LEMD3 Gene

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LEM domain containing 3

genes

1. Introduction

The *LEMD3* gene provides instructions for making a protein that is located in a cell structure called the nuclear envelope. The nuclear envelope surrounds the nucleus, acting as a barrier between the nucleus and the rest of the cell.

The LEMD3 protein helps control two chemical signaling pathways called the transforming growth factor beta (TGF-β) pathway and the bone morphogenic protein (BMP) pathway. The TGF-β and BMP pathways regulate various cellular processes, including cell growth and division (proliferation), the process by which cells mature to carry out special functions (differentiation), and the self-destruction of cells (apoptosis). These pathways are also involved in the growth of new bone.

Signaling through the BMP and TGF-β pathways turns on (activates) proteins called Smads, which attach (bind) to specific areas of DNA to activate certain genes. The LEMD3 protein interacts with Smads to reduce signaling through these pathways. In this way, the LEMD3 protein helps keep signaling at normal levels within the cell.

2. Health Conditions Related to Genetic Changes

2.1. Buschke-Ollendorff Syndrome

At least 23 mutations in the *LEMD3* gene have been found to cause Buschke-Ollendorff syndrome, a rare connective tissue disorder. (Connective tissues provide support, strength, and flexibility to organs and tissues throughout the body.) The condition is characterized by skin growths called connective tissue nevi and bone abnormalities, most commonly osteopoikilosis. Osteopoikilosis refers to small, round areas of increased bone density that can be seen on x-rays. Rarely, people with Buschke-Ollendorff syndrome have another bone abnormality called melorheostosis, which is characterized by excess bone growth on the surface of existing bones in a pattern resembling dripping candle wax.

Each of the known *LEMD3* gene mutations prevents the production of functional LEMD3 protein from one copy of the gene in each cell, which reduces the total amount of LEMD3 protein by about half. A shortage of this protein increases signaling through the BMP and TGF-β pathways. Studies suggest that the enhanced signaling increases the formation of bone tissue, resulting in areas of overly dense bone or excess bone growth. It is unclear how the increased signaling is related to the development of connective tissue nevi in people with Buschke-Ollendorff syndrome.

2.2. Other Disorders

LEMD3 gene mutations have also been found in people with isolated osteopoikilosis, a condition involving areas of increased bone density without the other features of Buschke-Ollendorff syndrome (described above). Occasionally, mutations in this gene cause osteopoikilosis and melorheostosis without connective tissue nevi. (Studies suggest that *LEMD3* gene mutations do not cause melorheostosis when this bone abnormality occurs alone.)

Researchers are working to understand why *LEMD3* gene mutations cause Buschke-Ollendorff syndrome in some people and isolated osteopoikilosis or osteopoikilosis with melorheostosis in others. In some cases, the same mutation has been found to cause all of these conditions in different members of a single family. Each of the known mutations reduces the amount of functional LEMD3 protein that is produced in cells, which abnormally enhances BMP and TGF-β signaling and leads to areas of increased bone density and excess bone growth.

3. Other Names for This Gene

- inner nuclear membrane protein Man1
- integral inner nuclear membrane protein
- LEM domain-containing protein 3
- MAN1
- MAN1_HUMAN

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