Use of genetics for personalized management of heritable thoracic aortic disease: How do we get there?

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The major diseases affecting the thoracic aorta are aortic aneurysms and acute aortic dissections. Medical treatments can slow the enlargement of aneurysms, but the mainstay of treatment to prevent premature death resulting from dissection is surgical repair of the thoracic aortic aneurysm, which is typically recommended when the aortic diameter reaches 5.0 to 5.5 cm. Studies of patients with acute aortic dissections, however, indicate that as many as 60% of dissections occur at aortic diameters smaller than 5.5 cm. Clinical predictors are therefore needed to distinguish those at risk for dissection at an aortic diameter smaller than 5.0 cm and to determine the aortic diameter that justifies the risk of surgical repair to prevent an acute aortic dissection. Data from genetic studies during the past decade have established that mutations in specific genes can distinguish patients at risk for the disease and predict the risk of early dissection at diameters smaller than 5.0 cm. This information has the potential to optimize the timing of aortic surgery to prevent acute dissections. (J Thorac Cardiovasc Surg 2015;149:S3-5)

The major diseases affecting the thoracic aorta are thoracic aortic aneurysms and thoracic acute aortic dissections (together termed TAADs). The natural history of ascending thoracic aortic aneurysm (TAA) is asymptomatic enlargement with time until the occurrence of an ascending aortic dissection (Stanford type A). Less deadly dissections originate in the descending thoracic aorta distal to the left subclavian artery (Stanford type B). Although medical treatments can slow aneurysm enlargement, the mainstay of treatment to prevent premature death resulting from a dissection is surgical repair of the TAA. This intervention is typically recommended when the aortic diameter reaches 5.0 to 5.5 cm¹; however, studies of patients with acute type A aortic dissections indicate that up to 60% of such dissections occur at aortic diameters smaller than 5.5 cm.² Clinical predictors are therefore needed to distinguish those at risk for dissection at an aortic diameter smaller than 5.0 cm and to determine the aortic diameter that justifies the risk of surgical repair to prevent an acute dissection. Genetic studies during the past decade have established that mutations in specific genes can distinguish patients at risk for the disease and predict the risk of early dissection at

diameters smaller than 5.0 cm. This information has the potential to optimize the timing of aortic surgery to prevent acute type A dissections.

It is established that patients with Marfan syndrome (MFS), an autosomal dominant syndrome with skeletal and ocular features, are highly predisposed toward TAAD development and typically have aortic root aneurysms.³ MFS results from mutations in *FBN1*, which encodes fibrillin-1, a component of elastin-associated microfibrils. Loeys-Dietz syndrome (LDS) is a syndrome related to MFS that also predisposes patients to TAAD development. Patients with LDS display arterial tortuosity, craniofacial abnormalities, and skeletal features associated with MFS, along with aneurysms and dissections of the aorta and other arteries and thin, translucent skin reminiscent of patients with vascular Ehlers-Danlos syndrome.⁴ LDS results from mutations in either the transforming growth factor- β receptor type I or II genes (*TGFBR1* and *TGFBR2*). More recently, heterozygous mutations in *SMAD3* and *TGFB2* have been identified in families that share some clinical features with MFS and LDS.⁵⁻⁷

Emerging clinical data on the phenotypes associated with specific genes provide evidence that the underlying mutation could inform patient management, including the timing of surgical repair of TAAs and the risk of additional vascular disease. For example, patients with MFS who have *FBN1* mutations have a low risk of acute aortic dissection at aortic diameters smaller than 5.5 cm and a low risk for aneurysms of other arteries.⁸ Interestingly, common genetic variants in the *FBN1* gene (single-nucleotide polymorphisms) increase the risk for TAAD in the general population,⁹ and ongoing studies are investigating whether these could help to determine which patients could be managed in a manner similar to patients with MFS.¹⁰ In contrast, data suggest that aortic dissections occur in patients with *TGFBR1* and *TGFBR2* mutations at aortic diameters smaller than 5.0 cm and that these patients also

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Abbreviations and Acronyms

FTAAD	= familial thoracic acute aortic dissection
LDS	= Loeys-Dietz syndrome
MFS	= Marfan syndrome
SMC	= smooth muscle cell
TAA	= ascending thoracic aortic aneurysm
TAAD	= thoracic aortic aneurysm and thoracic acute aortic dissection

have aneurysms and dissections of other arteries.^{4,11} These findings led to the recommendation in the American College of Cardiology Foundation and American Heart Association treatment guidelines for thoracic aortic disease that the underlying genetic mutation should dictate the timing of aortic repair. The current recommendation for patients with LDS is repair of the aorta at 4.2 cm¹; however, many European countries treat LDS and MFS similarly and perform repair when the aorta reaches 5.0 cm, surprisingly without observing premature dissections in either patients MFS or those with LDS.¹² In addition, studies suggest that the risk of aortic dissection with minimal enlargement may be less for individuals with *TGFBR1* mutations than for those with *TGFBR2* mutation.¹¹

As many as 20% of patients with nonsyndromic TAAD have first-degree relatives with a history of TAAD, indicating a significant genetic contribution to the disease. Analysis of these familial TAAD (FTAAD) pedigrees has shown that TAAD is primarily inherited as a single-gene, autosomal dominant condition with reduced penetrance.^{13,14} These families demonstrate variable expression of TAAD, with variation in the age of disease onset, risk of ascending aortic dissections at diameters smaller than 5.0 cm, prevalence of type B dissections, and involvement of the aortic root, the ascending aorta, or both (fusiform aneurysms involving the root and ascending aorta). In addition, families with FTAAD show variable cosegregation of other cardiovascular complications with TAAD. These may include bicuspid aortic valve, patent ductus arteriosus, abdominal aortic aneurysms, and other vascular diseases (eg, intracranial aneurysms, other arterial aneurysms, and occlusive arterial disease).^{13,15-18} Nine genes that predispose toward autosomal dominant FTAAD have been identified to date.^{6,7,11,15,17,19-21} *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFBR2* mutations have been identified in approximately 6% to 8% of families with FTAAD with no features of MFS or LDS, suggesting a similar pathogenesis for aneurysm formation between syndromic disease and FTAAD.^{6,7,11,20,22} Mutations in *ACTA2*, *MYH11*, *MYLK*, and *PRKG1* have also been identified in families with FTAAD without MFS or LDS features.

These genes are all involved in vascular smooth muscle cell (SMC) contraction and are termed *SMC contractile genes*. SMCs are arranged circumferentially in multiple layers in arteries. For contractile function, SMCs express smooth muscle-specific isoforms of α -actin and myosin (encoded by *ACTA2* and *MYH11*, respectively), which polymerize to form thin and thick filaments, respectively. *MYLK* and *PRKG1* encode kinases that control SMC contraction and relaxation, respectively. Loss-of-function mutations have been identified in *MYLK*, and gain-of-function mutations have been found in *PRKG1*.^{19,21} Of these, *ACTA2* is the most commonly altered gene in FTAAD and is responsible for disease in 14% of patients.¹⁷ The other contractile genes contribute to 4% of FTAAD. In addition to FTAAD, *ACTA2* mutations predispose toward development of occlusive vascular diseases in smaller arteries, including early-onset coronary artery disease, stroke, moyamoyalike cerebrovascular disease, and primary pulmonary hypertension.^{18,23,24}

We examined aortic disease, management, and outcome associated with the first aortic event (defined as dissection or TAA repair) in a cohort of patients with *ACTA2* mutations (unpublished data). Aortic disease presentation associated with *ACTA2* mutations differed from that associated with MFS. Patients with *ACTA2* mutations had fusiform aneurysms involving the aortic root and ascending aorta and were more likely to present with acute dissection than were patients with MFS. For individuals undergoing surgical repair of fusiform TAAs without evidence of dissection, the maximum diameter was either in the aortic root or in the ascending aorta and ranged from 4.2 to 6.5 cm. In contrast, the maximum diameter ranged from 3.8 to 9.5 cm at presentation with an acute type A dissection. Thus, although cardiovascular surgeons followed the guidelines established for patients with MFS, a third of the individuals with *ACTA2* mutations had dissection at aortic diameters smaller than 5 cm. These data suggest that surgical repair of a TAA in an individual with *ACTA2* mutation should be considered when the aorta reaches a diameter of 4.5 cm.

The question remains as to whether aortic diameter at the time of dissection can be used to guide decisions about when to repair the aorta in individuals with genetically triggered thoracic aortic disease. A recent study sought to determine whether thoracic aortic diameter or geometry was altered by acute type A aortic dissection by comparing computed tomographic images obtained within 2 years of a dissection with computed tomographic images obtained at presentation with dissection from patients who did not have MFS or a bicuspid aortic valve.²⁵ Most of the patients in the study had a type B dissection, and the dissection of the ascending aorta was retrograde. The ascending aorta was found to increase significantly in diameter and volume after dissection, suggesting that ascending aortic diameters noted at presentation after dissection do not accurately reflect the size of the

aorta just before and at the time of dissection. Importantly, however, the aortic root diameter was not seen to be significantly altered after an acute aortic dissection.

Guidelines for surgical repair of the aorta that are based on the aortic diameter at dissection thus cannot use the size of the dissected ascending aorta as a reliable gauge, but the size of the aortic root may be used as a reliable gauge because it is not distorted by dissections. Because the majority of genetically triggered aneurysms involve the aortic root, which is typically monitored to determine timing of surgical repair, the size of the aortic root specifically should be collected to assemble the most reliable data for setting surgical guidelines for aortic repair in patients with specific gene mutations.

In summary, many patients with genetically triggered thoracic aortic disease appear to have an increased risk of aortic dissection despite little to no enlargement of the aorta. The ideal way to determine the risk associated with each gene would be to obtain computed tomographic images proximately before dissection to determine the diameter of the aorta just before the dissection. Such images are rarely available, however, so data should be obtained from postdissection images and measurements made that include the aortic root and ascending aorta. Because these patients typically demonstrate aortic root enlargement, and studies have shown that aortic root diameter is not significantly distorted after dissection, postdissection aortic root measurements may be used to guide decisions about surgical intervention on the basis of aortic diameter. Ideally, better biomarkers than aortic diameter will be available to assess the risk of acute aortic dissection in the future. Until these have been developed, however, it is critical to ensure that the most accurate data are gathered to inform guidelines for surgical management of genetically triggered aortic disease.

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