FHL1 Gene

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Four and a half LIM domains 1

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1. Normal Function

The *FHL1* gene provides instructions for making three versions (isoforms) of a protein that plays an important role in muscles used for movement (skeletal muscles) and in the heart (cardiac muscle). The full-length isoform is known as FHL1A, or sometimes just FHL1. The other two isoforms, which are shorter, are called FHL1B and FHL1C.

FHL1A is the best-studied of the three FHL1 isoforms. Studies suggest that interactions between FHL1A and other proteins play a critical role in the assembly of sarcomeres, which are structures within muscle cells that are necessary for muscle tensing (contraction). These interactions also appear to be involved in chemical signaling within muscle cells, maintaining the structure of these cells, and influencing muscle growth and size.

Less is known about the FHL1B and FHL1C isoforms. FHL1B moves in and out of the nucleus and is also part of the nuclear envelope, which is a structure that surrounds the nucleus in cells. The protein's function in this structure is unknown. FHL1B and FHL1C are suspected to play roles in the normal structure and function of skeletal and cardiac muscles.

2. Health Conditions Related to Genetic Changes

2.1 Emery-Dreifuss Muscular Dystrophy

At least seven mutations in the *FHL1* gene have been found to cause Emery-Dreifuss muscular dystrophy. This condition affects skeletal and cardiac muscle, causing joint deformities called contractures, which restrict the movement of certain joints; muscle weakness and wasting that worsen over time; and heart problems, including an increased risk of sudden death.

Some of the *FHL1* gene mutations that cause Emery-Dreifuss muscular dystrophy change single protein building blocks (amino acids) in the FHL1 protein, while others insert or delete a small amount of DNA from the *FHL1* gene. All of the known mutations affect the FHL1A isoform. Depending on where the mutations occur, they may affect one or both of the other isoforms as well.

Studies suggest that mutations reduce the amount of functional FHL1 protein produced in cells or lead to the production of an abnormally short, nonfunctional version of the protein. A shortage of this protein disrupts the normal structure and function of cardiac and skeletal muscle cells. However, the exact mechanism by which these changes cause joint contractures, muscle weakness and wasting, and heart problems remains unknown.

2.2 Other Disorders

Several other muscle disorders also result from mutations in the *FHL1* gene. These include reducing body myopathy, X-linked scapuloperoneal myopathy, X-linked myopathy with postural muscle atrophy (XMPMA), and rigid spine syndrome. Together with Emery-Dreifuss muscular dystrophy, these conditions are known as *FHL1*-related myopathies or FHL1opathies. Features common among these disorders include skeletal muscle weakness, particularly in the shoulders and lower legs; contractures involving the joints of the spine (rigid spine); and heart abnormalities. However, the disorders differ in their age of onset, the severity of muscle weakness, and how quickly the signs and symptoms worsen.

More than 50 *FHL1* gene mutations have been associated with the *FHL1*-related myopathies. Each of these mutations affects some or all of the FHL1 isoforms. In general, mutations that affect all three isoforms cause more severe signs and symptoms than mutations that affect only one or two isoforms. Researchers have proposed several possible mechanisms by which *FHL1* mutations lead to the *FHL1*-related myopathies. In some cases, mutations lead to the production of a nonfunctional version of the protein or no protein at all. In others, mutations may result in the production of an abnormal version of the protein that can form clumps (called reducing bodies) within muscle cells. Reducing bodies have been found in people with reducing body myopathy, X-linked scapuloperoneal myopathy, and rigid spine syndrome, but it is unclear how they are related to the major features of these disorders.

3. Other Names for This Gene

- bA5A

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