of 31 patients, Dr Cameron mentions that he is reassessing the use of only 3 subannular sutures in patients who have extreme tissue fragility.[4]

Fukunaga and coauthors[1] provide a very important contribution and a modification of their technique; in recognition of the extreme fragility of the commissural triangles of the noncoronary cusp, they added 3 horizontal 4-0 polypropylene mattress sutures to this "paper-thin area." They provide an illustrative drawing. The authors do not precisely state it, but they bestow a lesson for all of us. With the very wide and expanding clinical application of valve-sparing root replacement, there remain specific circumstances and genetic conditions with the severest of tissue fragility in which the technical expertise of the most experienced aortic root surgeons, including the legendary Tirone David, may be necessary to achieve the desired long-term results.

References

1. Fukunaga N, Seidman MA, David TE. Valve-sparing root replacement in a patient with a filamin A variant. *J Thorac Cardiovasc Surg*. 2021;161:e353-5.
2. Reinstein E, Frentz S, Morgan T, Garcia-Minaur S, Leventer RJ, McGillivray G, et al. Vascular and connective tissue anomalies associated with X-linked periventricular heterotopia due to mutations in Filamin A. *Eur J Hum Genet*. 2013;21:494-502.
3. Chen MH, Choudhury S, Hirata M, Khalsa S, Chang B, Walsh CA. Thoracic aortic aneurysm in patients with loss of function Filamin A mutations: clinical characterization, genetics, and recommendations. *Am J Med Genet A*. 2018;176:337-50.
4. Liu RH, Fraser CD III, Zhou X, Cameron DE, Vricella LA, Hibino N. Pseudoaneurysm formation after valve sparing root replacement in children with Loeys–Dietz syndrome. *J Card Surg*. 2018;33:339-43.

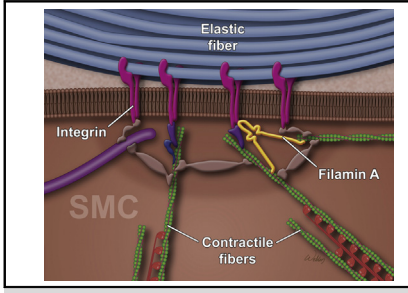
ADULT

See Article page e353.

Check for updates

Commentary: Genetics and surgical planning in heritable aortic disease—moving from "when to operate" to "how to operate"

Ashley Dawson, MD,[a] and Scott A. LeMaire, MD[a,b,c,d]



Filamin A links aortic smooth muscle cell contractile units to the extracellular matrix.

CENTRAL MESSAGE

Consistent reporting of tissue quality and repair techniques used in patients with heritable aortic disease will help surgeons develop an operative plan tailored to a patient's genetic mutation.

The efficiency and decreasing cost of genetic analysis have increased the identification of gene mutations associated with heritable thoracic aortic aneurysm and dissection (HTAAD). Curating causative genes requires carefully evaluating the disease phenotypes associated with each mutation.[1] Consistently reporting gene-specific clinical features has been important in the development of evidence-based recommendations with which to counsel patients with HTAAD and make decisions about the timing of aortic repair.[2,3] From a surgeon's perspective, knowing the tissue quality and recommended repair techniques

From the [a]Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, [b]Cardiovascular Research Institute, and [c]Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Tex; and [d]Department of Cardiovascular Surgery, Texas Heart Institute, Houston, Tex.

Dr Dawson's work is supported by a fellowship award through the University of Kentucky-Baylor College of Medicine Aortopathy Research Center within the American Heart Association Strategically Focused Vascular Disease Research Network (18SFRN33960114). Dr LeMaire's work is supported in part by the Jimmy and Roberta Howell Professorship in Cardiovascular Surgery at Baylor College of Medicine.

Disclosures: The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication May 18, 2020; accepted for publication May 18, 2020; available ahead of print June 5, 2020.

Address for reprints: Scott A. LeMaire, MD, Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, One Baylor Plaza, BCM 390, Houston, TX 77030 (E-mail: slemaire@bcm.edu).

J Thorac Cardiovasc Surg 2021;161:e358-9
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.05.063

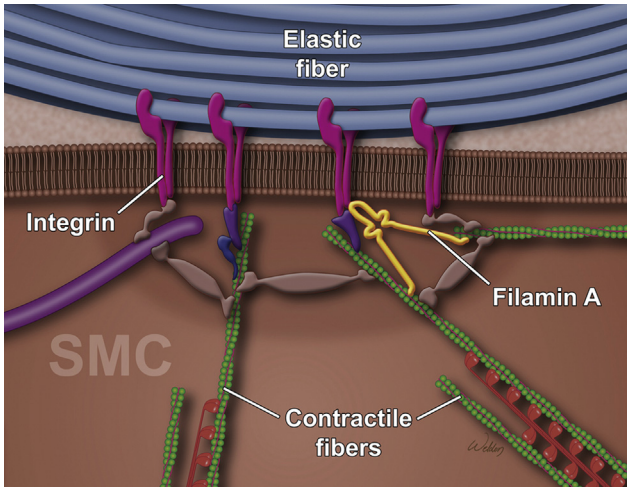


FIGURE 1. Filamin A links aortic smooth muscle cell contractile units to the extracellular matrix. *SMC*, Smooth muscle cell. Used with permission of Baylor College of Medicine.

associated with a mutation is also important when evaluating a patient with HTAAD preoperatively.

The article by Fukunaga and colleagues,[4] from an extremely experienced center that has made seminal contributions to the field, details their experience with uncommonly fragile tissue and the technical adjustments made to complete a valve-sparing aortic root replacement in a patient with HTAAD. This patient was found preoperatively to have a causative mutation in *FLNA*, an X-chromosome gene that codes for filamin A, an actin binding protein involved in the aortic mechanotransduction complex (Figure 1). As one of the proteins linking actin contractile filaments within smooth muscle cells to the extracellular matrix, filamin A plays a key role in maintaining mechanical homeostasis of the aortic wall.[5,6] Mutations in *FLNA* have been linked to HTAAD and described as having a similar systemic phenotype to vascular Ehlers-Danlos syndrome.[7] The tissue fragility described by the authors correlates with the challenges described by surgeons and alternative techniques needed in repairing arteries in those with vascular Ehlers-Danlos syndrome.[8] The authors support modifying operative techniques in patients with significantly friable tissue to avoid pseudoaneurysm formation due to tissue tearing as described by Liu and colleagues,[9] who detailed complications after valve-sparing aortic root repairs in patients with severe Loeys–Dietz syndrome (LDS). These modifications may not be necessary in all patients with LDS because, in general, LDS has been described as not having a consistently fragile tissue phenotype.[10] Variations in tissue fragility may be due to mutation-specific or patient-specific factors, and reporting the patient's complete clinical features may help inform surgeons about what to expect when evaluating similar patients.

These reports highlight the importance of understanding the technical implications of varying tissue types in HTAAD during surgical repair. Many causative mutations of HTAAD are rare, and surgical repairs in affected patients are performed infrequently even at the most experienced centers. Although best practices are typically informed by large studies, such studies are probably not feasible in the less common types of HTAAD. The report by Fukunaga and colleagues[4] and other reports of the gene-specific "intraoperative phenotype" of HTAAD provide valuable information for planning operative intervention. Although preoperative planning cannot replace intraoperative tissue evaluation, it can still be beneficial to anticipate the additional operative approaches that may be needed, particularly in patients with rare mutations. Anticipating which gene mutations—and potentially even which mutation variants—may necessitate modification of operative techniques provides an opportunity to expand precision medicine to the operating room in patients with HTAAD.

The authors thank Scott A. Weldon, MA, CMI, FAMI, for creating the illustration, and Stephen N. Palmer, PhD, ELS, at the Texas Heart Institute for providing editorial support.

References

1. Renard M, Francis C, Ghosh R, Scott AF, Witmer PD, Ades LC, et al. Clinical validity of genes for heritable thoracic aortic aneurysm and dissection. *J Am Coll Cardiol*. 2018;72:605-15.
2. Dawson A, LeMaire SA. Building on a genetic framework: can we personalize the timing of surgical repair for patients with heritable thoracic aortic disease? *J Thorac Cardiovasc Surg*. 2020;160:901-5.
3. Ouzounian M, LeMaire SA. How can genetic diagnosis inform the decision of when to operate? *J Vis Surg*. 2018;4:68.
4. Fukunaga N, Seidman MA, David TE. Valve-sparing root replacement in a patient with a filamin Avariant. *J Thorac Cardiovasc Surg*. 2021;161:e353-5.
5. Humphrey JD, Dufresne ER, Schwartz MA. Mechanotransduction and extracellular matrix homeostasis. *Nat Rev Mol Cell Biol*. 2014;15:802-12.
6. Karimi A, Milewicz DM. Structure of the elastin-contractile units in the thoracic aorta and how genes that cause thoracic aortic aneurysms and dissections disrupt this structure. *Can J Cardiol*. 2016;32:26-34.
7. Reinstein E, Frentz S, Morgan T, Garcia-Minaur S, Leventer RJ, McGillivray G, et al. Vascular and connective tissue anomalies associated with X-linked periventricular heterotopia due to mutations in Filamin A. *Eur J Hum Genet*. 2013;21:494-502.
8. Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. *J Vasc Surg*. 2005;42:98-106.
9. Liu RH, Fraser CD III, Zhou X, Cameron DE, Vricella LA, Hibino N. Pseudoaneurysm formation after valve sparing root replacement in children with Loeys-Dietz syndrome. *J Card Surg*. 2018;33:339-43.
10. Williams JA, Loeys BL, Nwakanma LU, Dietz HC, Spevak PJ, Patel ND, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg*. 2007;83:S757-63; discussion S85-90.