Genetic Disorders of the Thoracic Aorta and Indications for Surgery

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KEYWORDS

• Aortic aneurysm • Genetic disorders • Connective tissue disease • Aortic surgery
• Marfan syndrome

KEY POINTS

- Genetic disorders of the aorta are rare but can be life threatening.
- Genetic causes of many connective tissue diseases are well defined.
- Familial thoracic aortic aneurysm and bicuspid aortic valve aortopathy are heritable, but their genetic causes are not well known.
- Natural history of genetic thoracic aortic aneurysms is not well understood or predictable, and surgical guidelines for treatment remain imprecise.

INTRODUCTION

Thoracic aortic aneurysm (TAA) can be a life-threatening condition affecting a broad range of patients from the young to the elderly. It is estimated that greater than 20% of all TAAs have a genetic basis.[1,2] These aneurysms are much more likely to affect the aortic root and ascending aorta as opposed to the atherosclerotic or degenerative TAAs where the descending thoracic aorta is more commonly involved. TAAs associated with an underlying genetic predisposition can be challenging to diagnose and treat. Genetic and molecular pathways contributing to the pathophysiology of these aneurysms are still not fully understood and continue to be studied, but much progress has been made. To determine when surgical repair is indicated, we must be familiar with the mechanisms and natural history of genetic disorders of the thoracic aorta.

MARFAN SYNDROME

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by mutations in the fibrillin-1 (FBN1) gene. FBN1 is an extracellular matrix protein that plays a significant role in the strength and integrity of aortic tissue by promoting smooth muscle cell anchorage to elastin and collagen matrices.[3] FBN1 gene mutation leads to FBN1 deficiency and increased transforming growth factor-β (TGFB) leading to aortic inflammation and fibrosis and, ultimately, dilatation and aneurysm formation.[4] The ascending aorta, aortic root, and aortic annulus are the most commonly affected,[5] although the entire thoracic aorta can become aneurysmal over the lifetime of a patient with MFS. Clinically, MFS is diagnosed using the Ghent criteria.[6] A second locus for MFS (MFS2) is caused by mutations in TGFB receptor 2 (TGFBR2), forming a phenotype that likely shares characteristics with Loeys-Dietz syndrome (LDS).[7]

LOEYS-DIETZ SYNDROME

LDS is also an autosomal dominant connective tissue disorder caused by mutations in TGFBR1 and TGFBR2.[8] The severe weakening of the aortic tissue in LDS patients can lead to premature and

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aggressive aneurysms. Aortic dissection can often occur in young patients and without significant aortic dilatation similar to what is seen in patients with Ehlers-Danlos syndrome (EDS). Patients with MFS aortic dissection, however, often have concomitant ascending and aortic root aneurysms.[9]

Phenotypically, patients with LDS exhibit thin translucent skin with visible veins, dystrophic scars, craniofacial deformities such as bifid uvula and hypertelorism, and easy bruising and joint laxity.[10]

EHLERS-DANLOS SYNDROME TYPE IV (VASCULAR TYPE)

EDS is an autosomal dominant connective tissue disorder caused by mutations in the type III procollagen (COL3A1) gene. This mutation leads to defective type III procollagen, the most amply represented type of collagen normally found in the extracellular matrix of the aorta.[11] Patients with vascular type EDS can have rupture of not just the aorta but also of smaller arteries. As previously mentioned, EDS patients, similar to LDS patients, can subsequently have aortic dissection with normal-sized aortas. Phenotypically, patients with EDS have thin skin with visible veins, easy bruising, thin pinched nose, thin lips, prominent ears, hollow cheeks, and tight facial skin.[11]

FAMILIAL THORACIC AORTIC ANEURYSM

A significant family history of TAAs puts a patient at significant increased risk for the condition. This is still a growing area of research and is more difficult clinically to ascertain, as patients do not have an associated syndrome of visible or examinable features. Up to 20% of TAAs are familial in origin, and there have been genetic factors discovered that are heterogeneous and with variable pentrance.[1] Genes found to be associated with familial TAAs include those responsible for the contractile apparatus of smooth muscle cells (ACTA2, MYH11, MYLK, PRKG1) and additional TGFB pathway proteins such as SMAD3.[12]

BICUSPID AORTIC VALVE AORTOPATHY

Approximately 1% to 2% of the population is born with a bicuspid aortic valve (BAV) in a 2:1 male/female ratio, thus representing the most common congenital heart defect.[5] The bicuspid aortic valve can present with phenotypically heterogeneous malformations with different fusion patterns.[13] Patients with BAV are less predictable in terms of the development or progression of TAA. They can have varying degrees of aortopathy, and this may have a relationship with the BAV leaflet configuration. Those with a true bicuspid aortic valve with only 2 commissures and no raphe are less prone to aortic dilatation than those with fused leaflets and the presence of a raphe.[14]

BAV is usually not associated with genetic syndromes but can be found concomitantly with connective tissue disorders such as MFS, LDS, and EDS. BAV does run in families and is thus believed to be highly heritable, with 9% of first-degree relatives of people with BAV found to have the same congenital condition.[15] Despite this finding, a specific genetic defect has not been identified as a cause for BAV aortopathy. The inheritance pattern seems to be autosomal dominant with decreased penetrance and variable expressivity but may also have an X-linked etiology, as BAV occurs much more frequently in males. Multiple gene mutations are found to have an association in some BAV patients, but these familiar mutations may also represent an overlapping with thoracic familial thoracic aortic aneurysms or other genetic disorders. These gene mutations include NOTCH1, ACTA2, TFGB2, FBN1, KCNJ2, GATA5, Nkx2-5, and SMAD6.[16]

Patients with BAV aortopathy have a 25% to 35% risk of needing aortic surgery over their lifetime and a 53% risk of needing valve surgery.[13,17] Anatomically, approximately 50% of BAV patients who subsequently have TAA have enlargement of the aortic root and ascending aorta, 25% of the ascending aorta and arch, and 25% of either isolated aortic root or isolated ascending aorta.[18]

NATURAL HISTORY OF GENETIC CAUSES OF THORACIC AORTIC ANEURYSM

There are limited data documenting the natural history of patients with genetic disorders and TAAs because of their low incidence and limitations to study follow-up. Patients with MFS have a rate of growth of their TAAs of 0.5 to 1 mm per year. Familial TAAs can grow rapidly at 2.1 mm per year, whereas LDS can have rapid growth of greater than 10 mm per year. The rate of growth of the descending aorta is generally greater than that of the ascending aorta.[19] Patients with genetic disorders and familial TAAs have faster rates of growth of their aneurysms but also much higher incidences of rupture and dissection at smaller sizes.

Patients with BAV aortopathy can have rates of growth of their TAAs of 0.5 to 2 mm per year.[20] Although these TAAs grow faster than degenerative/hypertensive aneurysms, they have rates of rupture and dissection that are similar for their respective sizes.[17]