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Genes Predisposing to Thoracic Aortic Aneurysms and Dissections: Associated Phenotypes, Gene-Specific Management, and Genetic Testing

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Abstract

Thoracic aortic aneurysms leading to type A dissections (TAAD) are the major diseases affecting the aorta. A genetic predisposition for TAAD can occur as part of a genetic syndrome, as is the case for Marfan syndrome, due to mutations in *FBNI*, and Loeys-Dietz syndrome, which results from mutations in either *TGFBR1* or *TGFBR2*. A predisposition to TAAD in the absence of syndromic features can be inherited in an autosomal dominant manner with decreased penetrance and variable expression, termed familial TAAD. Familial TAAD exhibits clinical and genetic heterogeneity. Genetic heterogeneity for familial TAAD has been demonstrated by the identification of four genes leading to TAAD, including *TGFBR2* and *TGFBR1*, *MYH11*, and *ACTA2*. The phenotype and management of patients harboring mutations in these genes, along with genetic testing, will be addressed in this review.

Keywords

thoracic aortic aneurysm; aortic dissection; Marfan syndrome; Loeys Dietz syndrome; *FBNI*; *TGFBR1*; *TGFBR2*; *MYH11*; *ACTA2*

Introduction

Aortic aneurysms and dissections are the major diseases affecting the aorta in the thoracic cavity. Thoracic aortic aneurysms tend to be asymptomatic and may not be diagnosed until a catastrophic event occurs, typically an acute aortic dissection. An aortic dissection occurs when the blood in the aortic lumen enters the wall through an intimal tear and dissects along the plane of the aortic wall, leading to the creation of a false lumen. Aortic dissections originate primarily in the ascending aorta just above the aortic valve (ascending or type A dissections), but can also occur in the descending thoracic aorta just distal to the origin of the left subclavian artery (descending or type B). Rupture and dissection of an aneurysm is associated with a high degree of morbidity, mortality, and medical expenditure despite continued improvements in surgical techniques. In contrast, prophylactic repair of an ascending aortic aneurysm prior to rupture or dissection is associated with very low

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morbidity and mortality, leading to the current recommendation to repair the ascending aorta when a stable aortic aneurysm enlarges to a diameter of 5.0 – 5.5 cm¹. Therefore, prevention of untimely death from aortic dissections depends on the early identification of individuals predisposed to thoracic aortic disease, careful monitoring of the diameter of the ascending aorta, and timely surgical repair of diseased segments^{2,3}. Careful monitoring of the ascending aorta involves imaging of the entire ascending aorta and obtaining standard measurements at the level of the annulus, sinuses of Valsalva, supraaortic ridge or sinotubular junction, and the proximal ascending aorta. If the ascending aorta is not well visualized by echocardiogram, further imaging by CT or MRI scan is recommended.

It has been recognized for many years that there are genetic syndromes that predispose individuals to thoracic aortic aneurysms leading to type A dissections (referred to as TAAD). Most prominent among these syndromes is Marfan syndrome (MFS), where virtually every affected patient will have ascending aortic disease during their lifetime. More recently, Loays-Dietz syndrome (LDS) has been described, with a similar high risk for thoracic aortic disease. The majority of patients with TAAD do not have a characterized genetic syndrome. Despite the lack of syndromic features, many of these patients do have an inherited predisposition for TAAD, and current data indicate that there are many genes that predispose individuals to non-syndromic inherited TAAD. Four genes have been identified for familial TAAD, and these genes account for approximately 20% of familial inheritance of TAAD.

Marfan Syndrome and Loays-Dietz Syndrome

Marfan syndrome is an autosomal dominant syndrome with pleiotropic manifestations that involve the skeletal (pectus deformities, kyphoscoliosis, dolichostenomelia, arachnodactyly, and other features), ocular (ectopia lentis), pulmonary (apical lung blebs and pneumothoraxes), integumentary (striae), and cardiovascular system (TAAD and valvular insufficiencies). Progressive dilation of the aortic root, culminating in aortic dissection, is the major cause of morbidity and mortality in MFS patients^{2,4,5}. The management of aortic disease in MFS patients is well established¹.

MFS is the result of heterozygous mutations in the fibrillin-1 gene (*FBNI*) on chromosome 15. Fibrillin-1 is a large 35- kDa cysteine-rich glycoprotein that is a major component of extracellular matrix (ECM) structures called microfibrils, which are found at the periphery of elastic fibers. Over 600 *FBNI* mutations have been identified in patients with MFS (<http://www.umd.be:2030/>), and the majority of the mutations are missense mutations predicted to disrupt just one amino acid out of the 2,871 amino acids that comprise fibrillin-1. In addition to MFS, *FBNI* mutations may also result in a range of isolated clinical manifestations, including isolated ectopia lentis, skeletal features of MFS, and familial TAAD⁶⁻¹⁰.

The current diagnostic criteria, termed the Ghent criteria, rely primarily on the cardiovascular, ocular, and skeletal features for the diagnosis of MFS. Genetic testing, involving direct sequencing of *FBNI* and the identification of a mutation in the gene, is problematic for a number of reasons: (1) *FBNI* is a large gene and sequencing of all 65 exons is an expensive undertaking; (2) not all rare genetic variants cause MFS but may instead cause isolated ectopia lentis, skeletal features of MFS, familial TAAD, or no phenotype; (3) sequencing is not required to make a diagnosis when major features are present in the cardiac, ocular, and skeletal systems, such as the case of classic MFS; and (4) *FBNI* sequencing only identifies mutations in 72% and 91% of patients with classic MFS, suggesting that some mutations in the gene are “cryptic”^{11,12}. Therefore, direct sequencing of *FBNI* is currently not extensively used to confirm the diagnosis of MFS in an individual

with classic features of MFS. However, identifying the causative *FBN1* mutation leading to MFS in an individuals can be useful to determine if other relatives are affected and for prenatal diagnosis.

More than a decade ago, genetic heterogeneity for MFS was proposed and a second locus for MFS, termed the MFS2 locus, was mapped to chromosome 3p24 – 25^{13,14}. This locus was identified using a single large family, and whether or not the affected family members met the diagnostic criteria for MFS was controversial¹⁵. A heterozygous mutation in the gene encoding the transforming growth factor- β type 2 receptor (*TGFBR2*) was identified as the cause of disease in this family. *TGFBR2* missense mutations in the intracellular domain of the receptor were identified in three additional families with MFS.

Mutations in both *TGFBR2* and the transforming growth factor- β type 1 receptor gene (*TGFBR1*) have also been reported in a syndrome characterized by TAAD, arterial aneurysms and tortuosity, craniosynostosis, hypertelorism, cleft palate, bifid uvula, congenital heart disease, thin and translucent skin, and skeletal features of MFS, termed Loeys-Dietz Aortic Aneurysm Syndrome (LDS). LDS patients experience rupture or dissection of the aorta at young ages, and dissections have occurred with aortic diameters less than 4.5 cm.¹⁶ In addition, people with LDS have diffuse vascular disease, characterized by aneurysms and dissections of other arteries, including the cerebrovascular arteries and arteries branching off of the aorta. Almost all mutations identified are heterozygous missense mutations disrupting the intracellular kinase domain of these receptors, a domain critical for receptor cellular signaling with ligand binding.

In patients with TAAD and syndromic features of LDS, identification of a *TGFBR1* or *TGFBR2* mutation confirms the diagnosis of LDS. Therefore, sequencing of these genes plays a role in the diagnosis of LDS, and genetic testing should be considered in any patient with thoracic aortic disease and features of LDS. Currently, it is not known how often patients with aortic disease and features of LDS test negative for mutations in these genes.

Most current data support the conclusion that MFS patients with lens dislocation have underlying *FBN1* mutation. In patients who meet the diagnostic criteria for MFS but have features of LDS, genetic testing for a *TGFBR1* or *TGFBR2* mutation should be considered. Any MFS patient with a *TGFBR1* or *TGFBR2* mutation needs to be examined for features of LDS and clinically managed based on the underlying *TGFBR1* or *TGFBR1* mutation.

Confirmation of a *TGFBR1* or *TGFBR2* mutation changes the clinical management of the patient. Individuals harboring mutations in these genes have a propensity for rupture and dissection of the aorta at a younger age and smaller aortic diameters, and therefore aggressive management of ascending aortic aneurysms is currently recommended¹⁶⁻¹⁸. In addition, these patients should be monitored for aneurysms and dissections of other arteries. LDS patients do well with vascular surgical repair and do not have the friable and thin tissues observed in vascular Ehlers Danlos syndrome (EDS) patients. In addition, there are other management recommendations for complications involving systems other than the vascular system in LDS patients^{16,19}.

Familial Thoracic Aortic Aneurysms and Dissections

Although it has been clearly established for the past 40 years that patients with MFS are predisposed to TAAD, the genetic contribution to nonsyndromic TAAD was only defined in the past 10 years. The first family with multiple members with TAAD in whom MFS and vascular EDS was excluded was reported in 1989²⁰. The contribution of genetic factors to the etiology of nonsyndromic TAAD was more recently established with familial aggregation studies demonstrating that up to 19% of TAAD patients had a first degree

relative with TAAD^{21,22}. These studies also showed that individuals with a family history presented with disease at a significantly younger age than those with sporadic aneurysms^{22,23}.

Characterization of families with multiple members with TAAD indicated that the majority demonstrated an autosomal dominant mode of inheritance with decreased penetrance and variable expression with respect to the age of onset of the aortic disease, the location of the aneurysm, and the degree of aortic dilatation prior to dissection^{23,24}. Imaging of the aorta of at risk family members to identify asymptomatic aneurysms proved to be a critical aspect to identifying the mode of inheritance of TAAD. An age-related onset of aortic disease was evident in almost all families, with more individuals presenting with aortic disease as they age. In addition, there is a marked variability in the age of onset of the aortic disease within families that is more pronounced than the variability observed in families with MFS. Another factor, complicating identification of the mode of inheritance, is that family members can inherit the disease gene but not have aortic manifestations even at advanced ages. This incomplete penetrance of the phenotype in family members inheriting the genetic defect occurs primarily in women.

There is variability in the clinical features in families with multiple members with TAAD. In a small subset of TAAD families, family members experience aortic dissection with no aortic dilatation. There is also variability of the cardiovascular diseases segregating in the families with the TAAD. The association of bicuspid aortic valve (BAV) and TAAD as a familial condition has been frequently reported in the literature, leading to the suggestion that BAV and TAAD are manifestations of a single gene defect²⁵⁻²⁸. Family members can have BAV, TAAD, or both cardiovascular conditions. Similar to other TAAD families, the inheritance of the predisposition is autosomal dominant with incomplete penetrance²⁸. In addition, patent ductus arteriosus can segregate with TAAD in families^{29,30}.

The region of the initial ascending aortic enlargement is another variable observed in TAAD families. While some families manifest ascending aneurysms involving the sinuses of Valsalva, similar to patients with MFS and LDS, other families present with aneurysms that spare the sinuses of Valsalva, and instead occur in the ascending aorta and often extend into the arch of the aorta. Aneurysms involving the ascending aorta are typically associated with long-standing hypertension. The ascending aorta represents the most common location for thoracic aortic aneurysms.

Therefore, TAAD is frequently inherited in families. In addition to the TAAD segregating in these families, family members can have aneurysms and dissection of other arteries, including the abdominal aorta, cerebrovascular, or peripheral arteries. Relatives of patients with a family history of TAAD should undergo screening for aortic disease and any associated vascular disease, and referral to a geneticist should be considered for all families with multiple members with TAAD.

The clinical heterogeneity observed in our TAAD families predicted an underlying genetic heterogeneity for the disease. Four causative genes have been identified for familial TAAD. *TGFBR2* and *TGFBR1* mutations cause familial TAAD in the absence of features of LDS. In addition, the genes encoding smooth muscle-specific myosin heavy chain (*MYH11*) and smooth muscle-specific α -actin (*ACTA2*) also cause familial TAAD³¹⁻³³.

***TGFBR2* and *TGFBR1* Mutations in Familial Thoracic Aortic Aneurysms and Dissections**

TGFBR2 mutations are responsible for less than 5% of familial TAAD³¹. Strikingly, *TGFBR2* mutations that alter arginine 460 (R460) in the intracellular domain of the receptor are common in these families, indicating a strong genotype-phenotype correlation^{31,34}. On physical examination, these families do not have features of LDS, i.e. hypertelorism, bifid uvula or cleft palate, or craniosynostosis. Arterial tortuosity and translucent skin are absent in the subset of family members that have been evaluated for these features. Although the vast majority of affected individuals in these families present with TAAD, some have subsequently developed descending aortic disease and aneurysms of other arteries, including cerebral, carotid, and popliteal aneurysms. Three individuals with the *TGFBR2* R460 mutation have had dissections prior to reaching an aortic diameter of 5.0 cm. The smallest documented aortic diameter was 4.2 cm. Dissection of the thoracic aorta with minimal dilatation therefore supports the recommendation to prophylactically repair the aorta when an individual who carries the mutation reaches an aortic diameter of 4.2 cm³¹

Multigenerational TAAD families with *TGFBR1* mutations have also been described, and some affected members of these families do not have any features of LDS³⁵. In fact, the first family reported with familial TAAD, in which MFS and vascular EDS were excluded, has a *TGFBR1* mutation as the cause of the disease²⁰. Therefore, *TGFBR1* mutations can also lead to familial TAAD, but are a rare cause of the disease.

Therefore, *TGFBR1* and *TGFBR2* mutations lead to a spectrum of disease severity with LDS and early onset aortic disease (as young as 6 months of age) anchoring the spectrum at one end. At the other end of the severity spectrum are multigenerational families with *TGFBR1* or *TGFBR2* mutations who do not have features of LDS on physical examination. Note that some of these patients will have arterial tortuosity of the aorta or cerebrovascular arteries or minimal physical findings such as thin skin and bluish sclera. This fact raises the issue of whether patients at the mild end of the spectrum should be classified as having LDS or familial TAAD or just classified as having a *TGFBR1* or *TGFBR2* mutation.

The initial published descriptions of patients with LDS did not distinguish the features in patients with *TGFBR1* mutations from features in patients with *TGFBR2* mutations. Although these initial studies suggested the vascular disease management is the same whether the underlying mutation is in *TGFBR1* or *TGFBR2*, recent studies have indicated that the vascular disease may differ based on the underlying gene mutated. There are numerous reports of aortic dissections at small aortic diameters in patients with *TGFBR2* mutations and no reports of individuals with stable aneurysms greater than 5.0 cm. in diameter. In contrast, there are *TGFBR1* patients reported with stable aneurysms over 5.0 cm in diameter or who dissected at aortic diameters greater than 5.5 cm.³⁵. Further studies are needed to define the ideal clinical management of familial TAAD patients with *TGFBR1* mutations.

Clearly patients with TAAD and features of LDS, including minor features such as thin, translucent skin and atrophic scars should be tested for a *TGFBR1* or *TGFBR2* mutation. We would also recommend that TAAD families in which affected members go on to have aneurysms or dissections of other arteries, or have family members who present with dissections or aneurysms of other arteries, be tested for mutations in these genes. Even though these genes are responsible for only 1 – 4 % of familial TAAD, the potentially lifesaving and powerful information provided when the underlying mutation is identified raises the possibility that all familial TAAD patients should be tested.

Mutations in Genes for the Smooth Muscle-Specific Isoforms of α -Actin (*ACTA2*) and β -Myosin (*MYH11*)

The defective gene causing TAAD associated with patent ductus arteriosus (PDA) in a large French family was identified as *MYH11*, which encodes the smooth muscle cell (SMC)-specific myosin heavy chain, a major component of the contractile unit in SMCs³⁶. Sequencing DNA from three unrelated families with TAAD associated with PDA identified *MYH11* mutations in two of these families³⁷; the remaining family had a *TGFBR2* mutation as the cause of the TAAD and PDA. Subsequent analysis of 93 unrelated families with TAAD without PDA failed to identify any *MYH11* mutations. The spectrum of *MYH11* mutations identified for the familial TAAD/PDA phenotype is currently limited to four mutations: a small deletion, a splice site mutation, and two missense mutations. Therefore, *MYH11* mutations are responsible for disease in the rare family with TAAD associated with PDA and are not a common cause of familial TAAD.

We identified that mutations in another SMC-specific contractile protein, alpha-actin (*ACTA2*), also cause familial TAAD^{33,38}. Sequencing of 98 unrelated TAAD families revealed mutations in 14 families, indicating that *ACTA2* mutations were responsible for approximately 14% of familial TAAD and the most common genetic defect identified for this condition to date³³. Missense mutations are found throughout the protein, including recurrent mutations found in unrelated families, and predicted to produce a defective protein. Surprisingly, in the large family that was used to map the *ACTA2* gene, the R149C mutation segregated completely with the skin rash livedo reticularis, indicating this clinical feature is a marker of the mutant gene. In contrast to TAAD characterized by enlargement of the ascending aorta, livedo reticularis is a vascular rash due to occlusion of the dermal vessels. Other features identified to be associated in a subset of families with *ACTA2* mutations included iris flocculi, PDA, and BAV. The penetrance of TAAD in family members heterozygous for *ACTA2* mutations is low, with only half of *ACTA2* mutation carriers presenting with aortic disease, a finding that differs from other identified loci and genes for familial TAAD. The majority of affected individuals presented with acute type A dissections or type B dissections, with 16 of 24 deaths in *ACTA2* carriers occurring due to type A dissections. Only 2 of 13 individuals experienced type A dissections with a documented ascending aortic diameter less than 5.0 cm. Therefore the risk for dissection at smaller aortic diameters differs from *TGFBR2* mutations. In addition, aortic dissections occurred in 3 individuals under 20 years of age and two women died of dissections post partum. Finally, three boys had type B dissections complicated by rupture or aneurysm formation at the ages of 13, 16, and 21 years.

Further linkage analysis and association studies from 20 families with *ACTA2* mutations uncovered a concurrent predisposition among mutation carriers for occlusive vascular diseases, including early-onset ischemic stroke and coronary artery disease (CAD)³⁹. Included in the premature strokes were cases of primary Moyamoya disease, an early stroke syndrome characterized by bilateral occlusion of the distal internal carotid artery and collateral vessel formation, thereby establishing the first causal link between a genetic mutation and idiopathic Moyamoya disease³⁹. These occlusive lesions occur in young and middle-aged adults despite minimal or absent risk factors for vascular disease, such as hyperlipidemia, smoking, or diabetes. Thus, for *ACTA2* mutations, affected patients are not only predisposed to thoracic aortic disease, but also premature CAD and stroke. Genotype/phenotype correlations have emerged from these initial families studies. Interestingly, the arginine 258 *ACTA2* mutation is seen in families with TAAD and premature stroke, whereas other mutations predisposed to TAAD and CAD (alterations in arginine 149 or arginine 118).

The frequency of *ACTA2* mutations in familial TAAD suggests that diagnostic sequencing of this gene should be considered in all familial TAAD patients. Genetic testing for *MYH11* mutations should be considered in families with members with TAAD and PDA. It is important to note that it is not established which variants in *MYH11* predispose to aortic disease and further studies may be necessary to determine if a *MYH11* genetic variant is causative. If *MYH11* is negative, testing for *ACTA2* and *TGFBR1/2* should also be considered in TAAD/PDA families.

Although the screening and management of thoracic aortic disease can follow the management for all familial TAAD, the extent and frequency of screening for CAD or cerebrovascular disease is not as clearly delineated. Screening for CAD is recommended in *ACTA2* mutation carriers but data on which to base guidelines, such as the age in which screening should be initiated and how frequently this screening should happen, is still lacking. Screening for cerebrovascular disease is also recommended with the same unanswered questions. Carriers of *ACTA2* mutations known to predispose to Moyamoya disease should be considered for cerebrovascular imaging at a young age since this condition responds favorably to neurosurgical treatments. Further clinical studies are needed to determine the most effective management of the diffuse and diverse vascular diseases in patients with *ACTA2* mutations.

Summary

We have summarized the known genes causing a genetic predisposition to thoracic aortic disease and have provided information on the gene-specific phenotypes and gene-based recommendations for clinical management. Referral of patients with features of genetic syndromes or familial TAAD to a geneticist should be considered. In addition, a subset of patients with thoracic aortic disease need genetic testing. As the costs for diagnostic sequencing decreases and insurance companies more readily cover the costs, sequencing of the known genes should be done in all familial TAAD patients, which is already the approach at many centers. Identification of the causative gene is powerful information for the patient and family members, allowing for early identification of additional family members at risk for aortic disease and gene-based specific management. The GeneTests website (<http://www.genetests.org>) provides a directory of genetics specialists and a list of laboratories offering genetic testing for the genes that cause MFS, LDS, and familial TAAD. The four genes identified only account for 20% of familial TAAD, and therefore, there are further genes to be identified and general management guidelines are applied to these patients. At the same time, the genes identified to date have indicated that in the future, gene-specific management of the vascular diseases associated with specific mutations will provide the best care, a so-called personalized medicine approach to thoracic disease management based on the underlying mutation.

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