

LMNA Gene

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1. Introduction

The *LMNA* gene provides instructions for making several slightly different proteins called lamins. The two major proteins produced from this gene, lamin A and lamin C, are made in most of the body's cells. These proteins are made up of a nearly identical sequence of protein building blocks (amino acids). The small difference in the sequence makes lamin A longer than lamin C.

Lamins A and C are structural proteins called intermediate filament proteins. Intermediate filaments provide stability and strength to cells. Lamins A and C are supporting (scaffolding) components of the nuclear envelope, which is a structure that surrounds the nucleus in cells. Specifically, these proteins are located in the nuclear lamina, a mesh-like layer of intermediate filaments and other proteins that is attached to the inner membrane of the nuclear envelope. The nuclear envelope regulates the movement of molecules into and out of the nucleus. Lamins A and C are also found inside the nucleus, and researchers believe the proteins may play a role in regulating the activity (expression) of certain genes.

The lamin A protein must be processed within the cell before becoming part of the lamina. Its initial form, called prelamin A, undergoes a complex series of steps that are necessary for the protein to be inserted into the lamina. Lamin C does not have to undergo this processing before becoming part of the lamina.

2. Health Conditions Related to Genetic Changes

2.1. Emery-Dreifuss Muscular Dystrophy

More than 130 mutations in the *LMNA* gene have been identified in people with Emery-Dreifuss muscular dystrophy, a condition that affects muscles used for movement (skeletal muscles) and the heart (cardiac muscle). This condition is characterized by 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.

Most of the *LMNA* gene mutations that cause Emery-Dreifuss muscular dystrophy change single protein building blocks (amino acids) in lamins A and C, which alters the structure of these proteins. The effect of *LMNA* gene mutations within cells is unclear. Abnormal versions of lamins A and C may alter the activity of certain genes or weaken the structure of the nucleus, making cells more fragile. Researchers continue to investigate how *LMNA* mutations affect skeletal muscles and cardiac muscle, leading to the characteristic features of Emery-Dreifuss muscular dystrophy.

2.2. Familial Partial Lipodystrophy

Several mutations in the *LMNA* gene have been found to cause familial partial lipodystrophy type 2 (also known as familial partial lipodystrophy, Dunnigan type), a rare condition characterized by an abnormal distribution of fatty (adipose) tissue in the body. Adipose tissue is lost from the arms, legs, and hips, and excess fat is deposited in the face, neck, and abdomen. The abnormal fat storage is related to changes in the development and function of adipocytes, which are the fat-storing cells in adipose tissue. The effects of *LMNA* gene mutations on adipocytes are not well understood. Studies suggest that these mutations may weaken the nuclear envelope, ultimately leading to the premature death of these cells and leaving the body unable to store and use fats properly. These abnormalities of adipose tissue alter hormone production and affect many of the body's organs. However, it is unclear why the changes cause fat to be lost in some parts of the body and stored abnormally in others.

2.3. Hutchinson-Gilford Progeria Syndrome

A specific mutation in the *LMNA* gene has been found in most patients with Hutchinson-Gilford progeria syndrome, which is a condition that causes the dramatic, rapid appearance of aging beginning in childhood. This mutation changes a single DNA building block (nucleotide) in the gene. Specifically, the mutation replaces the nucleotide cytosine with the nucleotide thymine at position 1824 (written as C1824T). This mutation is also sometimes noted as Gly608Gly or G608G, which refers to the position in the lamin A protein affected by the mutation. Although the C1824T mutation is not predicted to change an amino acid, it alters the way the gene's instructions are used to make a protein. The C1824T mutation leads to an abnormal version of the lamin A protein called progerin, which is missing 50 amino acids near one end. The location of this mutation does not affect the production of lamin C. Other mutations in the *LMNA* gene have been identified in a small number of people with the features of Hutchinson-Gilford progeria syndrome.

The mutations responsible for this disorder result in an abnormal version of prelamin A that cannot be processed correctly within the cell. When the altered protein is incorporated into the lamina, it disrupts the shape of the nuclear envelope. Over time, a buildup of this altered protein appears to damage the structure and function of the nucleus, making cells more likely to die prematurely. Researchers are working to determine how these changes lead to the signs and symptoms of Hutchinson-Gilford progeria syndrome.

2.4. LMNA-Related Congenital Muscular Dystrophy

At least 15 mutations in the *LMNA* gene have been reported to cause *LMNA*-related congenital muscular dystrophy (L-CMD), a rare condition characterized by skeletal muscle weakness and atrophy beginning very early in life. Most of the mutations associated with this disorder change single amino acids in lamin A and lamin C, while a few add or remove a small number of amino acids from these proteins.

The mutations that cause L-CMD lead to the production of abnormal lamins. These malfunctioning proteins alter the structure of the nuclear envelope in ways that are not well understood. Researchers are working to determine how these changes affect muscle cells and lead to muscle weakness and atrophy in people with L-CMD.

Some of the mutations identified in people with L-CMD seem to be unique to this disorder, while others have also been reported in people with other *LMNA*-related conditions, such as Emery-Dreifuss muscular dystrophy (described above). It is unclear why certain mutations can cause different disorders in different people.

2.5. Mandibuloacral Dysplasia

At least four mutations in the *LMNA* gene cause mandibuloacral dysplasia type A (MADA). This condition is characterized by a variety of signs and symptoms, which can include bone abnormalities; mottled or patchy skin coloring; and loss of fatty tissue under the skin, particularly affecting the limbs (type A lipodystrophy). The *LMNA* gene mutations that cause this condition change single amino acids in the lamin A and lamin C proteins. The most common mutation replaces the amino acid arginine at position 527 with the amino acid histidine (written as Arg527His or R527H).

The effects of *LMNA* gene mutations in this condition are not well understood. The amino acid changes may affect the structure of the lamin A or lamin C protein, or both, and alter how they interact with other proteins in the nuclear lamina. Some researchers speculate that these changes disrupt the nuclear envelope, making cells more fragile; however, it is unclear how the altered lamin proteins contribute to the signs and symptoms of MADA.

2.6. Other Disorders

Mutations in the *LMNA* gene have been found to cause several other conditions. Health conditions that result from mutations in lamin proteins are known as laminopathies. These disorders often have overlapping signs and symptoms, and in some cases different conditions can result from the same *LMNA* mutation. Researchers suspect that some laminopathies represent variants of a single condition instead of separate disorders.

In addition to the health conditions listed above, mutations in the *LMNA* gene cause atypical progeroid syndrome (APS); the features of this condition are similar to those of Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia. As in Hutchinson-Gilford progeria syndrome, children with APS look as though they are aging prematurely, although the signs and symptoms of APS usually begin slightly later. APS can also cause similar abnormalities in bone development and fat distribution as mandibuloacral dysplasia, although they are typically milder in APS.

Mutations in the *LMNA* gene have also been identified in newborns with a disorder called lethal restrictive dermopathy. Infants with this disorder have tight, rigid skin; underdeveloped lungs; and other abnormalities. They do not usually survive past the first week of life.

Researchers have not determined how mutations in the *LMNA* gene result in this diverse group of disorders, but the multiple roles of the nuclear lamina in cells may help explain the wide variety of signs and symptoms.

3. Other Names for This Gene

- LMN1
- LMNA_HUMAN

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