

# Fibrillin microfibrils: Connective tissue pathways that regulate shape and signaling

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Fibrillins are large modular extracellular matrix proteins that form the backbone structure of "microfibrils." Fibrillin microfibrils are ubiquitous in the connective tissue space. The importance of fibrillin microfibrils to specific connective tissues is demonstrated by the phenotypic features of the Marfan syndrome (OMIM #154700), an autosomal dominant human disorder caused by mutations in FBN1. Individuals with the Marfan syndrome display several skeletal features (scoliosis, chest deformities, arachnodactyly, and tall stature) that are caused by the overgrowth of long bones. In addition, joint hypermobility and craniofacial manifestations (highly arched palate and overcrowding of teeth) are typical features of the Marfan syndrome. There are also cardiovascular and ocular phenotypes in the Marfan syndrome, consistent with the relative abundance of fibrillin microfibrils in the affected tissues.

Mutations in FBN2 result in a related human disorder called Beals syndrome or congenital contractural arachnodactyly (OMIM +121050). In affected individuals, joint contractures resolve with time. Resolution of this phenotype as well as limitation of the features of this disorder to skeletal tissues likely reflects the expression of FBN2, which is largely limited to fetal tissues<sup>1</sup>. During early fetal development, FBN2 expression is more robust than FBN1 expression, but as FBN1 expression increases during fetal development, FBN2 decreases. In later fetal tissues, both fibrillins are abundant and equally ubiquitous. However, in postnatal tissues, expression of FBN2 is very low, and fibrillin-2 protein is abundant only in peripheral nerves and perichondri-

um/periosteum<sup>2</sup>. Hence, congenital contractural arachnodactyly also reflects the relative abundance of fibrillin-2 in the affected tissues.

From these two human disorders, it can be concluded that fibrillin microfibrils are important regulators of skeletal growth and joint function. It has been thought that a defect in the periosteum/perichondrium might result in increased bone growth<sup>3</sup>. If a defect in the architectural scaffold of the periosteum/perichondrium could lead to a loss of restraint on the growing bone, then fibrillin microfibrils would function primarily as a kind of structural cap or boundary, limiting the growth of adjacent cells. Similarly, in the aorta or in the ciliary zonule, defects in fibrillin microfibrils could result in a mechanically compromised aortic wall, leading to aortic dissection, or to a mechanically compromised suspensory ligament, leading to dislocated lenses.

Recently, our investigations have indicated an additional role for fibrillin microfibrils. We propose that fibrillin microfibrils, together with associated molecules, constitute a connective tissue pathway that functions not only as an architectural or mechanical framework to properly shape and support the body but also as a mediator of growth factor signaling<sup>4</sup>. Several lines of evidence are consistent with this proposal. First, we have shown that Latent TGF $\beta$  Binding Proteins (LTBPs) are associated with fibrillin microfibrils and that LTBP-1 and LTBP-4 interact directly with fibrillin<sup>5</sup>. Through this interaction, latent complexes of TGF $\beta$  are properly targeted to the extracellular matrix and sequestered or presented. In *Fbn1* mutant mice, TGF $\beta$  signaling is dysregulated<sup>6,7</sup>. Second, we have shown that BMP-7 interacts directly with fibrillin and is targeted to the extracellular matrix<sup>8</sup>. Loss of *Fbn2* results in syndactyly<sup>9</sup>, which may be caused by inappropriate targeting of BMPs to the interdigital space. Third, another human disorder, autosomal dominant Weill-Marchesani syndrome, is caused by mutations in FBN1<sup>10,11</sup>. Interestingly, certain features of Weill-Marchesani syndrome are the opposite of features found in the Marfan syndrome. For example, instead of tall stature

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and arachnodactyly, individuals with WMS are short with brachydactyly. Instead of joint hypermobility, joint stiffness is a feature of WMS. We hypothesize that dysregulated BMP or GDF signaling may contribute to WMS.

Since mutations in *FBN1* can cause opposing skeletal phenotypes, we propose that fibrillin microfibrils must integrate opposing signals. Growth factors, like BMPs, GDFs, and TGF $\beta$ s, influence skeletal growth and function, and they also influence each other. The current challenge is to understand how a physical scaffold or architectural framework can integrate opposing signals that communicate with each other through cellular interactions.

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