REVIEW ARTICLE

Progress in the Diagnosis and Therapeutic Management of Genetic Aortic Disease

Avances en el diagnóstico y manejo terapéutico de la patología genética de la aorta

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This is not the end, it is not even the beginning of the end. But it is, perhaps, the end of the beginning.
WINSTON CHURCHILL

The most frequent expression of genetic aortic disease is dilatation or thoracic aortic aneurysm (TAA). The prevalence of TAA in the general population is 10.4 per 100,000 persons/year. (1) More than 20% of patients with TAA have a family history of aortic disease, indicating an evident genetic contribution. (2) More than 30 genes have been associated with the development of TAA. (3) Genetic aortic disease includes syndromic or isolated non-syndromic expressions.

SYNDROMIC GENETIC DISEASES

Genetic aortic diseases are often identified in the context of a syndrome with extra-cardiovascular signs and symptoms.

Marfan syndrome

Marfan syndrome (MFS) is a genetic disorder of the connective tissue caused by mutations in the FBN1 gene located in chromosome 15 (15q21.1), encoding fibrillin-1 protein. More than 2,000 FBN1 mutations have been described. (4)

Marfan syndrome has dominant autosomal inheritance, high penetrance and great intra and inter-familial variability, with an estimated prevalence of 1 case per 3,000-5,000 individuals. Approximately 75% of cases inherit the mutation from a parent and the remaining 25% correspond to de novo mutations.

Despite significant progress in the understanding of the molecular and genetic bases of MFS, (5) its diagnosis still relies on the clinical characteristics codified in the reviewed Ghent nosology, (6) where the coexistence of lens luxation and aortic root dilatation or dissection are key features to confirm the clinical diagnosis of the disease (Table 1). Family history of MFS or the presence of FBN1 mutation (known for its association with the aortic disorder) also contributes to the diagnosis. The remaining cardinal manifestations of MFS have been incorporated into a systemic score (Table 2); when this score is ≥7 it also contributes to the diagnosis.

The aortic disorder in MFS is the main marker of these patients' survival. (7, 8) Aortic dilatation constitutes one the chief criteria for the diagnosis (6) and should be established using population reference values , which according to age, gender and body surface area allow the calculation of the Z-score (number of standard deviations above the predicted mean). Aortic dilatation is considered when the aortic root has a Z-score ≥2 (or ≥3 in patients <20 years of age).

Once the MFS is diagnosed, it is essential to establish medical treatment and follow-up, and evaluate the indication of surgical treatment. Recent studies have postulated genetic predictors, as haploinsufficiency mutations, with worse prognosis than double negative mutations. (9) Furthermore, magnetic resonance imaging (MRI) evidences altered distensibility in patients with MFS with still non-dilated aorta. (10)

Betablockers are the established conventional treatment despite being supported by only one randomized open-label clinical trial conducted in 70 patients. (11) A meta-analysis concluded that this choice was questionable and that new clinical trials are necessary to establish its real benefit. (12) In 2003 it was shown that fibrillin-1 deficiency led to excessive activation of the TGFβ signaling pathway due to its decreased sequestration in the extracellular matrix. (13)

In the murine model of MFS, losartan was superior to atenolol in the prevention of aortic dilatation. (14) These data were confirmed in a retrospective study with only 18 pediatric patients, (15) promoting the onset of several clinical trials in different Marfan populations (children, adults, with or without aortic dilatation). Four of these studies have already been published:

1) The COMPARE study was the first clinical trial with angiotensin II receptor blockers (ARBs) in

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Absence of family history of MFS	Dilatation* or aortic root dissection AND lens subluxation. Dilatation* or aortic root dissection AND FBN1 mutation Dilatation* or aortic root dissection AND systemic score ≥7 points (see lower part of the table). Lens subluxation AND FBN1 mutation previously associated with aortic disorder.
With family history of MFS	Dilatation# or aortic root dissection. Lens subluxation. Systemic score ≥7points.

*Aortic root Z-score ≥2
Aortic root Z-score ≥2 in individuals >20 years or ≥3 in patients <20 years
MFS: Marfan syndrome; FBN1: Fibrillin-1 gene
Z-score calculator in http://www.marfan.org/dx/zscore

Table 1. Reviewed Ghent criteria for the diagnosis of Marfan syndrome and systemic score.

Variable	Total (n=704)	With event (n=87)
Musculoskeletal	Pectus carinatum	2 points
	Pectus excavatum ot thoracic assymetry	1 point
	Scoliosis o spondylolisthesis	1 point
	Reduced upper segment/lower segment ratio	If both are present without severe scoliosis: 1 point
	Increased arm span/height ratio (>1.05)	
	Arachnodactyly: Signs in the wrist and thumb	Both signs=3 points One sign=1 point
	Heel deformity	2 points
	Flat feet	1 point
	Acetabular protrusion	2 points
	Reduced elbow extensiom (<170º)	1 point
	Facial features: Dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, Downward slant of the eyes	In the presence of 3=1 point
Ocular	Myopia	>3 diopters=1 point
Cardiovascular	Mitral prolapse with or without mitral regurgitation	1 point
Lung	Pneumothorax	2 points
Skin	Skin stretches	1 point
Dura	Lumbosacral dural ectasia by CT scan or MRI	2 points

Table 2. Systemic score in Marfan syndrome

MFS published in 2013, (16) including 233 adult patients. Seventy-five percent of the losartan group and 70.1% of the control group of patients were also receiving betablockers. Aortic root dilatation was significantly lower in the losartan group than in the control group: 0.77±1.36 vs. 1.35±1.55 mm/3 years.

2) The Pediatric Heart Network Clinical Trial (17) compared atenolol vs. losartan treatment in 608 patients with ages ranging between 6 months and 25 years with Z-score >3. Results showed no differences between atenolol and losartan.
3) The French study MARFAN SARTAN (18) was a randomized, placebo-controlled clinical trial comparing losartan vs. placebo. A total of 303 patients were included, 86% receiving betablockers. Echocardiography assessment at 3 years revealed no significant differences between the two groups.
4) The LOAT clinical trial, (19) including 140 patients, was also unable to find differences between groups treated with losartan and atenolol, in aortic root growth assessed with MRI and neither in clinical events at 3 years of treatment. These results have been confirmed after more than 6 years of treatment. (20)

However, recent results of the AIMS trial, (21) including 104 patients treated with irbersartan and 88 with placebo, showed lower aortic root dilatation in the group treated with irbersartan (1.5 vs. 2.1 mm/3years, p=0.03). Therefore, more studies should be evaluated or the results of the different studies performed should be grouped to establish the benefit of ARBs compared with betablockers.

Loeys-Dietz syndrome

The Loeys-Dietz syndrome is an autosomal, dominant, connective tissue disorder associated with mutations in the transforming growth factor beta type 1 and 2

receptors (*TGFBR1* and *TGFBR2*), characterized by aortic and arterial aneurysms and dissections, hypertelorism and bifid uvula. (22)

Initial series evidenced a very aggressive evolution, with aortic dissections occurring in aortic vessels with lower diameters than in MFS patients, (23) which led to the recommendation of performing surgery at lower diameters. (24) However, later series did not show this high aggressivity. (25, 26)

Aortic aneurysms are very frequent (98%) and appear at early ages. In addition, up to 53% of patients develop aneurysms in other locations. In general, patients with more severe craniofacial manifestations present more severe arterial disease. The *TGFB3* mutation has been recently described, (27) which includes many characteristic findings of *TGFBR1* and *TGFBR2* mutations, as bifid uvula and cleft palate, but also characteristic aspects of MFS, such as thoracic abnormalities, greater height, joint laxity and arachnodactyly. However, no ectopia lentis or lens luxation has been reported.

Exaggerated arterial tortuosity is very characteristic of the Loeys-Dietz syndrome (Table 3). Some patients diagnosed with Marfan syndrome and negative for FBN1 mutations have TGFBR mutations. Also, 20% of patients with *TGFBR1* or *TGFBR2* mutations present an elevated MFS systemic score (≥7).

In the study of Jondeau et al. (28), event-free survival was significantly lower in men than in women in the group with *TGFBR1* mutation, whereas there was no difference between men and women in the group with *TGFBR2* mutation. In patients with *TGFBR2* mutation, a trend to present lower aortic diameter was found prior to type A dissection, suggesting greater aggressivity of the aortic phenotype with *TGFBR2*.

Vascular type or type IV Ehlers-Danlos syndrome

The Ehlers-Danlos syndrome is an autosomal, dominant, connective tissue disorder produced by a mutation in the COL3A1 gene encoding type 3 collagen. It is characterized by extreme vascular and visceral fragility, which may lead to spontaneous or with minimal trauma vascular and visceral ruptures. (29) Other manifestations, such as hyperelastic skin and hypermobile joints, are less marked than in other Ehlers-Danlos subtypes. Most deaths are produced by vascular ruptures.

Osteoarthritis syndrome

This syndrome was described as caused by SMAD-3 gene mutations. This gene encodes an important protein in TGF-beta signaling, (30) and affects 2% of familial TAA. It includes osteoarthritis or osteochondritis, aortic aneurysms and vessel tortuosities. (31) Craniofacial, skin, and skeleton manifestations may superimpose with MFS and Loeys-Dietz syndrome.

NON-SYNDROMIC GENETIC AORTIC DISEASES

Most TAA and familial aortic dissections occur in patients who cannot be framed in any of the already described syndromes. (32) Studies of familial aggregation suggest that 20% of patients with TAA or aortic dissections have a first degree relative with this history. (2) (Table 4). Some series have reported a relative risk of first degree relatives (2.8% in parents and sisters and 11% in brothers) from suffering TAA compared with control subjects. (33)

In these patients, complications generally tend to happen at earlier ages compared with patients with sporadic aneurysms (median age: 57 years vs. 64 years, respectively), though without attaining the precocity of syndromic TAA. Aortic dilatation may affect the tubular portion of the ascending aorta or the Valsalva sinuses. Both the age of clinical presentation and the velocity of lesion progression are very variable, even within the members of the same family. (34)

The most frequent mutations have been described in 4 genes: heavy chains of myosin-11 (MYH11), smooth muscle actin (ACTA 2) and *TGFBR1* and *TGFBR2*. The MYH11 gene encodes myosin heavy chains, which are associated with vascular smooth muscle contraction (Table 5). MYH11 gene mutations have been associated with TAA in patients with persistent ductus arteriosus. (36). The ACTA 2 gene encodes the α-actin protein isoform found in cells of vascular smooth muscle and affects cellular contraction. It has 50% penetrance and has been associated with livedo reticularis, iris floculi and Moya-Moya disease. (37-39)

DIAGNOSTIC STRATEGY

A genetic study in the index case and familial screening to detect cases at risk is recommended for syndromic aortic diseases, thus avoiding follow-up of non-carriers of the disease and the close follow-up of patients carrying the disease mutations. (40)

Current genetic studies are performed by next generation sequencing (NGS) technology, which is used in the form of gene panels targeting the genes of interest associated with the study disease. (41), or by a whole exome sequencing study. Despite its advantages, NGS often identifies multiple variants of uncertain meaning with difficult clinical interpretation, posing a significant diagnostic challenge.

Due to the high performance of the *FBN1* gene analysis when the syndromic clinical diagnosis is clear (76-93% sensitivity), the best strategy is to initiate *FBN1* analysis when there is suspicion of MFS (first sequencing and then search of deletions-duplications). However, the use of NGS gene panels may be useful due to the phenotypic overlapping between different syndromes and, in some cases, the absence of discriminating characteristics. In these panels, multiple genes are sought in the same analysis. There are currently several panels that include a variable number of genes (11-31), including *FBN1*, *TGFBR1*, *TGFBR2, TGFBR3, ACTA2, MYH11*, *FBN2, SMAD*3, *TGFB2, COL3A1, NOTCH1, SKI,* and *ELN*. (41) Nevertheless, the real performance of these panels in the clinical context is still undefined. To date, only 20%% of

Table 3. Differential diagnosis of Marfan syndrome in relation to other genetic aortic diseases

Differential diagnosis	Gene	Superposition with MFS	Differential characteristics
Loeys-Dietz syndrome	TGFBR1/2	• Aortic aneurysm • Musculoskeletal disorders • Dural ectasia • Skin stretches	• Bifid uvula (28%), cleft palate, hypertelorism, craneosynostosis, cervical instability. • Thin skin, easy bruising, atrophic scars. • Diffuse arterial aneurysms and arterial tortuosity • Absence of lens luxation
Ectopia lentis syndrome	FBN1, LTBP2, ADAMTSL4	• Lens luxation • Musculoskeletal disorders	• Absence of aortic dilatation
Shprintzen-Goldberg syndrome	SKI, FBN1	• Mitral prolapse • Musculoskeletal disorders • Myopia	• Craneosynostosis • Mental retardation • Hypertelorism • Cervical disorders (C1-C2) • Uncommon aortic dilatation
Congenital contractural arachnodactyly (Beals syndrome)	FBN2	• Mitral prolapse • Aortic dilatation • Musculoskeletal disorders	• Multiple flexion joint contractures (knees, elbow and fingers) • Crumpled ears • Without ocular anomalies
Stickler syndrome	COL2A1, COL9A1/2, COL11A1/2	• Myopia, retinal detachment • Joint laxity • Scoliosis • Mitral prolapse	• Hearing loss, • Early signs of arthrosis • Learning difficulties • Cleft palate • Chorioretinal and vitreous degeneration
Vascular Ehlers-Danlos syndrome	COL3A1	• Mitral prolapse • Musculoskeletal disorders • Aortic dilatation/dissection	• Aneurysms/midsize arterial fragility • Thin skin, easy bruising, dystrophic scars • Characteristic facial features
Homocystinuria	CBS	• Mitral prolapse • Lens luxation, myopia • Musculoskeletal disorders	• Arterial and venous thrombosis • Mental retardation • Epilepsy
MASS syndrome	FBN1 (not frequent)	• Mitral prolapse • Upper limit of aortic root diameter • Skin stretches • Musculoskeletal disorders (systemic score ≥5)	• Without progression to aortic dilatation • Absence of lens luxation

familial TAA is explained by these gene mutations. Genetic studies are indicated in patients with thoracic aortic dilatation, aneurysms or dissections without cardiovascular risk factors or bicuspid aortic valve, especially if they are young or have a family history of aortic diseases. Genetic tests are indicated in the parents, siblings and possibly children of a patient carrying a mutation and also in antenatal studies. A recent meta-analysis evidenced that in the screening of first or second degree relatives with familial or sporadic TAA, 25% of diagnostic tests were positive. (42)

FOLLOW-UP

Annual echocardiographic follow-up is enough when only the aortic root is affected, but the rest of the aorta should be evaluated by MRI and TC scan every 2-3 years. A complete study (CT scan or MRI) is recommended at the time of diagnosis to confirm the measurements obtained by transthoracic echocardiography. (43) Ideally, the difference between methods should be below 3 mm. When the aortic dilatation is close to the indication of surgical treatment (2 mm) or the annual progression has been ≥2 mm, controls should be performed every 6 months, and in case of doubt repeat the MRI or TC scan.

Echocardiography supplies information about the aortic valve disorder and the mitral regurgitation often secondary to mitral valve prolapse. It is also important to assess left ventricular function, which may be reduced even in the absence of heart valve disease. The complete vascular study should be repeated periodically at least every 3 years depending on the disease and the presence of family history of peripheral vascular disease.

Table 4. Hereditary thoracic aortic aneurysms

Gene (protein)	Syndrome or Disease
Genes encoding extracellular matrix proteins	
FBN1 (fibrillin-1)	Marfan syndrome
COL3A1 (procollagen type 3)	Vascular Ehlers-Danlos syndrome
TGF-β genes encoding the signaling pathway	
TGFβR1 (TGF-β receptor-1)	LDS or FTAAD
TGFβR2 (TGF-β receptor-2)	LDS or FTAAD
SMAD3 (SMAD3)	Osteoarthritis-aneurysm syndrome or LDS 3
TGFβ2 (TGF-β)	FTAAD or LDS 4
Cytoskeleton genes. Vascular smooth muscle contraction	
ACTA2 (alpha-actin)	FTAAD
MYH11(Myosin-11 heavy chain)	FTAAD
MLK (Myosin kinase light chain)	FTAAD
PRKG1 (cGMP-dependent protein kinase)	FTAAD

FTAAD: Familial thoracic aortic aneurysms and dissections; LDS: Loeys-Dietz syndrome; TGF: Transforming growth factor

Table 5. Non-syndromic familial thoracic aortic aneurysms

Responsible gene	%	Thoracic aortic aneurysm	Aortic dissection
TGFBR2 Gene encoding growth factor beta 2 receptor. Mutation in arginine 460 in 3p24-25 locus	5 %	TAA Same gene mutation in the Loeys-Dietz syndrome	Risk of aortic dissection with diameter <5 cm Similar recommendations to Loeys-Dietz syndrome
MYH11 Specific smooth muscle cell beta myosin 11 heavy chain. Localized in chromosome 16p	1%	TAA –persistent ductus arteriosus	Risk of aortic dissection with aortic diameter ≤4.5 cm
ACTA2 Gene encoding the alpha 2 region of smooth muscle actin. Localized in chromosome 16p	15%	TAA	Risk of type A acute aortic dissection with diameter <5.0 cm and at early ages. Risk of type B aortic dissection at ages <21 years
TGFBR1 Gene encoding the transforming growth factor beta 1 receptor Locus 9q33-34		TAA Same gene mutation in the Loeys-Dietz syndrome and in the Furlong syndrome	

During follow-up it is important to have strict control of hypertension and avoid smoking or moderately intense isometric exercise such as bodybuilding, weightlifting and competitive sports.

Medical treatment of TAA, excluding that provided in the context of MFS, has not been adequately studied. However, the beneficial effect of betablockers or ARBs should be considered. Some retrospective studies have suggested a beneficial role of statins in the reduction of dilatation and aortic complications. (44)

SURGICAL TREATMENT

The threshold for surgical indication in patients with MFS is 50 mm diameter at the level of the aortic root or the ascending aorta, and 45 mm may be considered in the presence of family history of early dissection, aortic enlargement ≥3 mm (with the same imaging technique and repeating the measurement at the same aortic level), severe aortic regurgitation or wish to become pregnant. (45)

Prophylactic surgery should be considered in individuals with confirmed *TGFBR1* and *TGFBR2* mutations with not excessively dilated aortas (45 mm). (46) This threshold could be reduced to 40 mm for women with *TGFBR2* mutations and associated phenotypical characteristics, as aortic tortuosity, hypertelorism and small body surface area.

Heart valve preserving surgery, the aortic remodeling technique or Yacoub technique and the reimplantation technique or David technique should be considered whenever possible, due to the lower rate of thromboembolism, bleeding and endocarditis. (47)

Descending thoracic aortic surgery in MFS should be indicated in the presence of maximum diameter ≥60 mm, and could be considered with smaller diameters according to the clinical context. Endovascular treatment is contraindicated outside emergencies. However, in the last years, good results of endovascular treatment have been reported in hybrid surgery implanting the endoprosthesis proximal end into the elephant trunk tube in the descending aorta.

CONCLUSIONS

The important progress in genetic diagnosis has provided a fast increase in the knowledge of syndromic and non-syndromic aortic disease, (47, 48) highlighting the marked intra and interfamilial heterogeneity in aortic disorders. Therefore, follow-up imaging studies should be expressed in reference units to allow greater accuracy in aortic size evaluation. Follow-up in these units, with adequate medical treatment, leads to a significant decrease in mortality. In addition, these centers usually have the best results in surgical treatment.

We have progressed a lot in a short time. However, there is still much to be discovered to identify the genetic component of most TAA, in order to establish the individual imaging predictors or biomarkers which define the aggressivity of the disease and select for each patient either prophylactic surgical treatment or recommend the most convenient lifestyle.

Conflicts of interest

None declared

(See authors' conflicts of interest forms on the website/ Supplementary material)

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