# Clinical, Diagnostic, and Therapeutic Aspects of the Marfan Syndrome

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Jason R. Cook and Francesco Ramirez

**Abstract**

Marfan syndrome (MFS) is a relatively common and often lethal disease of connective tissue. Medical, surgical and basic research advances over the last two decades have had a major positive impact on the clinical management of MFS patients. Life expectancy has increased significantly, more discriminating diagnostic criteria have been developed, a number of new clinical entities have been recognized, and exciting opportunities for drug-based therapy have emerged. Despite such a remarkable progress, MFS diagnosis remains difficult and aortic disease progression is very heterogeneous and clinical outcome is unpredictable. Ongoing research efforts are therefore exploiting animal models of MFS to identify novel diagnostic and prognostic biomarkers, genetic, epigenetic and environmental modifiers and druggable biological targets.

**Keywords**

Marfan syndrome • Mutations in gene for fibrillin-1 (*FBN1*) • Thoracic and abdominal aortic aneurysm • Valvulopathy • Ghent nosology • β-blockers • Calcium channel blockers • Angiotensin receptor blockers (ARBs) • Bone deformities

## 6.1 Introduction

Marfan syndrome [MFS; Online Mendelian Inheritance in Man (OMIM) #134797] is a relatively common multi-system disease that exhibits high penetrance and marked inter- and intrafamilial variability [1]. First described in an 1896 case report by Antoine-Bernard Marfan, MFS was subsequently identified by Victor McKusick as the archetypal "heritable disorder of connective tissue" [2, 3]. McKusick also hypothesized that the pleiotropic manifestations of MFS may reflect

J.R. Cook • F. Ramirez (✉)
Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
e-mail: jason.cook@mssm.edu; francesco.ramirez@mssm.edu

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structural or metabolic dysfunctions of an extracellular matrix (ECM) component. This prediction was eventually validated in 1991 with the identification of causative mutations in *FBN1*, the gene encoding the ECM protein fibrillin-1 [4, 5]. This seminal discovery, together with improved delineation of the phenotype, has resulted in stringent diagnostic criteria that more effectively distinguish MFS from clinically related conditions with different genetic lesions, repertoire of manifestations, natural history, and response to treatment [6, 7]. Similarly, advances in the surgical management of cardiovascular complications have substantially extended life expectancy in MFS patients [8]. Lastly, creation of mouse models of MFS has provided invaluable insights into disease-causing mechanisms that are being translated into new pharmacological interventions [9]. Clinical, diagnostic and treatment aspects of MFS are discussed in this chapter along with recent experimental findings relevant to the pathogenesis and therapy of organ-specific manifestations in this heritable disorder of connective tissue.

## 6.2 Clinical Phenotype

MFS is a pleiotropic disease with predominant manifestations in the cardiovascular, skeletal, and ocular systems; additionally, the skin, fascia, lung, skeletal muscle and adipose tissue may be involved [1]. MFS can manifest either at birth with a significantly dilated aorta that dissects and ruptures within the first months/years of life, or as a progressive disease that can be diagnosed as late as 30-40 years of age when the majority of fatal events usually occur in untreated patients [1, 10–14]. Extensive phenotypic variability, age-dependent onset of informative manifestations and high degree of spontaneous mutations however limit MFS diagnosis and management, particularly in children and adolescents [1].

### 6.2.1 Cardiovascular System

Cardiovascular abnormalities affect more than 80 % of MFS patients with severe consequences for fitness and survival [15, 16]. Common cardiovascular manifestations include enlargement of the aortic root and proximal ascending aorta, which often precipitate dissection and rupture of the vessel wall, pulmonary artery dilatation, which rarely dissects, and myxomatous valve changes, which can be associated with insufficiency of the mitral and aortic valves and progressive myocardial dysfunction.

*Aortopathy:* Dilatation of the aortic root frequently begins in utero, can be detected neonatally by echocardiography, and progresses at a heterogeneous and unpredictable rate [17–21]. Age-dependent histomorphological changes of the MFS aorta, sometimes improperly referred to as cystic medial necrosis, are associated with a stiffer vessel and include elastic lamellae fragmentation and disorganization, increased collagen and mucopolysaccharide accumulation, and a relative paucity of vascular smooth muscle cells (vSMCs) [22–24]. Other elastic arteries may also display medial degeneration but dilatation is uncommon, except in the pulmonary artery [25, 26].

Aortic root diameter is measured at the sinuses of Valsalva and normalized against age and body size (i.e.: body surface area; BSA); such a measurement is however complicated by the relatively greater BSA of MFS patients compared to unaffected individuals [7, 27]. While aortic size and elastance also increase in the general population as the result of aging and/or hemodynamic stress, these features progress significantly more rapidly in MFS patients; moreover, MFS patients dissect at a smaller aneurysm size than other individuals. Accordingly, prophylactic surgery is normally recommended when the diameter of the aortic root reaches ~5 cm, unless there is a family history of early dissection or dilatation progresses with unusual rapidity (>0.5–1 cm/year) [28].

While thoracic aortic aneurysm (TAA) is a major finding in MFS, abdominal aortic aneurysms (AAA) may also occur more typically in MFS patients who have undergone repair of the proximal aorta [29, 30]. In a few instances, MFS patients may also display AAA out of proportion to proximal aortic disease. Similar to TAA, AAA in MFS tends to dissect at a smaller diameter

than in non-MFS patients. AAA is a common manifestation associated with aging and environmental triggers, such as atherosclerosis and smoking [31–33]. Arterial stiffness is an independent risk factor for AAA dissection and increased stiffness in MFS occurs throughout the arterial tree [34–36].

*Pulmonary artery dilatation:* Dilatation of the pulmonary artery in MFS is rarely associated with dissection owing to the lower mean pressure within this vessel (>20 mmHg) compared to the ascending aorta (>80 mmHg) [26]. According to the LaPlace equation, tension in the vessel wall is proportional to the pressure within the vessel times the radius of the vessel divided by wall thickness. It follows that tension in the wall of the pulmonary artery is significantly less than in the ascending aorta, even though the aortic wall is slightly thicker, and increased systolic pressure produces greater tension thereby promoting aortic dissection. Dilatation of the pulmonary artery in MFS therefore suggests an underlying defect in vasculogenesis independent of hemodynamic pressure.

*Valvulopathies:* Multiple valvular abnormalities are frequently seen in MFS; they include myxomatous thickening with prolapse and regurgitation of the mitral and tricuspid valves, and insufficiency of the aortic and pulmonary valve leaflets [9, 37]. In contrast to the other valvular abnormalities, mitral valve prolapse (MVP) can have a major impact on cardiovascular function. Increased length and physical alterations of the mitral valve lead to regurgitation during systole, in association with precordial systolic murmur. MVP prevalence in MFS is ~75 % with 25 % of the cases manifesting myxomatous valve thickening [38–40]. By contrast, prevalence of MVP in the general population is about 1.3 % [41]. Although a common trait of adult MFS patients, neonatal MVP with severe mitral regurgitation can precipitate cardiac dysfunction and congestive heart failure when untreated. [42–44] Moreover, mitral valve repair can occasionally lead to TAA dissection and rupture due to acute changes in cardiac function and pressure [45].

*Cardiomyopathy:* Several studies of cardiac function in MFS have reported an increase in the size and mass of the left ventricle (LV) along with systolic and diastolic dysfunction [14, 46–49]. While it is generally believed that MVP with severe mitral regurgitation is the main determinant of LV and left atrial dysfunction, the occasional finding of dilated cardiomyopathy (DCM) in the absence of valvular disease has raised the possibility of a primary myocardial insufficiency in MFS [13, 14, 17, 49–51]. The relative abundance of fibrillin-1 assemblies in the myocardial matrix indirectly supports this hypothesis. Another untested possibility is that the stiffer aortic wall of MFS patients may contribute to cardiac dysfunction, by itself or in combination with valvular disease [52].

Whether or not spontaneous DCM is part of the MFS phenotype remains controversial due to conflicting studies of myocardial performance in affected patients and the lack of relevant data from mouse models of the disorder [17]. As a result, closer monitoring of heart function has yet to become the standard management of cardiovascular manifestations in MFS and no new pharmacological strategies are currently being investigated to curb DCM formation in this condition. This is a particularly important issue for patients with severe neonatal presentation of MFS who are at a significantly higher risk of succumbing to heart failure.

### 6.2.2 Skeletal System

The most striking and immediately evident MFS pathologies involve disproportionate linear overgrowth of tubular bones and ligament laxity, which promote malformations of the digits (arachnodactyly), limbs (dolichostenomelia), spine and anterior chest wall [6, 53]. Craniofacial deformities, dural erosion of bony tissue (dural ectasia), osteoarthritic changes secondary to prolonged protrusion of the femoral head (protusio acetabuli), hindfoot valgus with forefoot abduction and lowering of the midfoot (pes planus), and decreased bone mineral density (osteopenia) are additional skeletal findings in MFS [28, 54]. Craniofacial abnormalities include a long narrow skull (dolichocephaly), arched palate with teeth

crowding, recessed lower mandible (retrognathia) and orbital sockets (endopthalmos), downslanting palpebral fissures, and reduced cheek bone size (malar hypoplasia). Ligament/tendon laxity carries an increased risk of musculoskeletal injury through destabilization of joints (e.g.: knee and ankle sprains). Skeletal manifestations in MFS, albeit common, are the least sensitive diagnostic criteria due to considerable prevalence of these traits in the general population as well as in individuals afflicted with other connective tissue diseases. An important exception is the highly diagnostic "thumb and wrist" sign, which reflects the combined outcome of increased digits length (arachnodactyly) and ligament laxity [6].

Skeletal malformations can negatively impact MFS fitness, particularly in older individuals where late-onset complications are an emerging medical problem. Osteopenia is a case in point as inadequate protocols to compare bone mineral density (BMD) between affected and healthy individuals and lack of robust normative data for children hamper the ability to predict the risk of fractures [55, 56]. Pain is another poorly managed aspect of the MFS phenotype. Secondary manifestations of dural ectasia include low back pain, headache, proximal leg pain, weakness and numbness above and below the knee, and genital/rectal pain [57, 58]. Spine and chest deformities are a major morbidity factor in MFS for they cause sternal protrusion or depression (pectus carinatum and pectus excavatum, respectively), vertebral displacement and severe spine deformities in the form of scoliosis (lateral spine displacement) and/or lordosis and kyphosis (anterior and posterior spine displacements, respectively) [59, 60]. Moreover, a positive and significant correlation has been reported between aortic root dilation and heightened body growth during infancy and adolescence [61]. Surgical repair of severe chest deformities is sometimes required to improve cardiac and pulmonary function or increase the surgeon's ability to repair the ascending aorta [62]. These interventions are commonly performed after MFS patients reach skeletal maturity as to avoid the recurrence of chest abnormalities due to continued rib overgrowth. Bracing is usually inadequate to manage severely progressive scoliosis, and surgical repair carries significant risk of complications [59].

### 6.2.3 Ocular System

Major ocular abnormalities in MFS include lens dislocation (ectopia lentis), myopia and retinal detachment with the first manifestation being the most common occurrence (60 % of patients) [63]. Ectopia lentis is usually bilateral and non-progressive, and may range from asymptomatic displacement to significant sublaxation. Glaucoma and premature cataracts are recognized complications of severe ectopia lentis [64]. Refractive aids, pharmacological manipulation, and lensectomy are frequently employed to improve vision. Ocular globe elongation leading to myopia (nearsightedness) is the second most common ocular abnormality of MFS (~40 % incidence) [65, 66]. Albeit less frequent than other ocular manifestations (8 % frequency), retinal detachment is the most serious complication, generally manifesting in the mid-20s and often involving both eyes [67, 68]. The frequency of retinal detachment increases to ~23 % in MFS patients who manifest ectopia lentis. Retinal repair is challenging, particularly in young patients; however, new surgical techniques and instrumentations, together with more effective tools for early detection of ocular problems, have significantly improved the care of the MFS eye.

### 6.2.4 Other Organ Systems

Spontaneous pneumothorax, apical blebs, and bullous emphysema are lung abnormalities that can be associated with MFS [69–72]. Spontaneous pneumothorax, in particular, is considerably more frequent in MFS patients than in the general population and is thought to result from the rupture of an apical bleb [73]. Similar to the problems connected with normalizing TAA and BMD measurements, normalization of pulmonary function tests can frequently be confounded by the greater than the average limb-to-thorax length of MFS patients [74]. Cutaneous stretch marks

(striae atropicae) are commonly found on the axilla, arms, flanks, hip, mid and lower back of afflicted individuals [75, 76]. In contrast to the typical stretch marks associated with weight loss or pregnancy, those in MFS involve areas of flexural stress and may therefore reflect a mechanically impaired integumental matrix. MFS often display a myopathic appearance with little muscle mass that fails to increase in response to growth and exercise [76]. Individuals with neonatal onset of severe and rapidly progressive MFS have profound skeletal muscle hypoplasia and hypotonia throughout life. Adipose tissue deficiency is an anecdotal finding, particularly in MFS children and adolescents. However, several MFS patients have considerable muscle and adipose mass from an early age.

## 6.3 Diagnostic Criteria

Despite the seminal identification of the underlying genetic defect, MFS remains a clinical diagnosis that cannot be validated by a single molecular test. Diagnostic criteria originally published in the so-called Ghent nosology include major and minor criteria, organ involvement, and combined manifestations constituting major or minor criteria (Table 6.1) [66]. Specifically, the presence of one major criterion and involvement of an additional organ system are required for positive diagnosis in cases of documented family history or harboring a bona fide MFS (*FBN1*) mutation; in all other instances, major criteria in two different organ systems and involvement of a third organ system are required. A revised Ghent nosology has been published more recently that places a greater emphasis on aortic root enlargement/dissection, lens dislocation and MFS-causing *FBN1* mutations (Table 6.2) [28]. Accordingly, aortic root enlargement/dissection and lens dislocation are sufficient for MFS diagnosis even in the absence of any family history, whereas a bone fide *FBN1* mutation or a combination of systemic manifestations is required in the presence of only one of these cardinal MFS features. Systemic manifestations are scored according to a numerical matrix of individual traits in which a total score $\geq 7$ indicates systemic involvement [28]. Age-dependent onset of informative manifestations, particularly aortic root diameter, is a widely recognized problem in diagnosing young MFS patients with or without family history or disease-causing *FBN1* mutations. These individuals are therefore considered as being affected by a "non-specific connective tissue disorder" (in the absence of family history) or by "potential MFS" (in the presence of a *FBN1* mutation) and should be subject to regular follow-up until aortic growth reaches the threshold score of $Z \geq 3$ [39].

While the revised Ghent criteria are anticipated to decrease the number of false-positive diagnoses, two important issues remain that make MFS nosology a work in progress [77, 78]. As already alluded, normalization of aortic root diameter against BSA to generate an informative Z-score can be problematic with both pediatric and adult patients. The proposal of using a multivariate formula that takes into account potentially confounding criteria, such as age and gender, may ameliorate this problem [77]. Similarly, future review of the systemic score will validate whether the proposed $\geq 7$ systemic point threshold is indeed indicative of a major criterion.

## 6.4 Management and Treatment

Lifestyle modifications, regular echocardiographic assessment, pharmacological treatment and prophylactic surgery are the major tools currently used to manage the life-threatening cardiovascular complications of MFS. Reducing emotional stress, which may raise heart rate and blood pressure, and restricting physical activities, which may increase the risk of TAA rupture, are strongly emphasized [79]. MFS patients who wish to exercise are therefore recommended isotonic low-impact sports, such as swimming or biking, that reduce blood pressure and heart rate.

Serial echocardiographic imaging of the aorta is imperative due to the heterogeneous rate of aneurysm progression. Once diagnosed, patients are evaluated more frequently to establish baseline changes in aortic root dilatation [29]. Current

**Table 6.1** Ghent nosology

| System | Major criteria | Minor criteria |
|---|---|---|
| Cardiovascular | Ascending aortic dilation (involving sinus of Valsalva) | MVP |
| | Aortic dissection | Dilatation of the main pulmonary artery (<40 years) |
| | | Calcification of the mitral annulus (<40 years) |
| | | Dilatation or dissection of descending thoracic or abdominal aorta (<50 years) |
| Ocular | Ectopia lentis | Flat cornea |
| | | Elongated globe |
| | | Hypoplastic iris |
| Skeletal | At least 4 of the following: | Moderate severity pectus excavatum |
| | Pectus carinatum or pectus excavatum | Joint hypermobility |
| | Reduced upper to lower ratio | Highly arched palate |
| | Arm span to height ratio >1.05 | Facial appearance |
| | Wrist and thumb sign | Dolichocephaly |
| | Scoliosis of >20 or spondylolisthesis | Malar hypoplasia |
| | Reduced ext. of elbows (<170) | Enophthalmos |
| | Medial displacement of mdial malleolus | Retrognatia |
| | Protrusio acetabulae | Down-slanting palpebral fissures |
| Pulmonary | None | Spontaneous pneumothorax |
| | | Apical bleb |
| Skin | None | Striae atrophicae not associated with weight changes, pregnancy or stress |
| | | Recurrent or incisional hernia |
| Nervous | Lumbosacral dural ectasia by CT or MRI | None |
| Family/genetic history | Having a parent/child/sibling who meets these diagnostic criteria | None |
| | Presence of a mutation in *FBN1* known to cause MFS or haplotype around *FBN1* inherited by descent and associated with familial MFS | |

guidelines suggest that pediatric patients or patients with accelerated aortic root growth should be evaluated twice rather than once a year. The same consideration applies for patients who have undergone aortic root, ascending aorta, and/or arch replacement. As aneurysms can form distal to the site of surgical repair, annual CT or MRI scans should be employed to properly visualize the entire aorta [30].

Propranolol, a non-selective β-adrenergic antagonist (β-blocker), has been the mainstay MFS treatment since the mid-1990s [80–82]. Propranolol and other β-blockers are commonly prescribed to treat hypertension due to the ability of reducing cardiac output and peripheral vascular resistance and consequently, tension on the aorta. Although β-blockers are standard MFS care, data documenting the therapeutic benefits of these drugs are relative few and often controversial, particularly in treating MFS children [82, 83]. β-blockers are also used to prevent aortic complications in pregnant MFS women and to stabilize MFS patients with acute aortic dissection. Calcium channel blockers are

**Table 6.2** Revised Ghent nosology

| | Cardinal features (Need 1 of 3) | Systemic features (≥7 pts) |
|---|---|---|
| Cardiovascular | Aortic root Z-score > 2 | Mitral valve prolapse (1 pt) |
| Ocular | Ectopia lentis | Myopia > 3 diopters (1 pt) |
| Skeletal | | Wrist AND Thumb Sign (3pts) |
| | | Wrist or Thumb Sign (1 pt) |
| | | Pectus carinatum (2 pt) |
| | | Pectus excavatum/chest asymmetry (1 pt) |
| | | Protrusio acetabuli (1 pt) |
| | | Reduced upper span to lower span ratio AND increased arm/height ratio with no scoliosis (1 pt) |
| | | Scoliosis or thoracolumbar kyphosis (1 pt) |
| | | Reduced elbow extension (1 pt) |
| | | Facial features (3 or 5) (1 pt) |
| | | Dolichocephaly |
| | | Malar hypoplasia |
| | | Enophthalmos |
| | | Retrognatia |
| | | Down-slanting palpebral fissures |
| Pulmonary | | Pneumothorax (2 pt) |
| Skin | | Skin striae (1 pt) |
| Nervous | | Dural ectasia (2 pt) |
| Family/Genetic history | *FBN1* mutation identified in an individual with MFS | |

prescribed as second-line therapy for aortic complications in the 10–20 % of MFS patients who do not tolerate β-blockers. The treatment is supported by the positive outcomes of an early prospective study of six MFS patients treated with verapamil, and a very recent clinical trial comparing the impact of β-blockers and calcium channel-blockers on vascular function and central aortic pressure in sixteen MFS patients [84, 85]. On the other hand, antibiotic prophylaxis is strongly recommended whenever transient bacteremia may occur (e.g.: during dental cleaning) in MFS patients with documented valvular regurgitation and are therefore at a greater risk of endocarditis [86].

As described more extensively later, mouse models of MFS have revealed new therapeutic opportunities for TAA; principle among them is the use of drugs that target different components of the renin-angiotensin system, such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEi). Based on mouse findings, a non-randomized retrospective analysis of 18 pediatric MFS patients refractory to ACEi and β-blockade has documented appreciable decrease in aortic root growth after therapy with the ARB losartan was initiated [87]. Ongoing prospective clinical trials using larger cohorts of MFS patients will test the validity of this retrospective study [88–91]. In addition to ARB therapy, a single prospective study with MFS patients has documented that beneficial effect of the ACEi enalapril on reducing aortic root growth and aortic stiffness versus propranolol or atenolol [92]. Although ARBs are better tolerated than ACEi, both classes of medications are contraindicated during pregnancy due to teratogenicity; consequently, β-blockers are the only suitable therapy to prevent TAA dissection in pregnant women with MFS.

Mouse studies have also implicated inflammatory cells and matrix metalloproteinases (MMPs) in the process of medial degeneration that accompanies TAA progression in MFS [93, 94]. Inhibiting the activity of MMP-2 and -9, through doxycycline, or inflammatory cells, through statins, were both found to mitigate TAA progression in MFS mice [95–97]. A similar phenotypic improvement characterizes MFS mice lacking MMP2 and was associated with a decrease in improper TGFβ signaling [98]. Additionally, cell culture studies have shown that proteolytic fibrillin-1 peptides up-regulate MMP-1 expression [99]. Some of these findings have independently been validated in human patients by histological analyses of aortic specimens and abnormally high inflammation markers in plasma [100, 101]. On the other hand, MMP inhibition in AAA patients via administration of either doxycycline or statins has yielded controversial results [102, 103].

Although improved procedures to replace the diseased aorta have significantly reduced post-surgical complications in MFS to below 2 %, emergency surgery for acute dissection still carries a high degree of mortality (>10 %) [8]. The Bentall and De Bono procedure has been used for several years to repair the MFS aorta by replacing the aortic valve, root and ascending portion with a Dacron graft valve [104]. While the mortality associated with the Bentall and De Bono procedure is relatively low, replacement of the aortic valve with a mechanical valve requires patients to be on anticoagulant medications in increases the risk of endocarditis [105, 106]. A recent adaptation to simply replacing the aortic root and valve is to remodel the Dacron graft to reproduce the aortic sinuses (Yacoub or David II procedure) with the re-implantation of the patient's aortic valve (David I procedure) so to minimize the need for chronic anticoagulant therapy and antibiotic prophylaxis [109, 110]. While these surgical interventions can prevent further dilatation of the root and ascending aorta, careful monitoring is still required distal to the repair site to prevent dissection farther downstream [104]. Whenever possible, surgery in pediatric patients is delayed until adolescence so to avoid additional corrective interventions due to normal post-natal growth of the aorta [104].

## 6.5 Molecular Genetics

MFS is inherited as an autosomal dominant trait with an incidence of 1 per 5,000 live births of which ~25 % represent de novo mutations [76]. The *FBN1* gene resides on chromosome 15q21.1 and codes for a 350 kDa glycoprotein that mostly consists of 6-cysteines epidermal growth factor (EGF)-like and calcium-binding EGF (cb-EGF) modules interspersed by a few 8-cysteines motifs (TB/8-Cys) uniquely found in fibrillins and latent TGFβ-binding proteins (LTBPs) [5, 107]. Calcium binding stabilizes contiguous cb-EGFs into a rigid linear structure that is required for proper protein deposition in the ECM, polymerization into macromolecular aggregates, and protection from degradation by MMPs. *FBN1* defects include missense mutations and in-frame exon out-splicing or deletions that alter protein folding, secretion and/or assembly and enhance degradation of mutant molecules during tissue remodeling/repair, and mutations that cause nonsense-mediated RNA decay or whole gene deletion reducing the normal level of wild type proteins [38, 108]. Irrespective of whether *FBN1* mutations affect protein structure or expression, they similarly decrease the amount of immunoreactive fibrillin-1 in diseased tissues, indicating that the MFS phenotype largely reflects a sub-optimal threshold of functional microfibrils [109]. The vast majority of the more than a thousand MFS mutations identified thus far represent unique genetic lesions whose relative location and molecular identity are not predictors of phenotypic outcome [37]. Sole exception is the clustering of mutations causing the neonatal severe form of MFS within the middle third of fibrillin-1 where some mutations associated with adult MFS map as well [43, 110]. The possibility of deriving prognostic genotype-phenotype correlations is further complicated by the clinical variability of similar *FBN1* mutations among different patients or of the same mutation within individual families, which are both likely to reflect functional interactions between fibrillin-1 and other proteins (i.e., genetic modifiers).

While it is well established that MFS is a genetically homogenous condition, there are also rare instances in which *FBN1* mutations can cause clinically distinct phenotypes. Cases in point include the stiff skin syndrome (OMIM #184900), whose hallmark is severe dermal fibrosis associated with joint contracture and short stature, Weill-Marchesani syndrome (OMIM # 608328), which manifests MFS-like ocular manifestations but also exhibits short stature and increased joint stiffness and muscle mass, and acromicric dysplasia and geleophysic dysplasia (collectively referred to as acromilic dysplasias; OMIM #102370 and #614185, respectively), which overlap with Weill-Marchesani syndrome and to a lesser extent stiff skin syndrome, as they are characterized by severe short stature, joint stiffness and skin thickening [111–113]. These three conditions may therefore represent a clinical continuum resulting from different pathogenic mechanisms than those underlying MFS. The study of stiff skin syndrome has suggested that impaired interactions between extracellular fibrillin-1 assemblies and resident dermal cells represent one of such differentiating mechanisms [111]. This suggestion is based on the clustering of *FBN1* mutations in this extremely rare disorder around the sole integrin-binding site of fibrillin-1. Another distinctive mechanism emerging from recent findings in acromilic dysplasias is that interaction between fibrillin-1 and ADAMTSL2 might be required for proper assembly of an organized microfibfrilllar network, as the two ECM proteins bind to each other in vitro and some patients harbor *ADAMTSL2* mutations [113]. Shprintzen-Goldberg syndrome (OMIM #182212), which displays MFS-like skeletal and cardiovascular malformations as well as unique neurodevelopmental and cranial abnormalities, is another systemic disease of connective tissue very rarely associated with *FBN1* mutations [114].

## 6.6 Pathophysiology

Fibrillin-1 assemblies (microfibrils and elastic fibers) perform two critically important physiological functions; they provide the structural scaffold that imparts specific physical properties to various tissues and they regulate cell performance by interacting with integrin receptors and TGFβ family members. Microfibrils and elastic fibers are ubiquitous ECM components that are particularly abundant in tissues subject to stretching and expansile forces, in addition to being affected in MFS, such as the aortic wall, the perichondrium and the lens suspensory ligaments [115]. These correlative observations were originally interpreted to suggest that cardinal manifestations in MFS are accounted for loss of tissue integrity and implicitly key physical properties, such as aortic wall elasticity, physeal growth constrain, and ocular lens anchoring [9, 116]. Subsequent experiments with mice replicating the clinical spectrum of MFS have indicated that promiscuous TGFβ signaling (through both the canonical Smad2/3 [R-Smad] pathway and non-canonical mitogen-activated kinase [MAPK] pathways) is another major contributor to MFS pathogenesis [117–119]. Since these studies employed pan-TGFβ inhibitors, the identity of the TGFβ isoform(s) involved in various MFS manifestations remains to be determined.

Fibrillin-1 microfibrils localize, concentrate and stabilize latent TGFβ complexes by binding LTBPs [107]; they similarly interact in vitro with pro-BMP complexes conceivably to promote latency of bioactive ligands [120, 121]. It follows that *FBN1* mutations may also destabilize local growth factor bioavailability with negative consequences for resident cell performance [115]. Indeed, three mouse models of MFS have validated this hypothesis by implicating dysregulated TGFβ and BMP signaling in the pathogenesis of cardiovascular and skeletal manifestations. The emerging view from these animal studies is that *FBN1* mutations differently impact the formation, growth and function of various organ systems depending on how fibrillin-1 assemblies regulate the physical properties of individual tissues and the signaling of ECM-bound growth factors, and how different cell types respond to these highly contextual extrinsic stimuli [109].

*Aortic aneurysm: Fbn1*$^{mgR/mgR}$ mice produce ~20 % of the normal amount of fibrillin-1 and die from ruptured TAA within the first year of

life; they also exhibit severe rib cage and spine deformities, longer tubular bones, osteopenia, emphysema, DCM, and MVP [122, 123]. Newborn *Fbn1*$^{mgR/mgR}$ mice show a morphologically normal aortic wall that gradually degenerate through a maladaptive remodeling process that involves focal elastic lamellae calcification, inflammatory cell recruitment and activation, intimal hyperplasia, unorganized ECM accumulation and MMP-mediated elastolysis [122]. This mouse model of severely progressive MFS therefore demonstrated that secondary cellular events during post-natal life (as opposed to impaired elastogenesis during fetal development) account for aortic growth and degeneration. Newborn *Fbn1*$^{mgR/mgR}$ mice also exhibit impaired distal alveolar septation leading to destructive emphysema later in life, which is associated with increased TGFβ activity and epithelial cell death [119]. Perinatal TGFβ antagonism using a neutralizing antibody (Nab) has been shown to attenuate the severity of lung abnormalities, thereby linking fibrillin-1 deficiency and improper latent TGFβ activation to a specific MFS manifestation [119].

*Fbn1*$^{C1039G/+}$ mice express equal amounts of wild type and mutant fibrillin-1 molecules and have a normal life span because TAA does not precipitate vessel wall dissection and rupture [124]. *Fbn1*$^{C1039G/+}$ mice treated with either TGFβ Nab or the ARB losartan show a significant TAA improvement, as evidenced by normalized aortic wall thickness and architecture as well as TGFβ signaling [118], The last finding confirmed previous reports from animal models of cardiac and kidney fibrosis that the angiotensin type 1 receptor (AT1r) can stimulate TGFβ production through phosphorylation (p) of R-Smad proteins [125–127]. By contrast, the β-blocker propranolol, a drug commonly used to alleviate hemodynamic stress in MFS, has an intermediate benefit on aortic wall thickness but not on aortic wall architecture [118]. These mildly affected MFS mice therefore provided the experimental justification for launching several clinical trials to test whether or not ARB therapy is a more effective strategy than β-adrenergic receptor blockade against TAA progression in MFS patients [88, 89].

Based on the above studies, a model of aortic disease has been proposed whereby impaired sequestration of latent TGFβ complexes by a fibrillin-1 deficient matrix renders these signaling molecules more accessible to activation [119]. The model implies that the amount of available substrate (i.e.: latent TGFβ complexes) rather than substrate's activators (i.e.: MMPs, integrins and/or other molecules) is the limiting factor in aortic disease promotion. Subsequent work with *Fbn1*$^{C1039G/+}$ and *Fbn1*$^{-/-}$ mice (a.k.a. *Fbn1*$^{mgN/mgN}$ mice) has refined this disease model by implicating MAPKs in TAA formation [117, 128, 129]. In addition to high pR-Smad levels, the aortas of adult *Fbn1*$^{C1039G/+}$ mice also have greater than normal amounts of pERK1/2 that can be decreased by TGFβ Nab administration, implying growth factor signaling through both canonical and non-canonical pathways [130]. ERK1/2 activation was shown to be a major determinant of vascular disease as inhibition of this pathway improves TAA even more than TGFβ Nab without however normalizing pR-Smad levels [130]. Additional genetic and pharmacological findings indicated that signaling through AT1r drives ERK1/2 activation and that signaling through the angiotensin type 2 receptor (AT2r) inhibits it [129, 130]. Together, these observations suggested that fibrillin-1 mutations disrupt reciprocal interplays between angiotensin receptors and their downstream pathways that normally orchestrate aorta remodeling.

In spite of lacking fibrillin-1 molecules, *Fbn1*$^{-/-}$ mice complete fetal development and display a seemingly normal medial architecture at birth; however, they die soon after from catastrophic collapse of the aortic wall prior to overt expression of the secondary cellular abnormalities that characterize mouse models of adult MFS [128]. *Fbn1*$^{-/-}$ mice therefore recapitulate the early events that precipitate aortic disease in the neonatal lethal form of MFS. The aortas of newborn *Fbn1*$^{-/-}$ mice have abnormally high amounts of p-p38, a stress-response MAPK also involved in augmenting MMP activity [117]. Elevation of p-p38 MAPK levels in *Fbn1*$^{-/-}$ mice is detected prior to pR-Smad increase and can be partially reduced by p38 MAPK inhibition without however rescuing the

structural collapse of the aortic wall [117]. This mouse model of neonatal lethal MFS therefore suggested that, during the early stage of TAA formation, a mechanically impaired matrix stimulates MAPK-mediated stress responses promoting aortic tissue remodeling through ECM neo-synthesis (via TGFβ action) and degradation (via MMP action). This view furthermore predicts that dysregulated TGFβ bioavailability in the fibrillin-1 mutant matrix may exacerbate maladaptive tissue remodeling thereby leading to irreversible aortic wall degeneration [123].

As the aforementioned studies were performed with mice that replicate the neonatal lethal and mild (non-lethal) forms of MFS, the question arises whether the phenotypic outcome of anti-TGFβ therapy in these two animal models, albeit comparable, may reflect the targeting of the same disease effectors that however operate in distinct manners during the early (formation) and late (progression) stages of aortic disease. This question has important clinical implications given TGFβ central role in promoting physiological tissue maturation and growth during post-natal life, as well as ECM remodeling and repair in response to environmental stresses or injury [107]. In support of this argument, losartan treatment has been reported to normalize aortic diameter but not aortic wall architecture in *Fbn1*$^{mgR/mgR}$ mice, whose vascular severity is in between those of *Fbn1*$^{-/-}$ and *Fbn1*$^{C1039G/+}$ mice, with the result of delaying rather than preventing ruptured TAA [98, 123].

In conclusion, current evidence from genetic and pharmacological studies of MFS mice indicates that mutations in fibrillin-1 trigger multiple signaling (i.e., TGFβ, AT1r and AT2r pathways), cellular (i.e., SMC and immune cells) and catabolic events (i.e., MMP-mediated elastolysis) that cooperate in promoting and sustaining vascular disease onset and progression. A future research challenge to translate these findings into a more effective clinical management of aortic aneurysm in MFS is therefore to tease out the determinants responsible for disease onset from those supporting disease progression [131].

*Osteopenia:* Even though reduced BMD is a relatively minor problem in MFS, the study of osteopenia in *Fbn1* mutant mice has provided compelling evidence for organ-specific disease mechanisms. As such, these investigations have raised the possibility that therapeutic interventions in MFS should be tailored against individual manifestations. Increased bone resorption is the main cause of bone loss in adult (3 month-old) *Fbn1*$^{mgR/mgR}$ mice [123]. The phenotype is correlated at the cellular level with osteoblasts that differentiate more rapidly and support osteoclastogenesis more strongly than the wild type counterparts. As expected, osteopenia in MFS mice is normalized by systemic administration of alendronate, a bisphosphanate commonly used to prevent bone degradation.

Cultured osteoblasts from *Fbn1*$^{mgR/mgR}$ mice show elevated TGFβ and BMP signaling due to improper regulation of growth factor bioavailability by a fibrillin-1 deficient matrix. [123, 132] TGFβ and BMP complexes regulate bone formation differently. TGFβ signals promote osteoprogenitor cell recruitment from marrow stem cells (MSCs) and inhibit pre-osteoblast maturation, whereas BMP signals stimulate both processes [132, 133]. These growth factors are also involved in regulating bone resorption by stimulating osteoblasts to produce pro- and anti-osteoclastogenic factors [134]. Fibrillin-1 microfibrils therefore appear to act as extrinsic structural regulators of both bone anabolism and bone catabolism by calibrating the balance between local TGFβ and BMP signals. In line with this dual regulatory function, osteopenia is partially improved in *Fbn1*$^{mgR/mgR}$ mice treated with TGFβ Nab (our unpublished data). On the other hand, losartan administration does not improve BMD even though mutant osteoblasts express AT1r and AT1r signaling is unaffected [123]. Taken at face value, these findings exclude involvement in deregulated bone homeostasis of the same pathogenic mechanism responsible for TAA formation. Fibrillin-1 deficiency also impacts MSC performance, conceivably because of perturbed growth factors bioavailability, as bone marrow preparations from 3 month-old *Fbn1*$^{mgR/mgR}$ mice yield a greater number of colony-forming unit fibroblasts [135]. It follows that premature depletion of osteoprogenitor cells might exacerbate osteoclast-driven bone loss in

aging MFS mice, and that anti-TGFβ therapy alone might not counteract this disease process in the absence of additional interventions curbing abnormally high pro-osteogenic BMP signals.

Skeletal deformities are a significant morbidity factor in MFS, but the underlying mechanism remains a topic of speculations. One view argues that *FBN1* mutations lead to disproportionate bone lengthening because they impair the physical properties of the perichondrium, whereas another view postulates that dysregulated bioavailability of fibrillin-1 interacting growth factors is the principle driver of the abnormality [109, 136]. Our preliminary evidence from *Fbn1* conditional null mice suggests that the main tissue source of the phenotype is the perichondrium, which is involved in both imparting physeal constrain on bone lengthening and communicating with the growth plate during bone formation [137]. Future mouse studies are expected to delineate the physiological role of perichondrial fibrillin-1 and perhaps identify pharmacological means to curb post-natal bone overgrowth in MFS.

## 6.7 Future Perspectives

While improvements in medical and surgical therapy have nearly normalized life expectancy in MFS, there is an urgent need to properly evaluate the risks and benefits of current and emerging classes of medications so to formalize a new standard of care. As in the past, clinical progress will continue to rely on basic science findings and vice versa. Pre-clinical trials in mouse models of MFS will enable to compare the efficacy of different pharmacological formulations and multi-drug combinations. Application of computational systems biology protocols to the study of MFS will complement these investigations by providing an integrated and unbiased identification of new biological targets for therapy. Data from ongoing and future clinical trials in large and well-defined cohorts of MFS patients will in turn validate evidence gathered from mouse studies and in turn raise new questions that can be addressed experimentally. It is safe to anticipate that such an iterative process will ultimately lead to improved care of MFS patients, in addition to emphasizing the usefulness of characterizing relatively rare monogenic diseases to delineate fundamental pathophysiological mechanisms that are involved in more common clinical conditions.

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