Treatment guidelines for thoracic aortic aneurysms and dissections based on the underlying causative gene

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Thoracic aortic aneurysms leading to acute aortic dissections (TAADs) are a common cause of premature death in the United States.[1,2] The natural history of ascending aortic aneurysms is to progressively enlarge over time and ultimately lead to life-threatening acute aortic dissection or aortic rupture. Although medical treatments can slow the enlargement of ascending aortic aneurysms, the mainstay of prevention of aortic dissection is surgical repair when the aortic diameter expands to 5.5 cm or more.[2] However, aortic dissections occur in some patients who have little or no aortic enlargement. In fact, data from the International Registry of Aortic Dissections indicate that nearly 60% of aneurysms dissect at aortic diameters of less than 5.5 cm.[3] Because approximately one half of patients with acute ascending aortic dissection die suddenly without reaching a hospital, preventing premature deaths necessitates identifying subjects at risk for aortic dissection, carefully monitoring the diameter of the ascending aorta, and performing timely elective surgical repair. Therefore improved clinical predictors are needed not only to identify who is at risk for TAADs but also to determine the aortic diameter that justifies the risk of surgical repair of a thoracic aortic aneurysm to prevent an acute aortic dissection.

Hypertension and the presence of a congenital bicuspid aortic valve (BAV) are risk factors for the disease, but a genetic predisposition also plays a prominent role in etiology.[2] For many years, it has been known that patients with Marfan syndrome (MFS), an autosomal dominant syndrome with skeletal and ocular features, are highly predisposed to TAADs.[4] MFS results from mutations in *FBN1*, which encodes fibrillin-1, a component of elastin-associated microfibrils.[5] Loeys–Dietz syndrome (LDS) also predisposes patients to TAADs, along with craniofacial abnormalities, skeletal features of MFS, arterial tortuosity, and aneurysms and dissections of other arteries.[6,7] Arterial involvement beyond the ascending aorta is widespread but primarily involves the thoracic arterial circulation, including the coronary, subclavian, pulmonary, and intercostal arteries, and surgical intervention is generally successful.[8] LDS results from mutations in either the transforming growth factor β receptor type I or II genes (*TGFBR1* or *TGFBR2*).

Clinical studies of MFS and LDS have provided the first evidence that the timing of surgical repair of thoracic aortic aneurysms can be dictated by the underlying mutated gene causing the disease. Both syndromes lead to aneurysms involving the aortic root (defined as the segment of the ascending aorta extending from the valvular annulus to the sinotubular junction and including the sinuses of Valsalva). Patients with MFS with *FBN1* mutations are at a low risk for acute dissections until the aorta is greater than 5.5 cm in diameter.[9] In contrast, accumulating data from our research and that of others suggest that patients with a *TGFBR2* mutation (patients with either LDS or a family history of TAADs [FTAAD], as described below) experience aortic dissections with minimal enlargement of the aorta, leading to the recommendation that patients with a *TGFBR2* mutation undergo surgical repair of an aortic aneurysm when the diameter reaches 4.2 cm.[2] In addition to determining the risk of aortic dissection at a given diameter, current data suggest that the underlying mutation also dictates the risk for further vascular disease beyond the ascending thoracic aorta. For example, patients with *TGFBR2* mutations are at a high risk for aneurysms and dissections beyond the aortic root, including cerebrovascular disease,[7,10] whereas the risk for involvement of other arteries is low in patients with MFS.

We and others have determined that up to 19% of patients with TAADs without a genetic syndrome have FTAAD, indicating a significant genetic component to this disease.[11,12] FTAAD is primarily inherited in families as an autosomal dominant condition with decreased penetrance, primarily in women.[12,13] The familial aortic disease is variable in its expression of thoracic aortic disease, including varying age of disease onset, severity of presentation, and whether the aortic aneurysm involves the aortic root or the ascending aorta, sparing the root. There is interfamilial variability in FTAAD, with a subset of families with members who experience aortic dissections with little to no enlargement of the ascending aorta.[13] Additionally, variability in these families is evident in the clinical features that are associated with or segregate with the thoracic aortic disease in family members, which can include intracranial aneurysms, iliac and popliteal artery aneurysms, occlusive vascular diseases

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(early-onset stroke and coronary artery disease), abdominal aortic aneurysms, patent ductus arteriosus (PDA), and bicuspid aortic valve (BAV).[14,15]

We have identified *TGFBR1* and *TGFBR2* mutations in approximately 3% to 5% of FTAAD families whose members do not have features of LDS, suggesting a similar pathogenesis for disease in these FTAAD families.[8,16,17] In FTAAD families with *TGFBR2* mutations, aortic dissections occur with minimal enlargement of the aortic root. Therefore the recommendation for surgical repair of an aortic aneurysm when the diameter reaches 4.2 cm applies to both patients with LDS and patients with FTAAD. Interestingly, FTAAD can result from mutations in either *TGFBR1* or *TGFBR2*, but data are emerging in these families to support the notion that there are differences in vascular disease presentation and risk for dissection based on whether *TGFBR1* or *TGFBR2* is the causative gene.[10]

We and others have begun to identify additional genes for FTAAD. We have determined that the most frequently mutated gene is the smooth muscle cell (SMC)–specific isoform of α-actin, *ACTA2*, which is responsible for 10% to 14% of familial thoracic aortic disease.[15] A large French family was used by other investigators to map and identify mutations in the SMC-specific isoform of β-myosin heavy chain, *MYH11*.[18] These genes encode the major proteins found in SMC contractile units, which function to contract the SMC to withstand the stress of pulsatile blood flow and regulate flow and pressure. We have hypothesized that proper SMC contraction is implicated in maintaining the structural integrity of the ascending aorta, with disruption of SMC contractile function leading to TAADs.[19]

Analysis of thoracic aortic disease in patients with *ACTA2* mutations reveals some clinical features of the disease. The penetrance of TAADs in patients with *ACTA2* mutations is approximately 50%; that is, half of the *ACTA2* mutation carriers do not have thoracic aortic disease. The low penetrance of *ACTA2* mutations differs from what is observed at other identified loci and genes for FTAAD, with an age-related penetrance that is higher.[16,20] The majority of the patients with *ACTA2* mutations presented with acute ascending (type A) or descending (type B) aortic dissections, and 16 of the 24 deaths were due to type A dissections. Two patients experienced type A dissections at documented ascending aortic diameters of 4.5 and 4.6 cm, respectively, whereas 11 patients had dissections at aortic diameters of greater than 5.0 cm. Aortic dissections occurred in 3 patients less than 20 years of age, and 2 women died of dissections postpartum. Three young men had type B dissections complicated by rupture or aneurysm formation at 13, 16, and 21 years of age. Finally, a rare patient with *ACTA2* mutation can present with BAV or PDA.

Investigations into other vascular disease beyond thoracic aortic disease revealed that *ACTA2* mutations predispose not only to TAADs but also to occlusive vascular diseases, including early-onset coronary artery disease, stroke, and Moyamoya disease (a rare stroke syndrome).[21] An investigation into occlusive vascular diseases in patients with FTAAD with *ACTA2* mutations was initiated when we observed that all mutation carriers in a family had livedo reticularis, a skin rash caused by occlusion of the dermal arteries, irrespective of whether they had aortic disease.[15] Additionally, we noted that the vasa vasorum in the aortas of patients with *ACTA2* mutations were occluded due to SMC proliferation. Subsequent linkage and association studies confirmed that *ACTA2* mutations also cause occlusive vascular diseases, such as coronary artery disease and stroke, before the age of 55 years in men and 60 years in women. Moreover, a subset of *ACTA2* mutations also predispose to Moyamoya disease, a rare cerebrovascular syndrome characterized by bilateral occlusion or stenosis of the terminal internal carotid arteries and the formation of collateral vessel networks at the base of the brain, so-called Moyamoya vessels.[22,23] These data demonstrate that diffuse vascular disease resulting from either occluded or dilated arteries can be caused by a mutation in a single gene and have direct implications for clinical management of patients with *ACTA2* mutations.

MYH11 mutations are a rare cause of FTAAD and only occur in families in which 1 or more members with TAADs also have PDA.[18,24,25] Limited data of thoracic aortic disease in patients with *MYH11* mutations suggest that these patients have aneurysms involving the ascending aorta and can experience aortic dissections with aortic diameters of 4.4 cm.[25]

Because fewer than 20% of FTAAD families have mutations in one of the known genes, specific management for the majority of FTAAD families is still not defined. For these families, we recommend that the aortic disease presentation in the affected family members be assessed, along with other vascular disease or clinical features, and that the management be based on this assessment. If family members have experienced dissections at aortic diameters of less than 5.0 cm, then surgical repair for other affected family members at diameters of less than 5.0 cm should be considered. In families with TAADs associated with BAV, studies have indicated that the component features, BAV and TAADs, are independent manifestations of a single-gene defect.[14] Therefore family members need to have routine aortic imaging, irrespective of whether BAV is present.

In summary, as novel FTAAD genes are discovered, clinical features associated with each gene are identified that inform the clinical management of patients based on the underlying genetic mutation. Based on these findings, we are recommending that if the underlying gene causing the predisposition to thoracic aortic disease is identified in a patient or family, the management of the aortic disease and risk for additional vascular diseases be based on the causative gene.

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