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Commentary

Role of *FBN1* Mutations in the Pathogenesis of Marfan Syndrome

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DESCRIPTION

Marfan Syndrome (MFS) is a heritable connective tissue disorder characterized by variable involvement of the skeletal, ocular, and cardiovascular systems. It is primarily caused by mutations in the FBN1 gene, which encodes fibrillin-1, a large glycoprotein essential for the formation and function of elastic fibers in connective tissues. The disruption of *FBN1* leads to the multisystemic manifestations observed in Marfan syndrome, with the most life-threatening complications arising from cardiovascular abnormalities such as aortic aneurysm and dissection. Understanding the role of *FBN1* mutations in the pathogenesis of Marfan syndrome has been crucial for diagnosis, prognosis, and the development of targeted therapies.

The *FBN1* gene, located on chromosome 15q21.1, encodes fibrillin-1, which is a major component of microfibrils in the Extracellular Matrix (ECM). These microfibrils provide structural support and elasticity to connective tissues, particularly in the aorta, ligaments, and eyes. Fibrillin-1 also plays a regulatory role in controlling the bioavailability of Transforming Growth Factor-Beta (TGF-β), a cytokine involved in cellular growth and differentiation. Mutations in the *FBN1* gene impair the synthesis, assembly, or function of fibrillin-1, thereby weakening connective tissues and dysregulating TGF-β signaling, which collectively contribute to the clinical features of Marfan syndrome.

More than 3,000 mutations in the *FBN1* gene have been identified, including missense, nonsense, frameshift, and splice-site mutations. Most of these mutations lead to haploinsufficiency or dominant-negative effects, resulting in either reduced amounts of functional fibrillin-1 or the production of defective protein that disrupts microfibril assembly. The phenotypic variability of Marfan syndrome is partly explained by the type and location of *FBN1* mutations. For instance, mutations affecting the calcium-binding Epidermal Growth Factor-like (cbEGF) domains often result in severe cardiovascular manifestations, while other mutations may predominantly affect skeletal features.

The link between *FBN1* mutations and aberrant TGF-β signaling has been a significant breakthrough in understanding Marfan syndrome pathogenesis. Normally, fibrillin-1 binds latent TGF-β complexes in the ECM, controlling their activation. Mutations in *FBN1* disrupt this sequestration, leading to excessive TGF-β signaling. Elevated TGF-β activity contributes to abnormal cellular responses such as excessive extracellular matrix remodeling, inflammation, and tissue degeneration, particularly in the aortic wall. This mechanism underpins the progressive aortic dilation and risk of dissection observed in affected patients, highlighting a key therapeutic target.

Clinically, Marfan syndrome presents with a spectrum of manifestations including tall stature, arachnodactyly (long fingers), scoliosis, lens dislocation (ectopia lentis), and most critically, aortic root dilation. Genetic testing for *FBN1* mutations has become a cornerstone in confirming diagnosis, especially in patients with borderline clinical features or those without a family history. Molecular diagnosis aids in early detection, risk stratification, and guiding surveillance protocols for cardiovascular complications, which are the primary cause of mortality in Marfan syndrome.

The identification of *FBN1* mutations has also spurred the development of targeted therapies. Angiotensin II Receptor Blockers (ARBs), such as losartan, have been shown to mitigate the effects of dysregulated TGF-β signaling, reducing the rate of aortic dilation in Marfan patients. This pharmacologic approach represents a paradigm shift from solely symptomatic treatment toward molecularly informed intervention. Ongoing research continues to explore additional pathways affected by *FBN1* mutations, with the goal of improving patient outcomes.

Despite advances, challenges remain in correlating specific *FBN1* mutations with clinical prognosis due to the syndrome's phenotypic heterogeneity. Modifier genes, environmental factors, and epigenetic influences also contribute to the variability in disease expression. Future studies focusing on comprehensive genomic analyses and functional assays of *FBN1* variants will enhance our understanding of genotype-phenotype relationships and enable personalized management strategies.

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CONCLUSION

Mutations in the *FBN1* gene are central to the pathogenesis of Marfan syndrome, disrupting connective tissue integrity and dysregulating TGF-β signaling. Molecular insights into *FBN1* function and mutation effects have improved diagnostic precision and opened new therapeutic avenues. Continued research into the complex mechanisms linking *FBN1* mutations to clinical outcomes promises to advance the care and quality of life for individuals affected by this challenging disorder.