

# FBN1 Gene

Subjects: **Genetics & Heredity**

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Fibrillin 1: The FBN1 gene provides instructions for making a large protein called fibrillin-1.

genes

## 1. Normal Function

This protein is transported out of cells into the extracellular matrix, which is an intricate lattice of proteins and other molecules that forms in the spaces between cells. In this matrix, molecules of fibrillin-1 attach (bind) to each other and to other proteins to form threadlike filaments called microfibrils. Microfibrils form elastic fibers, which enable the skin, ligaments, and blood vessels to stretch. Microfibrils also provide support to more rigid tissues such as bones and the tissues that support the nerves, muscles, and lenses of the eyes.

Microfibrils store a protein called transforming growth factor beta (TGF- $\beta$ ), a critical growth factor. TGF- $\beta$  affects development by helping to control the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (motility), and the self-destruction of cells (apoptosis). Microfibrils help regulate the availability of TGF- $\beta$ , which is turned off (inactivated) when stored in microfibrils and turned on (activated) when released.

## 2. Health Conditions Related to Genetic Changes

### 2.1 Acromicric Dysplasia

At least nine *FBN1* gene mutations have been identified in people with acromicric dysplasia. This condition is characterized by severely short stature, short limbs, stiff joints, and distinctive facial features.

*FBN1* gene mutations that cause acromicric dysplasia are located in an area of the gene called exons 41 and 42, and change single protein building blocks (amino acids) in a region of the fibrillin-1 protein called TGF- $\beta$  binding-protein-like domain 5. The mutations result in a reduction and disorganization of the microfibrils. Without enough normal microfibrils to store TGF- $\beta$ , the growth factor is abnormally active. These effects likely contribute to the physical abnormalities that occur in acromicric dysplasia, but the mechanisms are unclear.

It is unknown why the *FBN1* gene mutations that cause acromicric dysplasia lead to short stature, while certain other *FBN1* gene mutations that also increase TGF- $\beta$  activity cause a disorder called Marfan syndrome (see

below), which is characterized by tall stature.

## 2.2 Isolated Ectopia Lentis

More than 30 mutations in the *FBN1* gene have been found to cause isolated ectopia lentis. In this condition, the lens in one or both eyes is off-center (displaced), which leads to vision problems. Most of the *FBN1* gene mutations that cause this condition change single amino acids in the fibrillin-1 protein. As a result, the production of normal fibrillin-1 protein is reduced, leading to a decrease in microfibril formation or the formation of impaired microfibrils. Without enough functional microfibrils to anchor the lens in its central position at the front of the eye, the lens becomes displaced, resulting in isolated ectopia lentis and related vision problems.

Ectopia lentis is classified as isolated when it occurs alone, without signs and symptoms affecting other body systems. However, some people initially diagnosed with isolated ectopia lentis caused by *FBN1* gene mutations later develop additional features typical of a condition called Marfan syndrome (described below), such as abnormalities of the large blood vessel that distributes blood from the heart to the rest of the body (the aorta). In these cases, the diagnosis often changes from isolated ectopia lentis to Marfan syndrome.

## 2.3 Marfan Syndrome

Researchers have identified more than 1,300 *FBN1* gene mutations that cause Marfan syndrome, a disorder that affects the connective tissue supporting the body's joints and organs. Abnormalities in the connective tissue lead to heart and eye problems in people with this disorder. In addition, affected individuals are usually tall and slender with elongated fingers and toes and other skeletal abnormalities. Most of the mutations that cause Marfan syndrome change a single amino acid in the fibrillin-1 protein. The remaining *FBN1* gene mutations result in an abnormal fibrillin-1 protein that cannot function properly. *FBN1* gene mutations that cause Marfan syndrome reduce the amount of fibrillin-1 produced by the cell, alter the structure or stability of fibrillin-1, or impair the transport of fibrillin-1 out of the cell. These mutations lead to a severe reduction in the amount of fibrillin-1 available to form microfibrils. Without enough microfibrils, excess TGF- $\beta$  growth factors are activated and elasticity in many tissues is decreased, leading to overgrowth and instability of tissues and the signs and symptoms of Marfan syndrome.

## 2.4 Weill-Marchesani Syndrome

Mutations in the *FBN1* gene have also been identified in Weill-Marchesani syndrome. One of the identified mutations deletes part of the gene, leading to the production of an unstable version of the fibrillin-1 protein. The unstable protein likely interferes with the assembly of microfibrils. Abnormal microfibrils weaken connective tissue, which causes the eye, heart, and skeletal abnormalities associated with Weill-Marchesani syndrome.

## 2.5 Familial Thoracic Aortic Aneurysm and Dissection

## 2.6 Geleophysic Dysplasia

## 2.7 Shprintzen-Goldberg Syndrome

## 2.8 Other Disorders

Mutations in the *FBN1* gene can cause a condition called stiff skin syndrome. This condition is characterized by very hard, thick skin covering most of the body. The abnormal skin limits movement and can lead to joint deformities called contractures that restrict the movement of certain joints. The signs and symptoms of stiff skin syndrome usually become apparent in infancy to mid-childhood.

Mutations in the *FBN1* gene can cause another condition called MASS syndrome. This condition involves abnormalities in several parts of the body, including the mitral valve (one of the valves that controls blood flow through the heart), the aorta (a large blood vessel that distributes blood from the heart to the rest of the body), the skeleton, and the skin.

It is unknown why different mutations in the *FBN1* gene cause such a variety of disorders.

## 3. Other Names for This Gene

- FBN
- FBN1\_HUMAN
- fibrillin 1 (Marfan syndrome)
- MFS1
- SGS

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