Nonsyndromic Thoracic Aortic Aneurysms and Dissections—Is Screening Possible?

Thais Faggion Vinholo, BS, MSc,[*] Mohammad A. Zafar, MD,[*] Bulat A. Ziganshin, MD,[,†] and John A. Elefteriades, MD, PhD (Hon)[*]*

Nonsyndromic thoracic aortic aneurysm and dissection (TAAD) account for 95% of all TAAD cases and comprise a subset in which the lack of obvious clinical signs makes diagnosis a challenge. Despite the potentially fatal natural history, timely diagnosis and prophylactic surgical intervention allow restoration of near-normal life expectancy in TAAD patients, underlining the critical importance of screening tests. To date, more than 30 TAAD disease-causing genes have been identified, and over 30% of nonsyndromic TAAD patients have a genetic mutation in 1 or more of these genes. Whole exome sequencing allows routine genetic testing in a clinical setting by screening for all TAAD-related genes, thus facilitating personalized aortic care. Additionally, increased vigilance upon diagnosis of certain TAAD-related diseases ("guilty associates") and the emergence of modern radiologic and novel serologic screening tests will further bolster efforts to detect undiagnosed asymptomatic nonsyndromic TAAD.

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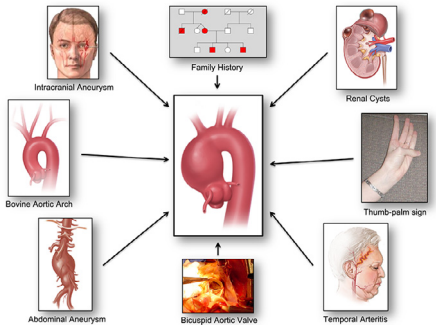

Paradigm of "Guilt by Association" for detection of silent thoracic aortic aneurysms.

Central Message

Screening for nonsyndromic TAAD is valuable and is becoming a cornerstone of clinical aortic care, helping to capture undiagnosed asymptomatic patients before they suffer a devastating complication.

INTRODUCTION

Although the prevalence of thoracic aortic aneurysm (TAA) is relatively high, occurring in approximately 1% of the general population,[1] timely diagnosis of this pathologic entity remains a challenge for clinicians. TAAs usually grow slowly and silently to the point of either dissection and/or rupture, with the most common presenting symptom being death.[2] In fact, aneurysm and dissection of the aorta is one of the major causes of death in humans, accounting for 1–2% of deaths in Western countries.[1] However, even this statistic may represent an underestimation, as sudden deaths are commonly attributed to coronary artery disease, when in fact the cause of death may have been from an aortic event: a postmortem study using computerized tomography at autopsy identified Type A aortic dissection as the cause of death in 7% of out-of-hospital cardiopulmonary arrests.[3]

Despite the natural virulence of TAAD, elective surgical intervention can be performed with remarkable safety in the present era, restoring survival to that of the general "healthy" population.[4] In our experience, mortality in all categories of elective ascending aortic and arch operations ranges only from 0% to 1.9%.[5–8]

Therefore, the critical challenge at hand is to identify undiagnosed asymptomatic patients via screening, so as to allow monitoring and timely surgical intervention to change the potentially lethal fate of TAA.

Over the past 2 decades, it has become evident that TAADs, especially those involving the ascending and transverse arch portion of the aorta, are often familial in nature and be passed on from one generation to the next. To date, more than 30 genes have been discovered that cause TAAD, which provide the basis for genetic testing and even potential screening of individuals for this mainly asymptomatic condition. In this manuscript, we review the current understanding of the genetics of TAAD and discuss the role of genetic testing in providing care for such patients.

*Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut
†Department of Cardiovascular and Endovascular Surgery, Kazan State Medical University, Kazan, Russia

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Address reprint requests to John A. Elefteriades, MD, PhD (Hon), Aortic Institute at Yale-New Haven, Yale University School of Medicine, Clinic Building CB 317, 789 Howard Avenue, New Haven, CT 06519. E-mail: john.elefteriades@yale.edu

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SYNDROMIC VS NONSYNDROMIC THORACIC AORTIC ANEURYSM AND DISSECTION

Thoracic aortic aneurysm and dissection (TAAD) can be divided into 2 entities: syndromic and nonsyndromic. Syndromic TAAD involves other organ systems in addition to the aorta, whereas nonsyndromic TAAD is confined to the aorta. The involvement of other organ systems can provide overt clinical signs of disease to alert the physician. Syndromic patients suffer from systemic diseases such as Marfan syndrome, Loeyz-Dietz syndrome, Ehlers-Danlos syndrome, arterial tortuosity syndrome, aneurysm-osteoarthritis syndrome, and cutis laxa syndrome.[9] However, these syndromes only contribute approximately 5% of all TAADs, whereas familial and sporadic nonsyndromic TAAD account for 95% of TAAD.[9,10] Furthermore, the distinct cardiovascular, musculoskeletal, and ocular phenotypic manifestations of syndromic TAAD may bring these patients to medical attention earlier in their disease, whereas the lack of overt clinical stigmata in nonsyndromic TAAD patients delays diagnosis, underlining the importance of screening in this regard.

FAMILIAL PATTERNS OF NONSYNDROMIC TAAD

The discovery of familial aggregation of abdominal aortic aneurysms (AAA) by Tilson at Yale in 1984[11] ultimately triggered a search for genetic factors contributing to the development of TAA in the late 1990s.[12,13]

Nonsyndromic TAAD can be divided into familial or sporadic, with familial nonsyndromic TAAD referring to the instance when more than one family member harbors an arterial aneurysm (familial clustering). Our previous studies confirmed the role of genetics in the causation of TAA by way of detailed family pedigree analyses.[12,14] Among patients with nonsyndromic TAAD, we demonstrated that 21.5% had familial clustering and followed a predominantly autosomal dominant mode of inheritance.[14] However, this 21.5% statistic almost certainly represents an underestimation, as most family members of affected patients have not undergone the aortic imaging (echocardiography or computed tomography) necessary to reveal an aneurysm.[14] Compared to the sporadic form, we also found that patients in the familial category of the disease manifested an earlier age at presentation (58.2 vs 65.7 years) and a higher growth rate (0.21 vs 0.16 cm/y),[14] highlighting the virulence of familial TAAD and arguing strongly in favor of routine screening of all first-order family members of patients presenting with TAA. In fact, recent recommendations stipulate that second-degree relatives of patients with familial nonsyndromic TAAD should also be screened, as this results in diagnosing otherwise silent disease in a significant number of patients (Fig. 1).[15]

The genetic predisposition observed in the realm of nonsyndromic TAAD kicked off an aggressive search for new genes that could be related to the development of TAAD.

GENES ASSOCIATED WITH TAAD

It is now widely accepted by the medical community that while descending aortic aneurysms are degenerative in nature and linked to pathologies such as atherosclerosis, hyperlipidemia, and hypertension, the etiology of ascending aortic aneurysms is predominantly linked to a crucial genetic component.[10,16]

To date, gene discovery efforts have identified over 30 genes associated with the development of thoracic aortic aneurysm or dissection (TAAD). In fact, over 30% of familial nonsyndromic TAAD patients harbor a pathogenic variant in one or more of these genes.[17] From among these 30-plus genes, pathogenic variants in only 14 were found to be related with familial nonsyndromic TAAD,[18] while the remaining genes are associated with syndromic TAAD.

Most of the identified genes encode proteins related to extracellular matrix (*FBN1, FBN2, COL3A1, EFEMP2, ELN, EMILIN1, MFAP5, LOX, BGN*), smooth muscle cell contractile units (*MYH11, ACTA2, MYLK, PRKG1, FLNA, MAT2A, FOXE3*), or TGF-Beta signaling pathways (*TGFBR1* and *TGFBR2, TGFB2* and *TGFB3, SMAD, SKI, SLC2A10*).[9] The medial layer of the aorta is predominantly composed of smooth muscle cells. Therefore, it is intuitive that mutations occurring in genes that encode elements of the contractile unit within a muscle cell could disrupt the medial layer.[9] Consequently, this impairment decreases the ability of these cells to properly regulate and remodel the extracellular matrix of the aortic tunica media.[19]

Mutations in *ACTA2*, a smooth muscle cell gene, have proven to be the most common causative aberration in nonsyndromic TAD, accounting for 12−21% of cases.[18] Literature review of *ACTA2* mutation patients identifies cases where dissection has occurred at aortic dimensions less than 5 cm, making it extremely important to identify patients with these mutations, so that prophylactic aortic repair can take place prior to the usual recommended threshold of 5−5.5 cm.

KIF6, one of the more recently identified genes that poses a risk for aortic dissection, was first linked with coronary heart disease (CHD).[20] The *KIF6* gene codes for a protein from the kinesin superfamily, which is involved in the important role of intracellular transportation (KIF6).[20] The *KIF6* 719Arg variant, specifically, was shown to increase the risk of patients developing CHD. Our group studied the possibility of mutations in this gene predisposing to TAAD.[20] Even after controlling the potential confounding variable of patients having CHD, presence of the KIF6719Arg variant was associated with 2-fold higher odds of aortic dissection compared with noncarriers.[20]

Despite the fact that nonsyndromic TAAD has been studied as a separate entity from syndromic TAAD, genetic studies have shown an overlap among genes between syndromic and nonsyndromic patients. For example, mutations in *FBN1*, the gene related to the pathogenesis of aortic disease in Marfan's syndrome, have also been associated with sporadic nonsyndromic TAAD.[21] Furthermore, there are certain mutations that have proven to predispose to aortic dissection at a smaller diameter, necessitating surgical intervention at an earlier stage (Fig. 2).[17]

With the burgeoning armamentarium of culprit genes at our disposal, genetic screening of individual patients provides a personalized insight into the development and progression of the disease, thereby better guiding surgical intervention.

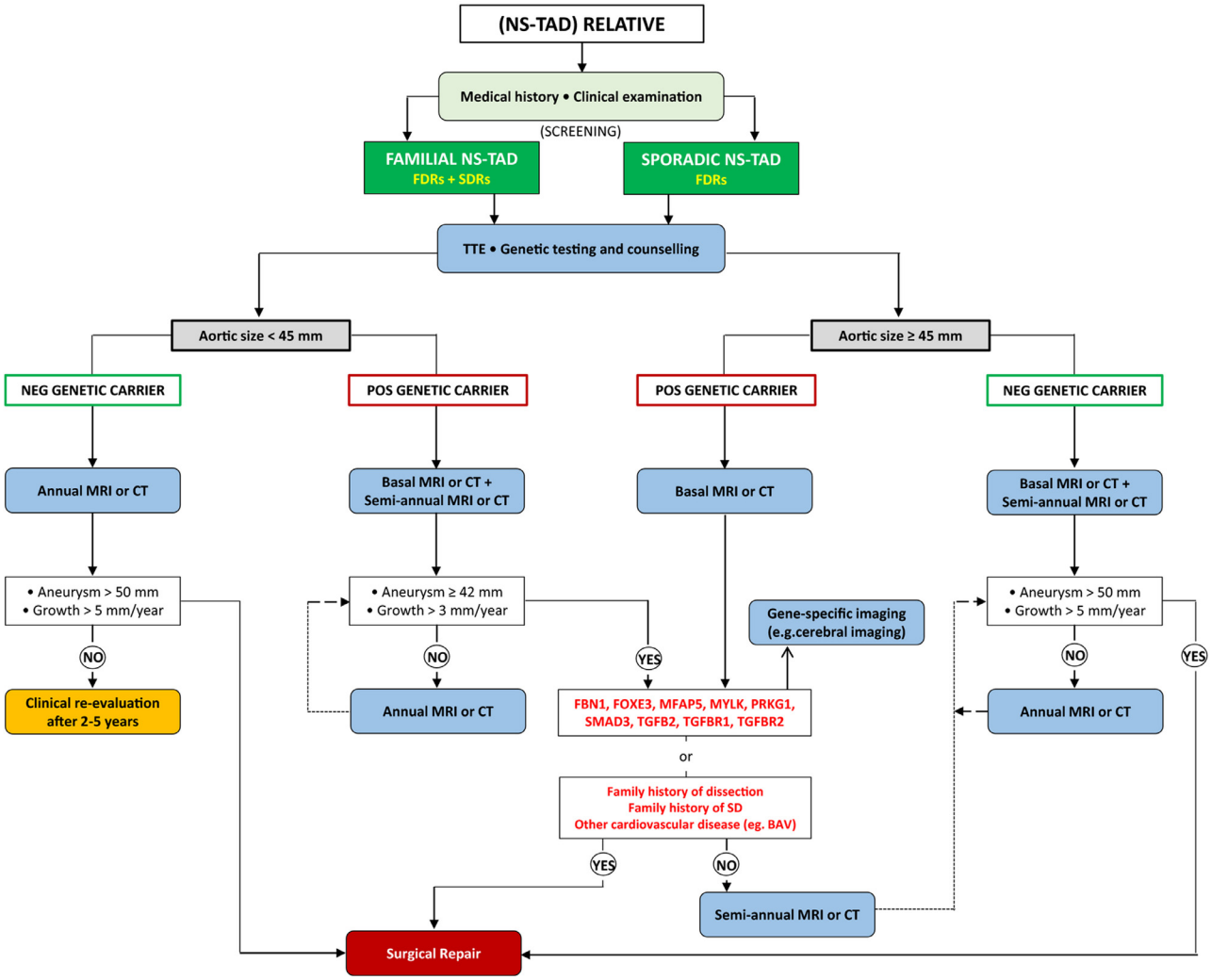

Figure 1. Proposed flow chart for a dedicated screening program for relatives of patients affected by nonsyndromic diseases of the thoracic aorta based on the authors' extensive literature review. The figure represents the best judgment of the authors. BAV, bicuspid aortic valve; CT, computed tomography; FDRs, first-degree relatives; MRI, magnetic resonance imaging; NS-TAD, nonsyndromic thoracic aortic disease; SDRs, second-degree relatives; TTE, transthoracic echocardiogram. (Reproduced with permission from ref. 15).

Furthermore, molecular genetic analysis provides invaluable information to family members of the proband, for they may be carrying the same mutation. Determining whether family members carry the proband's aortic mutation is useful no matter what the result. Carriers can be followed very closely, while noncarriers are relieved of the emotional burden of expecting an aneurysm and undergoing serial monitoring. While different family members can carry the same pathogenic variant, the presentation of each individual might be substantially different due to variable penetrance.

ROUTINE GENETIC TESTING FOR TAA

Since 2012, we have been ordering genetic screening by way of whole exome sequencing (WES) on nearly all patients presenting to the Yale Aortic Institute. WES encompasses DNA sequencing of all coding regions (exons) of a genome and provides the following benefits: (1) it is comprehensive, including (but not limited to) testing all the 30-plus TAAD genes that have been identified to date (all in one single test done at one laboratory); (2) data can be reanalyzed retrospectively because the entire exome is sequenced, permitting testing of new disease-causing genes as they are discovered; (3) it is usually more affordable and efficient than testing individually for specific genes and syndromes in various laboratories; and (4) it provides genome-wide data that can be "mined" for new mutations.[16] The fact that the genes identified to date only account for approximately 30% of aortic diseases in nonsyndromic TAAD patients leads us to believe that there are many more genes yet to be discovered.[18]

The information gleaned from WES becomes very valuable for family members of the proband. Once an individual is found to have a specific mutation, we look for that specific

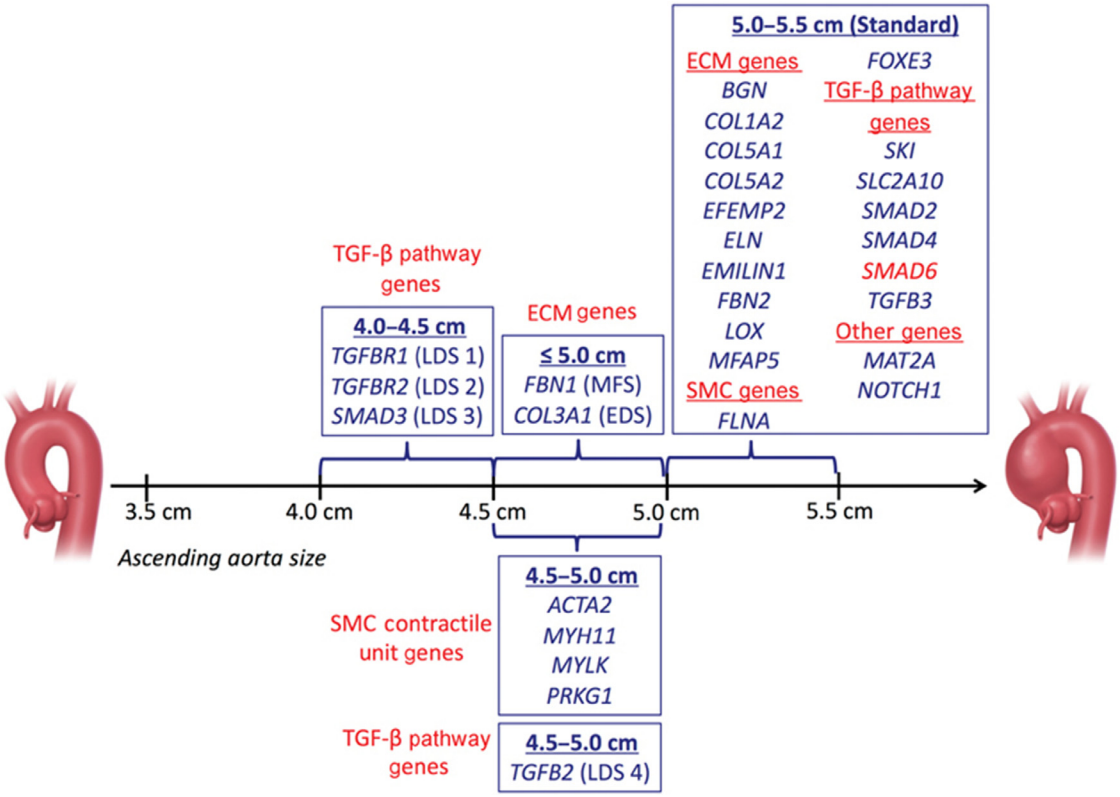

Figure 2. Ascending aorta dimensions for prophylactic surgical intervention. Any gene newly reported during the past year to be associated with TAAD is highlighted in red. ECM, extracellular matrix; SMC, smooth muscle cell; TAAD, thoracic aortic aneurysm and/or dissection; TGF, transforming growth factor. (Reproduced with permission from ref. 17).

mutation using the less complex and cheaper "single-site" Sanger sequencing method in their family members.[22] In this technique, sequencing is targeted to the gene already shown to harbor an anomalous variant in the proband genome.[22] This way, instead of going through the "whole genetic alphabet" we can focus on the more likely culprit "letter" found in the proband. To date, we have tested over 400 TAAD patients using WES (Fig. 3).

We recently completed (to the best of our knowledge) the largest genetic analysis of nonsyndromic TAAD to date, in concert with our colleagues from the United Kingdom (on blood and saliva samples from UK patients and surgical aortic specimens from Yale Aortic Institute patients) using targeted polymerase chain reaction and a next-generation sequencing-based panel.[21] Identified genetic variants were classified as either "pathogenic," "likely pathogenic," "variant of uncertain significance," or "likely benign" according to the American College of Medical Genetics and Genomics.[23] We found that most pathogenic or likely pathogenic variants were found in genes recognized to cause syndromic TAAD (*FBN1, TGFBR1, TGFBR2, COL1A1, COL1A2, COL3A1, COL5A1*, and *COL5A2* genes). Furthermore, the probability of carrying a pathogenic or likely pathogenic variant was elevated in patients with a syndromic element, ascending aortic aneurysm, positive family history of aortopathy, and early age at presentation.[21]

"GUILT BY ASSOCIATION—PARADIGM FOR DETECTING A SILENT KILLER"

Previous studies by our group have identified a number of diseases, or "guilty associates" that have a close association with TAAD (Fig. 4).[24] These include intracranial aneurysm, bovine aortic arch, abdominal aortic aneurysm, renal cysts, bicuspid aortic valve, family history of aortic/aneurysm disease, thumb-palm test, temporal arteritis, and aortic coarctation.[24] Diagnosis of these clinical conditions should prompt thorough screening for TAA.

RADIOGRAPHIC SCREENING

The current US Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease recommend imaging of the aorta for all first-degree relatives of patients diagnosed with TAAD. If one of the imaging screenings of a first-degree relative comes back positive, it is recommended that second-degree relatives also be screened for aortic dilation.[25]

The most widely used imaging modalities for TAA screening include echocardiography (transthoracic and transesophageal), computed tomography (CT) scan, and magnetic resonance imaging (MRI). FDG-PET/CT imaging, a vascular metabolic imaging technique pioneered by Sakalihasan and colleagues from Liege (Belgium), is also emerging as a method to monitor aortic aneurysm disease progression and to predict the risk of

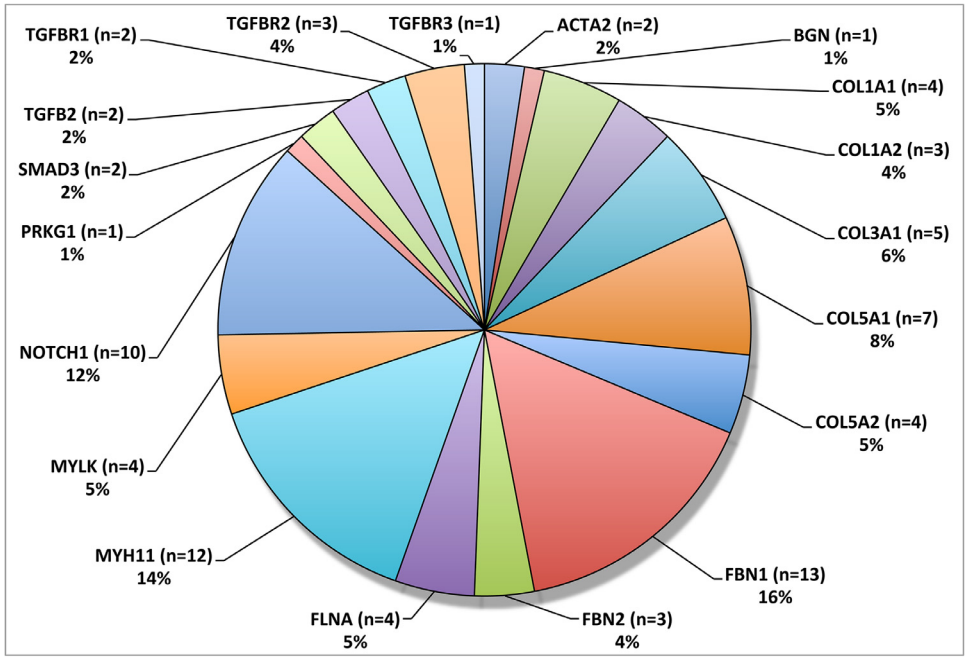

Figure 3. Frequency distribution of genetic defects in TAAD-related genes based on the Yale Aortic Institute routine genetic testing program. (In part based on data from ref. 16).

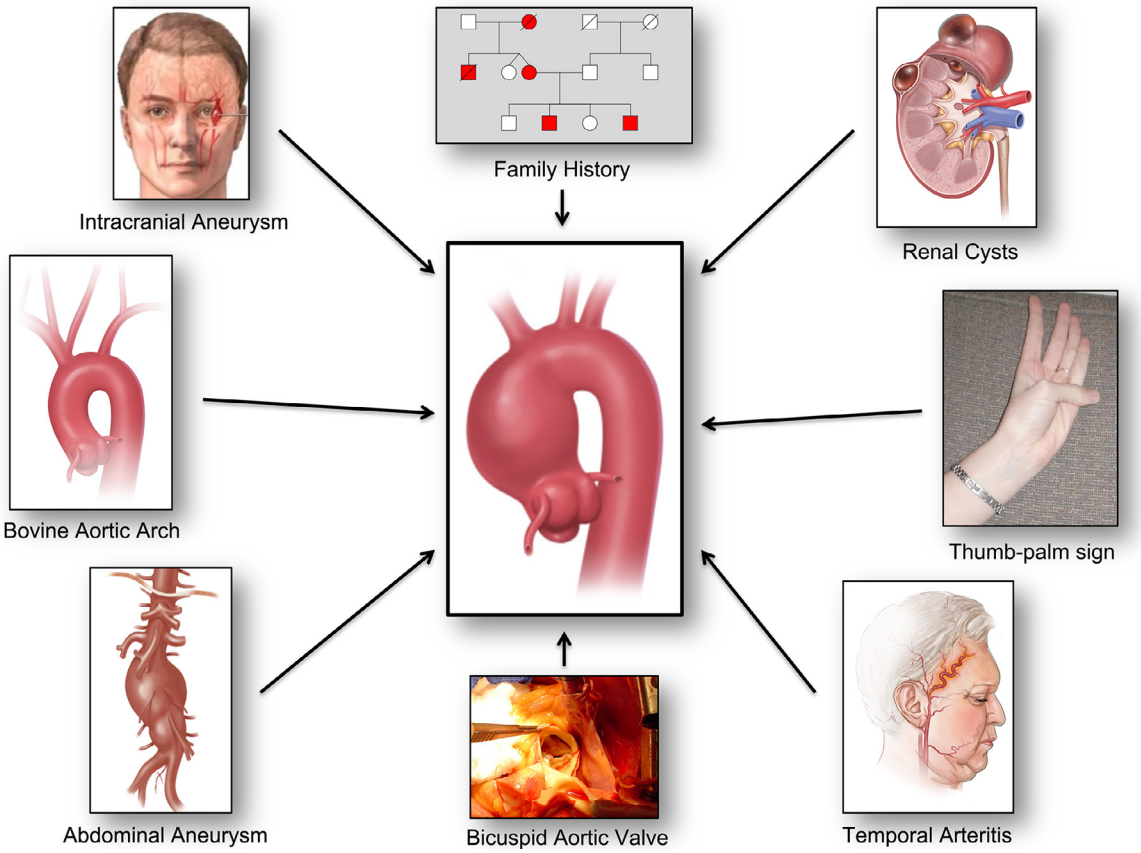

Figure 4. Paradigm of "Guilt by Association" for detection of silent thoracic aortic aneurysms. (Reproduced with permission from ref. 24).

adverse aortic events, based on intensity of fluorodeoxyglucose (FDG) uptake by inflammatory cells.[26]

There exists no "gold-standard" imaging modality for TAAs, with each method having its own limitations and advantages. Echocardiography is most useful for visualizing the aortic root, and CT and MRI for the remaining segments of the aorta (mid ascending, arch, and descending aorta). The use of all 3 modalities allows for a comprehensive assessment of the aorta.[27]

Radiographic screening of aneurysms is extremely valuable and addresses the most directly correlated factor for aortic operation: the size of the aneurysm. However, imaging alone does not suffice. We cannot image the entire general population, where detection of asymptomatic TAA is paramount. However, negative imaging may lead to missed aneurysms that have not yet reached a detectable size. There are times when negative events might occur without the aorta having gone through a significant enlargement, especially in the setting of pathogenic TAAD-causing genetic mutations, as detailed previously. This emphasizes the urgent need for biomarkers for TAAs, and better screening tools for nonsyndromic TAD, as we describe immediately below.

PROSPECTIVE SCREENING: RNA SIGNATURE

In addition to looking at the genetic profile of our patients (DNA), we are currently working on identifying RNA expression patterns in peripheral blood that could be diagnostic for TAA. Success in such work would constitute a major advancement in the clinical care of the general population. Our previous study identified a distinct gene expression "RNA signature" in peripheral blood that was able successfully to identify whether a patient had an aneurysm with over 80% overall accuracy.[28] Furthermore, this RNA Signature test was able to differentiate very accurately between ascending vs descending aortic aneurysm, and between familial or sporadic TAA.[28] We are currently completing a follow-up study aimed at validating our previous findings and developing a clinically useful simple blood test that can not only detect and monitor aneurysm disease, but also biologically predict the risk of catastrophic aortic events based on the differential expression of aneurysm-related RNAs.

CONCLUSION

With the array of novel genetic, radiologic and serologic tests becoming available in the context of aneurysm disease of the aorta, screening for nonsyndromic TAAD in the current era is very much possible—certainly for family members of aneurysm patients, and, we hope for the general population or selected subgroups of the general population.

Screening of nonsyndromic TAAD is very valuable and is becoming a cornerstone of clinical aortic care, helping to capture undiagnosed asymptomatic patients before they suffer a devastating complication. We are already witnessing patients and affected family members being detected and safely stewarded through protective surgery.

Whereas radiological screening does address one of the most important determinants for prophylactic surgical intervention, the size of the aneurysm, many nonsyndromic TAAD patients in whom surgery is indicated may well be missed when relying on imaging alone. Aortic size is not always a reliable indicator for surgical intervention since some patients may develop aortic dissection or rupture before reaching the 5.5 cm guideline-defined threshold for surgical intervention,[26,29] depending on their genetic profile. Genetic screening allows provision of personalized aortic care, tailored to each individual patient, as well as prognostic information on disease development and progression according to the involved gene. As genetic testing for TAA becomes more widely available and further genes and mutations are discovered, more undiagnosed and asymptomatic cases of nonsyndromic TAAD will be captured before lethal events, substantially changing the fate of this silent killer.

REFERENCES

1. Verstraeten A, Luyckx I, Loeys B: Aetiology and management of hereditary aortopathy. Nat Rev Cardiol 14:197–208, 2017. https://doi.org/10.1038/nrcardio.2016.211
2. Elefteriades JA: Thoracic aortic aneurysm: Reading the enemy's playbook. Curr Prob Cardi 33:203–277, 2008. https://doi.org/10.1016/j.cpcardiol.2008.01.004
3. Tanaka Y, Sakata K, Sakurai Y, et al: Prevalence of type A acute aortic dissection in patients with out-of-hospital cardiopulmonary arrest. Am J Cardiol 117:1826–1830, 2016. https://doi.org/10.1016/j.amjcard.2016.03.015
4. Zafar MA, Farkas EA, Javier A, et al: Are thromboembolic and bleeding complications a drawback for composite aortic root replacement? Ann Thorac Surg 94:737–743, 2012. https://doi.org/10.1016/j.athoracsur.2012.04.007
5. Mok SCM, Ma WG, Mansour A, et al: Twenty-five year outcomes following composite graft aortic root replacement. J Card Surg 32:99–109, 2017. https://doi.org/10.1111/jocs.12875
6. Peterss S, Charilaou P, Dumfarth J, et al: Aortic valve disease with ascending aortic aneurysm: Impact of concomitant root-sparing (supracoronary) aortic replacement in nonsyndromic patients. J Thorac Cardiovasc Surg 152:791–798, 2016. https://doi.org/10.1016/j.jtcvs.2016.05.020
7. Ziganshin BA, Rajbanshi BG, Tranquilli M, et al: Straight deep hypothermic circulatory arrest for cerebral protection during aortic arch surgery: Safe and effective. J Thorac Cardiovasc Surg 148:888–900, 2014. https://doi.org/10.1016/j.jtcvs.2014.05.027
8. Ziganshin BA, Zafar MA, Elefteriades JA: Descending threshold for ascending aortic aneurysmectomy: Is it time for a "Left-Shift" in Guidelines? J Thorac Cardiovasc Surg 157:37–42, 2018. https://doi.org/10.1016/j.jtcvs.2018.07.114
9. Elefteriades JA, Brownstein AJ, Ziganshin BA: Clinical and molecular genetics of aortic dissection in Melissano G, Chiesea R, Hiraki A, (eds): Aortic Dissection Patients: True Stories and the Innovations That Saved Their Lives. Edi. Ermes, 2016, pp 49–80
10. Ahmad MM, Kiani IA, Ammar KA, et al: Ascending aortic aneurysm is an inherited disease: A contemporary literature review based on Hill's criteria of specificity, strength of association, and biological coherence. Cardiol Rev 25:268–278, 2017. https://doi.org/10.1097/CRD.0000000000000146
11. Tilson MD, Seashore MR: Fifty families with abdominal aortic aneurysms in two or more first-order relatives. Am J Surg 147:551–553, 1984. https://doi.org/10.1016/0002-9610(84)90020-5
12. Coady MA, Davies RR, Roberts M, et al: Familial patterns of thoracic aortic aneurysms. Arch Surg 134:361–367, 1999. https://doi.org/10.1001/archsurg.134.4.361
13. Biddinger A, Rocklin M, Coselli J, et al: Familial thoracic aortic dilatations and dissection: A case control study. J Vasc Surg 25:506–511, 1997. https://doi.org/10.1016/S0741-5214(97)70261-1

14. Albornoz G, Coady MA, Roberts M, et al: Familial thoracic aortic aneurysms and dissections—Incidence, modes of inheritance, and phenotypic patterns. Ann Thorac Surg 82:1400–1405, 2006. https://doi.org/10.1016/j.athoracsur.2006.04.098
15. Mariscalco G, Debiec R, Elefteriades JA, et al: Systematic review of studies that have evaluated screening tests in relatives of patients affected by nonsyndromic thoracic aortic disease. J Am Heart Assoc 7:e009302, 2018. https://doi.org/10.1161/JAHA.118.009302
16. Ziganshin BA, Bailey AE, Coons C, et al: Routine genetic testing for thoracic aortic aneurysm and dissection in a clinical setting. Ann Thorac Surg 100:1604–1612, 2015. https://doi.org/10.1016/j.athoracsur.2015.04.106
17. Brownstein AJ, Ziganshin BA, Kuivaniemi H, et al: Genes associated with thoracic aortic aneurysm and dissection: An update and clinical implications. Aorta (Stamford) 6:13–20, 2018. https://doi.org/10.12945/j.aorta.2017.17.003
18. Brownstein AJ, Ziganshin BA, Elefteriades JA: Human aortic aneurysm genomic dictionary: Is it possible. Indian J Thorac Cardiovasc Surg 35: S57–66, 2019. https://doi.org/10.1007/s12055-018-0659-6
19. Brownstein AJ, Ziganshin BA, Elefteriades JA: Genetic disorders of the vasculature in Sawyer D, Vasan R, (eds): Encyclopedia of Cardiovascular Research and Medicine. Reference Module in Biomedical Sciences, Elsevier Inc, 2018, pp 327–367. https://doi.org/10.1016/B978-0-12-809657-4.99692-3
20. Iakoubova OA, Tong CH, Catanese J, et al: KIF6 719Arg genetic variant and risk for thoracic aortic dissection. Aorta (Stamford) 4:83–90, 2016. https://doi.org/10.12945/j.aorta.2016.16.003
21. Weerakkody R, Ross D, Parry DA, et al: Targeted genetic analysis in a large cohort of familial and sporadic cases of aneurysm or dissection of the thoracic aorta. Genet Med 20:1414–1422, 2018. https://doi.org/10.1038/gim.2018.27
22. Ziganshin BA, Elefteriades JA: Genetic impact on thoracic aortic aneurysms in Eskandari MK, Pearce WH, Yao JST, (eds): Current Vascular Surgery: Northwestern Vascular Symposium, PMPH-USA, Ltd., 2017, pp 461–480. https://doi.org/10.1038/gim.2018.27
23. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–424, 2015. https://doi.org/10.1038/gim.2015.30.Standards
24. Elefteriades JA, Sang A, Kuzmik G, et al: Guilt by association: Paradigm for detecting a silent killer (thoracic aortic aneurysm). Open Heart 2:e000169, 2015. https://doi.org/10.1136/openhrt-2014-000169
25. Hiratzka LF, Bakris GL, Beckman JA, et al: 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol 55:e27–e129, 2010. https://doi.org/10.1016/j.jacc.2010.02.015
26. Tanweer M, Zafar MA, Saeyeldin A, et al: "Getting beyond diameter": When to replace the aorta? J Vis Surg 4:124, 2018. https://doi.org/10.21037/jovs.2018.06.04
27. Elefteriades JA, Farkas EA: Thoracic aortic aneurysm. Clinically pertinent controversies and uncertainties. J Am Coll Cardiol 55:841–857, 2010. https://doi.org/10.1016/j.jacc.2009.08.084
28. Wang Y, Barbacioru CC, Shiffman D, et al: Gene expression signature in peripheral blood detects thoracic aortic aneurysm. PLoS One 2:e1050, 2007. https://doi.org/10.1371/journal.pone.0001050
29. Paruchuri V, Salhab KF, Kuzmik G, et al: Aortic size distribution in the general population: Explaining the size paradox in aortic dissection. Cardiology 131:265–272, 2015. https://doi.org/10.1159/000381281