evolving research studying the implications of underlying genetic aberrations with new genetic testing continues to become available. In this review, we evaluate the current literature surrounding the diagnosis and management of heritable thoracic aortic disease, as well as novel therapeutic approaches and future directions of research.
Keywords: genetic aortopathy; genetic arteriopathy; heritable thoracic aortic disease; aortic aneurysm; aortic dissection; vascular surgery

Introduction

Aortic disease consists of a wide array of pathologic conditions, such as aneurysms, acute aortic syndromes (dissection, rupture, intramural hematoma, etc.), and others. Despite continued evolution in the diagnosis and management of these conditions, there remains a large healthcare burden from aortic disease. From 1990-2010, the global death rates from aortic aneurysmal disease increased from 2.49 per 100,000 to 2.78 per 100,000, with even worse rates in developing countries.[1] A large, population-based study in Ontario, Canada, over a 12-year period (2002-2014), showed an increased incidence of thoracic aortic aneurysms (TAA) and dissections during the study period.[2] Additionally, in 2019, published data from the Center for Disease Control and Prevention showed that nearly 10,000 deaths were attributed to aortic aneurysms or dissections.[3] Due to these incidence rates, multiple database studies have shown temporal trends of increased utilization of aortic surgery over the last few decades, especially with more innovative endovascular techniques.[4-6]

With increasing numbers of patients suffering from aortic disease, it is important to determine patient populations at risk. One of these patient populations includes those with genetic aortopathies. Underlying genetic aberrations can cause the aorta to undergo vascular remodeling, which portends to aortic aneurysm formation or dissection.[7] The thoracic aorta, unlike the abdominal aorta, tends to be the area most affected by these genetic disorders, which are commonly termed heritable thoracic aortic disease (HTAD).[8] HTAD generally involves younger patients when compared to sporadic aortic disease.[9,10] Additionally, some HTAD patients have shorter median survival compared to non-affected cohorts, which highlights the importance of early diagnosis and optimized management.

The purpose of this literature review is to give an in-depth narrative about genetic aortopathies. It will cover anatomy and genetic basics of aortic disease, clinical phenotypic features of genetic syndromes, genetic testing, and, importantly, diagnosis and management of these challenging patients.

Methods

This review utilized PubMed for all references. Key search terms were “genetic aortopathy,” “heritable aortic disease,” “heritable thoracic aortic disease,” “Marfan syndrome,” “Ehlers-Danlos syndrome,” “Loeys-Diez syndrome,” and “genetic testing of aortic disease.”

Background

A brief background of aorta anatomy and common aortic disease will be discussed. This review focuses on genetic aortopathies, so the information provided here is limited to basic knowledge.

Anatomy

The aorta delivers oxygenated blood to end organs from the left ventricle, and the aortic wall is made up of the inner tunica intima, the middle tunica media, and the outer tunica adventitia. The aorta can be categorized into two anatomic components: abdominal

aorta and thoracic aorta. The abdominal aorta contains suprarenal and infrarenal segments. The thoracic aorta includes the aortic root, ascending aorta, aortic arch, and descending segments. The aorta bifurcates into bilateral common iliac arteries at the level of the fourth lumbar vertebrae.

Aortic disease

Aortic disease can involve any segment of the aorta, acutely or chronically. The most common forms of aortic disease are aneurysms or dissections.

Aortic aneurysms. An aortic aneurysm is defined as a localized increase of aortic diameter that is seen as greater than 1.5 times the expected diameter.[11] They are broken down into abdominal aortic aneurysms (AAA) and TAA. AAAs are mainly correlated to risk factors of atherosclerotic disease, and the genetic understanding of AAAs is limited.[8] TAAs have greater genetic predilection, and disease can affect one or multiple thoracic aorta segments: aortic root/ascending aorta (60%); descending aorta (40%); aortic arch (10%); and thoracoabdominal aorta (10%).[12] Most HTADs involve the aortic root or ascending aorta.

Aortic dissections. Aortic dissections are a part of a spectrum of aortic diseases referred to as acute aortic syndromes, and involves disruption of the media layer of the aortic wall leading to an intimal flap separating a true and false lumen.[13] Classic aortic dissections are anatomically classified into either the DeBakey or Stanford systems, which accounts for the origin of the intimal tear and extent of dissection or whether there is involvement of the ascending aorta, respectively, as previously described.[14] Prompt diagnosis of aortic dissection is crucial, as mortality rates have been shown to increase 1-2% per hour after initial insult without appropriate therapy.[15]

Genetic basis of aortic diseases

HTAD primarily consists of aortic aneurysms or dissections with evidence of an underlying familial component or pathogenic genetic variant.[16] Marfan syndrome was the first HTAD heavily studied, dating back to the 1950s. Since then, multiple other connective tissue disorders have been found to contribute to the formation of HTAD.

Overview of genetic factors in aortic diseases

Early research in HTAD focused on Marfan syndrome and Ehlers-Danlos syndrome, which involve dysfunctional proteins in the extracellular matrix of the aortic tunica media.[7,17] With the expansion of genomic-related research, the transforming growth factor-beta (TGF-β) pathway appears to play a key role in the formation of TAAs when alterations occur.[18] Thus, the three major groups of genes currently identified to contribute to HTAD are proteins involved in vascular smooth muscle contractility, proteins involving the extracellular matrix, and TGF-β signaling pathways.[19] Last, HTADs can be grouped into syndromic HTAD, nonsyndromic HTAD, or congenital conditions (i.e., Turner syndrome, bicuspid aortic valve).[20]

Familial aggregation and heritability

Most HTADs are autosomal dominant, which leads to a 50% chance of inheritance in offspring of affected individuals.[21] Up to 20% of TAA or aortic dissection cases have a family history of aortic disease.[22] Population studies have demonstrated familial cases of HTAD have an increased risk of developing TAA or aortic dissection when compared to sporadic cases.[22,23] This is important in affected families in terms of risk profiling among parents considering pregnancy and early testing or surveillance. **Table 1** illustrates inheritance patterns of the major identified HTADs.

Genetic mutations and aortopathies

There are nearly 40 genes identified that contribute to HTAD.[24] The number of genes identified will continue to expand with the application of genome-wide association studies.[25] Genetic aortopathies can be categorized into syndromic, nonsyndromic, or congenital conditions. Syndromic HTAD consists of those HTADs that have associated extracardiac features that can manifest on physical exam or diagnostic workup. Nonsyndromic HTADs are familial HTADs without evidence of connective tissue disorders, bicuspid aortic valves, or other congenital conditions. Congenital conditions include bicuspid aortic valve aortopathy, Turner syndrome, and others. **Table 1** demonstrates the major aortopathies identified to date, with their associated genetic variants and proteins/pathways.

Marfan Syndrome. Marfan syndrome may be the most well-known HTAD. It was discovered in the 1950s,[26] and is an autosomal dominant disorder that leads to a genetic variant in the *FBN1* gene on chromosome 15q21.1.[27] This codes for fibrillin-1, which is a glycoprotein involved in the extracellular matrix as a microfibril, and it plays a role in the elasticity of connective tissue.[28] In Marfan syndrome, missense mutations of fibrillin-1 leads to altered structural integrity in the aortic wall, and the loss of functional fibrillin-1, essential in TGF-β sequestration, also leads to an increase in TGF-β bioavailability.[29] Both mechanisms contribute to aortic aneurysm formation.

Vascular Ehlers-Danlos Syndrome. Vascular Ehlers-Danlos syndrome, or Ehlers-Danlos type IV, is an autosomal dominant connective tissue disorder involving the *COL3A1* gene on chromosome 2q24.3-q31.[30] This gene codes for type III procollagen—a fibrillar collagen involved in the structural integrity of arterial walls via linkage of α chains.[31] This defect leads to increased risk of arterial dissections or aneurysm formation.

Loeys-Dietz Syndrome. Loeys-Dietz syndrome is an autosomal dominant aortic aneurysm syndrome discovered in 2005 that consisted of a classic triad of hypertelorism, bifid uvula or cleft palate, and aortic or arterial aneurysms.[32] Since initial discovery, there are now several described variants with different genetic mutations and physical manifestations. The pathophysiology behind this syndrome consists of primarily *de novo* mutations in the TGF-β signaling pathway.[33] These mutations lead to increased TGF-β activity, which predisposes to aneurysmal formation.

Other syndromic aortopathies. Shprintzen-Goldberg syndrome is an autosomal dominant disorder with a genetic variant in *SKI* on chromosome 1p36, which represses TGF-β signaling.[34,35] Ehlers-Danlos syndrome with periventricular nodular heterotopia is an X-linked disorder causing pathogenic variants in the *FLNA* gene, which codes for a cytoskeletal protein named Filamin-A.[36] Meester-Loeys syndrome is an X-linked form of syndromic HTAD that results in loss-of-function mutations in *BGN*, coding for

biglycan, which results in alterations in the TGF-β pathway.[37] *LOX*-related HTAD is an autosomal dominant HTAD, and it is caused by variants in the coding of lysyl oxidase, which is an extracellular matrix crosslinking enzyme.[38] Smooth muscle dysfunction syndrome is a rare connective tissue disorder resulting in HTAD from *de novo* missense mutations in *ACTA2*, R179H that codes for α-actin, a smooth muscle cell contractile protein, which leads to smooth muscle cell dysfunction and predisposition to HTAD.[39] Arterial tortuosity syndrome is an autosomal recessive HTAD caused by loss-of-function mutations in *SLC2A10*, which codes the glucose transport protein GLUT10.[40,41] Turner syndrome, a well-known X-linked disorder, can also be related to aortopathy when genetic variants are seen in SHOX, TIMP1, and TIMP3.[42,43]

Familial thoracic aortic aneurysm and dissection (FTAAD) genes. Nonsyndromic HTAD, also referred to as FTAAD, are a group of HTADs that have no obvious connective tissue disorder associations. Compared to sporadic TAA, these patients present younger and have faster growth rates.[10,44] These disorders are primarily autosomal dominant, and they commonly involve vascular smooth muscle dysfunction, which leads to defects in mechanotransduction and compromises vascular wall structural integrity.[45,46] Commonly involved genes, also listed in **Table 1**, are *ACTA2*, *MYH11*, *MYLK*, *PRKG1*, *MAT2A*, *MFAP5*, *FOXE3*, *THSD4*, and *FBN1*.[47-56] As seen in this review, some of these genes are involved in syndromic disorders as well. However, there have been cases with these genetic defects being seen in isolated HTAD.

***Congenital conditions*.** Besides syndromic and non-syndromic HTADs, there are a few congenital disorders with underlying pathogenic genetic variants that predispose to the development of TAA and aortic dissection. The primary ones discussed here are bicuspid aortic valve aortopathy, autosomal dominant polycystic kidney disease, and Turner syndrome. Congenital bicuspid aortic valve (BAV) is the fusion of two aortic valve leaflets and can predispose patients to aortopathy.[55] Prior studies have evaluated the role of hemodynamic changes to the aortic wall due to aberrant flow through BAVs.[58-60] However, recent studies have shown that the likely mechanism behind the aortopathy is due to genetic variants affecting molecular and cellular mechanisms.[61,62] For instance, Jiao et al., hypothesized that BAV aortopathy was due to aberrant differentiation affecting neural crest-derived smooth muscle cells, which help form the aortic root and ascending aorta.[63] Other genetic factors, most notably *NOTCH1*, have been shown to contribute to BAV aortopathy.[57,64,65] Additionally, autosomal dominant polycystic kidney disease is associated with an increased risk of aortic dilation and HTAD.[66,67]

Clinical presentation and phenotypic variability

In syndromic HTAD, as opposed to non-syndromic HTAD, there are classical syndromic features on physical exam that can help key in on potential patients with syndromic HTAD. **Table 2** demonstrates some of these key characteristics. A detailed family history is very important in aiding in the correct diagnosis of HTAD. Additionally, certain phenotypic findings in HTAD, depending on their severity, can be correlated with more severe aortic disease.

Clinical features of heritable aortic diseases

In syndromic HTAD, there are certain syndromic features associated with each disease. For instance, Marfan syndrome is classically associated with marfanoid habitus, pectus deformities, and arachnodactyly, among other characteristics. Common cardiac and extracardiac findings are seen in **Table 3**.

Age-related, sex-related phenotypic variability and genotype-phenotype correlations

Certain phenotypic characteristics carry certain levels of risk, based off their severity in relation to age, sex, or genotypes. In patients with Loeys-Dietz syndrome, vascular complications tend to occur at a young age and have a high rate of mortality.[18] One study showed that females with thoracic aortic disease had a higher rate of mortality, which is consistent with prior literature, and within that study population, *FBN1* and *MYLK* mutations were associated with higher risk.[68] Last, genotype-phenotype correlation studies are scarce in HTAD but more studies aimed at understanding these relationships are imperative, so that appropriate counseling can be performed. In Turner syndrome, mutations in *TIMP1/TIMP3* genes are correlated with BAV, which puts these patients at increased risk of developing aortic aneurysms or dissection.[69] Another study looked at the correlation between sudden cardiac death and genetic pathogenic variants. It found several genes with overlap between spontaneous aortic dissection as well as spontaneous coronary artery dissection.[70] Last, when compared to *TGFBR2* and *FBN1* variants, patients who carry *ACTA2* mutations tend to present with aortic dissection.[71]

Diagnostic modalities

After a detailed family history and physical exam, there are multiple diagnostic tools to evaluate the aorta as well as genetic testing and screening tools. For instance, in Marfan syndrome, the revised Ghent nosology is used to aid in the diagnosis.[72] When looking at HTAD patients, it is imperative to utilize a multidisciplinary approach. **Table 4** shows current diagnostic and surveillance guidelines for some HTADs.

Imaging

Initial diagnostic evaluation in suspected patients with HTAD is usually performed with transthoracic echocardiography (TTE).[20] This modality can evaluate aortic valve morphology, looking for BAV in Turner's syndrome patients, for example, as well as evaluate the aortic root and ascending aorta. For patients with Marfan syndrome, initial surveillance is done every 6 months after baseline evaluation, and it can be extended to annually if growth rate is stable.[20] In patients with HTAD, additional imaging with a computed tomography scan or magnetic resonance imaging should be performed if the TTE does not evaluate the aortic root or ascending aorta conclusively.

Genetic testing, counseling, and screening of family

Genetic testing of HTAD continues to evolve. Upfront counseling is vital to appropriately educate patients and their family members—as not all individuals will be open to genetic testing. Genetic testing and screening can be associated with psychological side effects.[73] It is currently recommend to screen patients with TAA or aortic dissection by inquiring about family history of aortic disease, unexplained sudden deaths, or other aneurysmal disease outside of the aorta.[20] Additionally, genetic testing should be

offered for the patients with the following risk factors for HTAD: aortic disease with syndromic features; aortic disease in patients <60 years old; family history of aortic disease or other aneurysmal disease in a first- or second-degree relative; or a history of sudden cardiac death at a young age in a first- or second-degree relative.[20] If a pathogenic genetic variant is found, cascade testing should be performed on at-risk family members.[19,21,74,75]

Management and treatment

Management of HTAD relies on early screening and diagnosis, exercise restrictions, smoking cessation, and medical or surgical therapy. For medical therapy, cardiovascular medications are recommended for certain HTADs to theoretically decrease aortic wall stress. For surgery, there are various aortic diameter cut-off points for most HTADs. Both medical recommendations and surgical recommendations, when reported, are listed in **Table 5**.

Exercise restrictions. High-intensity exercise can subject the aortic wall to high levels of stress due to rapid elevation in blood pressure. Specifically, isometric exercises have shown to increase the ascending aortic diameter in BAV patients and is generally recommended against for patients with Marfan and Loeys-Dietz syndromes.[76-78] Currently, there are no definitive guidelines on exact exercise limitations.

Smoking cessation. Tobacco use is a major risk factor for the development of aortic aneurysms.[79,80] Smoking can lead to defects in the connective tissue of the aorta and increases the risk of aneurysmal rupture.[81] Therefore, all patients with aortic aneurysms should be advised to stop smoking.

Medical management. Beta-blockers and angiotensin II type I receptor antagonists (ARB) have been shown to potentially decrease aortic aneurysm growth, specifically in Marfan and Loeys-Dietz patients.[82-84] Beta blockers have been shown to decrease heart rate and reduce myocardial contractility, which slows down aortic root growth.[85] ARBs have shown to decrease TGF-β signaling as well as reduce matrix metalloproteinase activation, which can improve aortic contractility.[86] Specific recommendations for medical therapy can be found in **Table 5**.

Surgical management. ACC/AHA guidelines were updated in 2022 to determine at what aortic diameter certain HTADs should undergo repair.[20] Additionally, the European Society of Cardiology released guidelines in 2014 as well,[87] which give evidence-based recommendations in the prophylactic surgical care of HTAD patients. **Table 5** lists current recommendations from these two sources.

***Open vs. endovascular surgery*.** For proximal aortic surgery involving the aortic root and ascending aorta, open surgery remains the preferred approach. However, there is growing literature on the safety and feasibility of endovascular surgery for the proximal aorta.[88-90] For type B repairs in HTAD involving the descending thoracic aorta, endovascular repairs have been shown safe and effective but there has been limited long-term follow-up.[91]

Long-term follow-up and monitoring. Following surgical repair, patients with HTAD should undergo routine surveillance based off the ACC/AHA guidelines.[20] Marfan syndrome patients should undergo annual screening, which can be extended to biannual screening if aortic size remains unchanged. Additionally, these patients are at risk for AAA development, and screening them every 3-5 years is reasonable. Loeys-Dietz patients are at increased risk of aneurysmal disease in other vascular beds and should undergo imaging surveillance for these arteries every 2-3 years. (**Table 6**) Similar follow-up recommendations can be found in the published guidelines.

Pregnancy considerations

Pre-pregnancy guidance and counseling should be offered to patients with syndromic or nonsyndromic HTAD given the increased risk of aortic events during pregnancy.[92-95] This includes genetic counseling, aortic imaging, and counseling about the risks of aortic dissection in pregnancy.[20] During delivery, if HTAD patients have a chronic aortic dissection, cesarean delivery is recommended. However, if the aortic diameter is <4.0 cm, vaginal delivery can be offered, when appropriate.[20] Additional recommendations regarding prophylactic surgery prior to pregnancy can be seen in **Table 7**.

Novel Therapeutic Approaches and Research Trends

There is ongoing research regarding novel therapeutic targets to attenuate the progression in HTADs. One study is looking at targeting BEST3 in smooth muscle cells through the MEKK2/3 pathway.[96] BEST3 deficiency in smooth muscle cells in mice has been shown recently to activate the MEKK2/3 pathway, which can lead to spontaneous aortic dissection.[97] Another potential target is ALDH2.[98] Humans and mice with deficient ALDH2 have been associated with a decreased risk of aortic dissection, which could lead to a therapeutic target through ALDH2 inhibition. Last, endogenous Anxa1 has been shown to decrease aortic dissection by inhibiting vascular smooth muscle cell alterations.[99]

Conclusion

Early detection of HTAD remains imperative to enable deployment of a multidisciplinary approach to the management of these patients. With updated medical and surgical guidelines, the management continues to evolve and become more personalized. Additionally, genetic therapies and precision medicine studies are ongoing and hope to further close the knowledge gap on this heterogenous disease process.

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