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Genetic Testing in Thoracic Aortic Disease—When, Why, and How?

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ABSTRACT

Advances in genetic technology over the past 10 years have revealed the polygenic basis of thoracic aortic aneurysm and thoracic aortic acute dissection (TAAD) in a subset of patients. There is mounting evidence to show that clinical risk stratification for aneurysmal dilatation and acute dissection can be based on genotype for some of the known genes, allowing individualized medical and surgical management with the aim of reducing morbidity and mortality. This evidence has led to a recommendation by the American College of Cardiology Foundation and the American Heart Association that the underlying genetic mutation should dictate the timing of aortic repair. Other benefits of identifying a specific genetic cause include prediction of multisystem involvement in syndromic forms of TAAD and cascade

RÉSUMÉ

Au cours des 10 dernières années, les progrès en matière de génétique ont permis de cerner la nature polygénique de l'anévrisme de l'aorte thoracique et de la dissection aortique aiguë chez un sous-groupe de patients. De plus en plus de données indiquent qu'il est possible d'effectuer une stratification du risque de dilatation anévrismale et de dissection aortique aiguë en fonction de la présence ou de l'absence d'un certain nombre de gènes, ce qui permettrait de mieux cibler la prise en charge médicale et chirurgicale des patients et ainsi de réduire la morbidité et la mortalité. C'est en se basant sur ces données que l'American College of Cardiology Foundation et l'American Heart Association ont recommandé que le moment de la chirurgie de réparation aortique soit fixé en fonction de la présence ou de l'absence

Advances in genetic technology over the past 10 years have revealed the heterogeneous genetic basis of thoracic aortic aneurysm and thoracic aortic acute dissection (TAAD) in a subset of patients. There is mounting evidence to show that clinical risk stratification for aneurysmal dilatation and acute dissection can be based on genotype for some of the known genes, allowing individualized medical and surgical management with the aim of reducing morbidity and mortality. This evidence has led to a 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.[1] Other benefits of identifying a specific genetic cause include surveillance for multisystem involvement in syndromic forms of TAAD and cascade screening for other at-risk family members. Molecular genetics laboratories now offer "panel" testing for genes known to be involved in TAAD, both syndromic and nonsyndromic forms. This approach is beneficial because it maximizes the possibility of making a molecular diagnosis, even if the patient's phenotype is not classic for an associated syndrome. The specific genes tested vary between laboratories and are regularly updated to reflect new gene discoveries.[2] Mutation analysis for genes associated with TAAD in a clinical setting is typically ordered by health care providers with expertise in cardiac genetics. We present an approach to assist cardiologists and vascular surgeons in recognizing which patients would benefit from genetic testing, provide justification for testing, and outline a practical approach to ordering the test.

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See page 134 for disclosure information.

Clinical Scenario 1

A 29-year-old man presented with nontraumatic acute-onset severe anterior chest pain. He had no personal or family history of cardiovascular disease but had previously required serial casting for congenital talipes and bracing for

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screening for other at-risk family members. Mutation analysis for genes associated with TAAD in a clinical setting is typically ordered by geneticists or cardiologists with an interest or expertise in cardiac genetics. We present an approach to assist cardiologists and vascular surgeons in recognizing which patients would benefit from genetic testing, provide justification for such testing, and outline a practical approach to ordering the tests.

de mutations génétiques chez le patient. Le dépistage génétique permettra également de prévoir la possibilité d'une défaillance multisystémique dans les formes syndromiques de la dissection aortique aiguë et de procéder à un dépistage systématique chez les familles exposées à un risque. En pratique clinique, le dépistage des mutations génétiques associées à la dissection aortique aiguë est habituellement demandé par des généticiens ou des cardiologues qui possèdent une expertise en génétique cardiaque ou qui s'intéressent tout particulièrement à ce domaine. Nous vous présentons ici une approche destinée aux cardiologues et aux chirurgiens vasculaires qui leur permettra de : déterminer quels patients sont susceptibles de bénéficier de ce type de dépistage; de connaître les facteurs qui le justifient; et de se familiariser avec les modalités pratiques pour commander un tel dépistage génétique.

scoliosis. He had also undergone surgical repair of a cleft palate. On examination, his heart rate was 110 bpm and his blood pressure was 90/55 mm Hg. The lungs were clear. There was a diastolic decrescendo murmur heard along the right sternal border. A chest radiograph showed a widened mediastinum. Multiplane transesophageal echocardiography revealed intimal dissection flaps in the proximal ascending aorta, with aortic valve regurgitation.

Clinical Scenario 2

A 32-year-old woman presented to her family physician with a long-standing history of constipation and urinary retention. An abdominal ultrasonographic scan revealed an incidental finding of dilated suprarenal abdominal aorta, leading to examination by full-body magnetic resonance imaging/magnetic resonance angiography. Her aortic arch and common carotid arteries were also dilated, and there were bilateral stenoses of the terminal internal carotid arteries. Physical examination revealed mydriasis, with no systemic features of a connective tissue disorder.

When and Why Should Genetic Testing Be Offered?

Justification for genetic testing in individuals with TAAD is based on the clinical utility of identifying a specific genetic mutation. Table 1 summarizes the individualized medical, surgical, and surveillance guidelines associated with single-gene causes of TAAD, both syndromic and nonsyndromic forms. As part of routine care for any individual presenting with TAAD, cardiologists and vascular surgeons should consider offering genetic testing or referring to a specialist genetics clinic where this can be undertaken if any of the following factors are present:

- Medical history or physical examination findings (or both) consistent with a syndromic form of TAAD (Table 2)
- Family history of TAAD, sudden death, or family members with syndromic features
- Early age of onset of TAAD, age younger than 65 years, especially in the absence of cardiovascular risk factors such as hypertension, smoking, or hyperlipidemia
- Involvement of the aortic root and ascending aorta
- Involvement of the arch or descending aorta (can also be considered an indication for testing in the presence of other suggestive factors)
- Cystic medial degeneration or histopathologic condition of native aorta

Genetic consultation is not indicated for acquired causes of TAAD, eg, inflammatory aortitis.

Which Genetic Tests Should Be Offered?

The availability of gene panels that include genes associated with syndromic and nonsyndromic TAAD is now revealing a broader phenotypic spectrum associated with mutations in each gene than was previously known. For example, Proost et al.[3] highlighted the detection of pathogenic mutations in *FBN1* and *COL3A1* in 2 individuals with TAAD not previously suspected of having Marfan syndrome or vascular Ehlers-Danlos syndrome, respectively. This type of unexpected finding argues against dividing individuals with TAAD into "syndromic" and "nonsyndromic" categories for the purposes of choosing individual genes to test to maximize the chance of finding the truly pathogenic mutation for an individual patient. However, when large numbers of genes are tested at the same time, there is a higher chance of finding variants of uncertain significance (VUS). Limiting the genes tested to those that are most likely to be disease causing, eg, in a patient with suspected Marfan syndrome, testing only *FBN1,* is therefore recommended when the phenotype is highly specific to reduce the burden of clinical interpretation. At the current time, an estimated 20% of individuals with TAAD and a family history of TAAD are likely to have a mutation detected in a known TAAD gene, suggesting that there are many more genes to be discovered. When deciding which laboratory to use for genetic testing, clinicians are advised to review the most up to date test information, which may be accessed through the GeneTests website (https://www.genetests.org/).

Identification of a clearly pathogenic mutation in the proband allows for cascade testing of family members for the familial mutation. Genetic testing in adult family members may be diagnostic in the case of those already known to have features of the disease or predictive in those who are asymptomatic. Ideally, genetic testing should be done only after clinical assessment, including aortic imaging, because mutation analysis is not 100% sensitive as a result of the small