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Review Article

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Marfan Syndrome: An Updated Review of Pathogenesis, Clinical Presentation, Diagnostic Evaluation, and Contemporary Management Strategies

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Abstract

Marfan Syndrome (MFS) is an autosomal dominant connective-tissue disorder most often caused by pathogenic variants in FBN1, the gene encoding fibrillin-1. Abnormal microfibrils compromise extracellular-matrix integrity and influence transforming growth factor-beta (TGF-β) signaling. The disorder has variable expression and primarily affects the cardiovascular, ocular, and skeletal systems. Aortic-root dilatation and dissection are the most serious complications; ectopia lentis, myopia, disproportionate limb length, chest-wall deformities, and scoliosis are also common. Diagnosis integrates clinical examination, family history, cardiovascular imaging, ophthalmic assessment, and molecular testing under the revised Ghent nosology. Management requires lifelong multidisciplinary surveillance, individualized use of beta-blockers and/or angiotensin II receptor blockers, and timely prophylactic aortic surgery when indicated. This review summarizes the genetic basis, pathophysiology, clinical features, diagnosis, complications, current management, and emerging research directions [1,2-9,11].

Keywords: Marfan syndrome; FBN1; fibrillin-1; aortic aneurysm; ectopia lentis; Ghent nosology; beta-blockers; angiotensin II receptor blockers.

Introduction

Marfan syndrome is an inherited connective-tissue disorder with variable manifestations across several organ systems. Its clinical importance arises particularly from progressive aortic disease, which may lead to aneurysm or life-threatening dissection if not recognized. Skeletal and ocular features can provide diagnostic clues, but no single external characteristic is sufficient to establish the diagnosis. Most cases are associated with pathogenic variants in FBN1, which encodes fibrillin-1, a key extracellular-matrix glycoprotein. The condition is usually autosomal dominant, although de novo variants occur in people without a family history. Clinical severity differs substantially, even among relatives carrying the same variant. This review outlines current knowledge of disease mechanisms and the approach to diagnosis, surveillance, and treatment [1,2,8].

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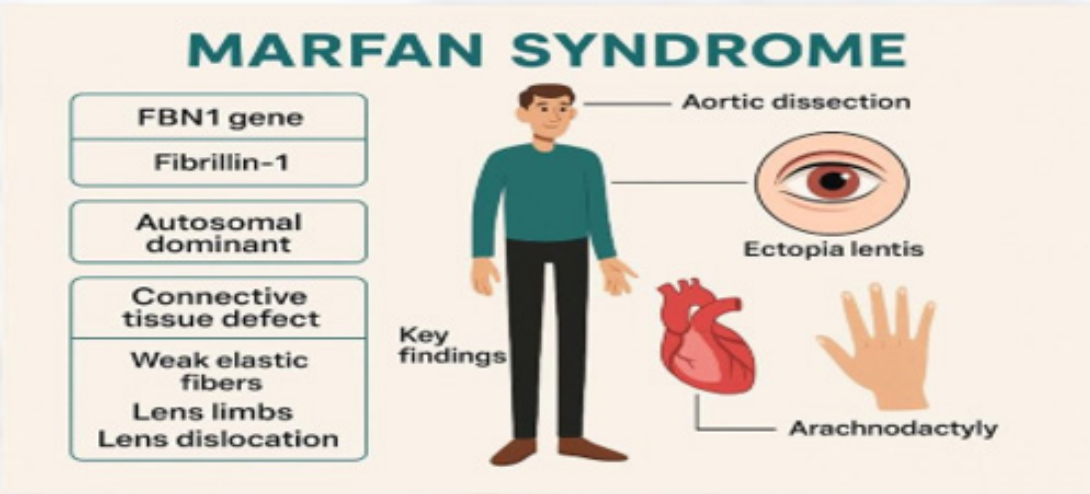


Figure 1: Marfan Syndrome.

Etiology and Genetic Basis

Fibrillin-1 forms microfibrils that support elastic tissues and contribute to extracellular-matrix organization. Pathogenic FBN1 variants can alter protein production, structure, or function, weakening connective tissues and affecting signaling regulation. Approximately one quarter of cases arise from a de novo variant; therefore, absence of a family history does not exclude MFS. Genetic counseling helps families understand inheritance, testing options, and the potential 50% transmission risk from an affected heterozygous parent [2,11-29].

Pathophysiology

MFS reflects both a structural matrix defect and dysregulated cellular signaling. Disorganized fibrillin-1 microfibrils compromise tissue mechanics and alter the regulation of latent TGF-β complexes. Experimental work has implicated excessive or altered TGF-β-related signaling in aortic-wall remodeling, although the pathway is complex and findings should not be interpreted as a single explanation for every manifestation. Changes in elastic-fiber architecture and vascular smooth-muscle function contribute to progressive aortic enlargement. These mechanisms underpin continued research into therapies beyond reducing hemodynamic stress [4,17-20,30-34].

Clinical Manifestations

Cardiovascular

Cardiovascular disease determines much of the long-term risk. Aortic-root dilatation can progress to aneurysm, dissection, or rupture. Mitral valve prolapse, mitral regurgitation, and aortic regurgitation may also occur. Serial echocardiography is commonly used to measure the aortic root and assess valve function; CT or MRI may be needed to evaluate other aortic segments or clarify measurements [9,23].

Ocular

Ectopia lentis (displacement of the crystalline lens) is a characteristic feature. Myopia, astigmatism, retinal detachment, early cataract, glaucoma, and visual impairment can also occur. Regular ophthalmologic assessment is important because some complications require prompt specialist care [1,16].

Skeletal and other systems

Features may include tall stature, disproportionately long limbs, arachnodactyly, pectus excavatum or carinatum, scoliosis, joint laxity, and musculoskeletal discomfort. Findings vary by age and individual. Dural ectasia, skin striae, and pulmonary manifestations may occur in some patients. Skeletal features should be assessed in context because they overlap with other connective-tissue disorders [1,16].

Diagnosis and Differential Diagnosis

The revised Ghent nosology emphasizes aortic-root disease, ectopia lentis, FBN1 pathogenic variants, systemic features, and family history. Assessment typically includes medical and family history, physical examination, echocardiography or other aortic imaging, slit-lamp examination, and molecular testing when appropriate. Genetic testing is particularly useful when clinical findings are incomplete, atypical, or shared with other heritable aortopathies. Differential diagnoses include Loeys–Dietz syndrome, vascular Ehlers-Danlos syndrome, and other familial thoracic aortic aneurysm conditions. A variant of uncertain significance alone does not confirm MFS; results must be interpreted with clinical evidence and, when appropriate, specialist genetic counseling. Diagnostic criteria may need reassessment over time as features evolve.

Complications and Prognosis

The principal serious complication is aortic dissection, preceded in some patients by progressive aortic-root enlargement.

Valve dysfunction may contribute to cardiac symptoms. Ocular complications can threaten vision, while scoliosis and chest-wall abnormalities may cause functional limitations or discomfort. Prognosis has improved with early recognition, regular imaging, medical therapy, and preventive surgery, but risk remains variable and lifelong follow-up is required [9,22,33].

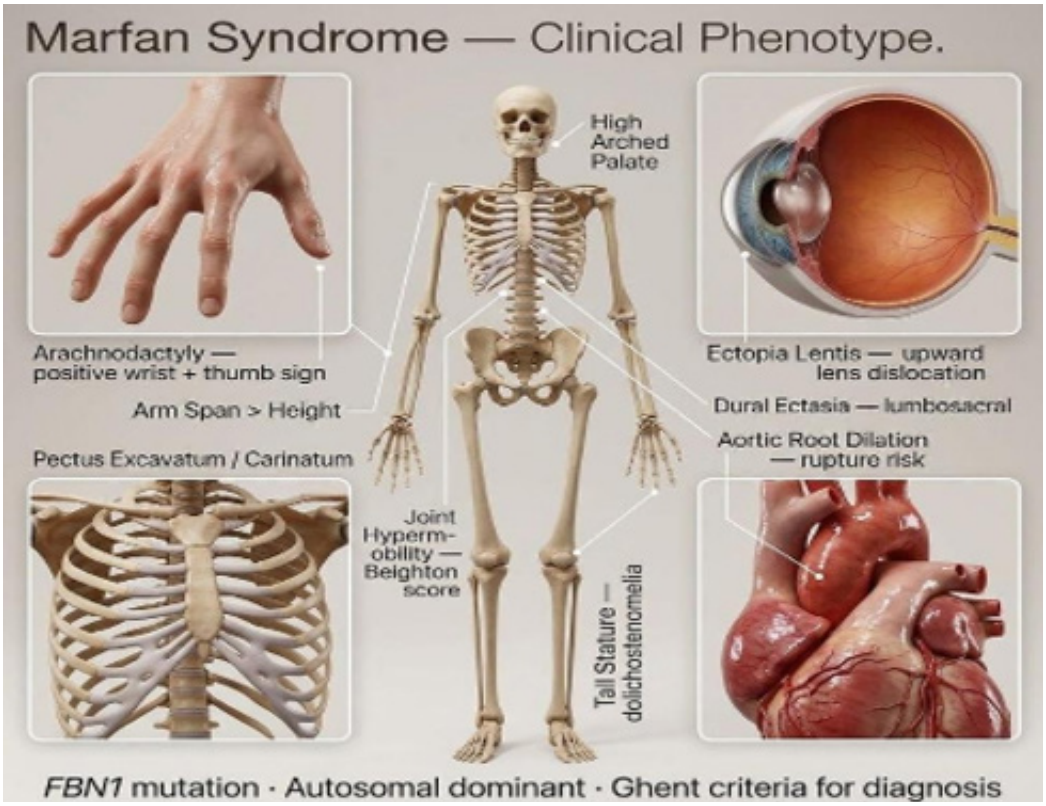


Figure 2: Marfan Syndrome-Clinical Phenotype.

Management and Treatment

Pharmacological management

Beta-blockers reduce heart rate and contractility and may reduce aortic-wall stress. Angiotensin II receptor blockers (ARBs), including losartan, are also used in appropriate patients. Clinical trials have not established universal superiority of one class over the other; medication choice and combination therapy depend on age, blood pressure, aortic measurements, tolerance, and clinician assessment. Treatment should be individualized and monitored [5-7,12,26].

Imaging, surgery, and specialist care

Regular cardiovascular imaging tracks aortic size and growth rate. Preventive aortic-root surgery is considered according to aortic dimensions, rate of enlargement, family history, body size, valve function, and other risk factors. Valve-sparing root replacement may be appropriate for selected patients at experienced centers. Acute dissection is an emergency. Ocular care may include corrective lenses or specialist procedures; orthopedic care and physiotherapy may help selected skeletal problems [9,15,23].

Lifestyle and Genetic Counseling

Activity recommendations should reflect aortic status and individual risk; high-intensity isometric exertion and collision sports may be discouraged in patients at elevated risk. Patients should discuss safe exercise with their clinical team rather than applying a universal restriction. Genetic counseling supports family testing and early assessment of relatives. Lifelong coordinated care commonly involves cardiology, genetics, ophthalmology, and orthopedics [11,16].

Recent Advances and Discussion

Research has shifted from a purely mechanical model of connective-tissue weakness toward a broader model incorporating extracellular-matrix biology, TGF-β-related signaling, vascular remodeling, and genetic variation. This has supported investigation of ARBs and other pathway-directed approaches, but experimental findings do not automatically establish clinical benefit. Evidence from comparative trials supports individualized pharmacotherapy and ongoing surveillance. Aortic diameter remains a key clinical marker, but dissection risk is also influenced by growth rate, family history, body size, and the underlying genetic condition. Cardiac

MRI and 4D-flow MRI are being investigated to characterize aortic flow and wall-related hemodynamics; they complement rather than replace established assessment until their added predictive value is validated [9,26,34]. Genotype-phenotype associations may eventually improve risk stratification, but current prediction remains imperfect.

Emerging research includes non-canonical signaling pathways, circulating biomarkers such as microRNAs, and gene-based approaches targeting FBN1. These approaches remain investigational and require evidence of safety, reliable delivery, and meaningful clinical outcomes. Larger longitudinal studies combining genetic, imaging, and clinical data are needed to refine personalized surveillance and treatment [9,26,34,35].

Conclusion

Marfan syndrome is a variable inherited connective-tissue disorder with potentially serious cardiovascular complications and important ocular and skeletal manifestations. Recognition of FBN1-related disease, use of established diagnostic criteria, regular aortic surveillance, appropriate medication, and timely surgery have improved care. Because clinical progression and risk differ among individuals, lifelong multidisciplinary management and genetic counseling remain essential [1,9,11]. Future work in molecular therapy, biomarkers, and advanced imaging may further support personalized care.

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