FLNA Gene

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Filamin A

genes

1. Normal Function

The *FLNA* gene provides instructions for producing the protein filamin A, which helps build cells' extensive internal network of protein filaments called the cytoskeleton. The cytoskeleton gives structure to cells and allows them the flexibility to change shape. The cytoskeleton is also important for certain processes inside the cells, such as the movement of proteins within the cell and the breakdown of unneeded proteins. Filamin A primarily attaches (binds) to another protein called actin and helps it form the branching network of filaments that make up the cytoskeleton. Filamin A can also bind to many other proteins in the cell to carry out various functions, including the attachment of cells to one another (cell adhesion), cell movement (migration), determination of cell shape, the relay of signals within cells, and cell survival. These numerous functions involving filamin A have been found to play roles in regulating skeletal and brain development, the formation of heart tissue and blood vessels, blood clotting, skin elasticity, the maintenance of lung tissue, and the function of the digestive system.

Filamin A is also involved in the organization of the extracellular matrix, which is the lattice of proteins and other molecules outside the cell. Filamin A binds to proteins called integrins, which span the cell membrane and anchor cells to the extracellular matrix. Through this binding, cells are correctly positioned and signals can be exchanged between the cell and the extracellular matrix.

2. Health Conditions Related to Genetic Changes

2.1 Frontometaphyseal Dysplasia

More than 15 mutations in regions of the *FLNA* gene called exons 4, 22, 29, 33, and 44 through 46 have been identified in people with frontometaphyseal dysplasia. This condition is a member of a group of related conditions called otopalatodigital spectrum disorders, which also includes otopalatodigital syndrome type 1, otopalatodigital syndrome type 2, frontometaphyseal dysplasia, and Melnick-Needles syndrome (described below). Frontometaphyseal dysplasia involves abnormalities in skeletal development, particularly involving the joints, and other health problems, including kidney, heart, and lung defects. The *FLNA* gene mutations that cause frontometaphyseal dysplasia are described as "gain of function" because they appear to enhance the activity of the

filamin A protein or give the protein a new, atypical function. Different mutations in the *FLNA* gene appear to produce specific changes in the protein, resulting in particular signs and symptoms that are classified as individual *FLNA*-related disorders. Researchers believe that the mutations involved in frontometaphyseal dysplasia may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of the condition.

2.2 Intestinal Pseudo-Obstruction

At least three mutations in the *FLNA* gene have been identified in people with intestinal pseudo-obstruction, a condition characterized by impairment of the muscle contractions that move food through the digestive tract (peristalsis).

The *FLNA* gene mutations that cause intestinal pseudo-obstruction include deletions or duplications of genetic material. The mutations are thought to reduce levels of the filamin A protein or impair its function; this type of mutation is called "loss of function." Research suggests that decreased filamin A function may affect the shape of cells in the smooth muscles of the gastrointestinal tract during development before birth, causing abnormalities in the layering of these muscles. Smooth muscles line the internal organs; they contract and relax without being consciously controlled. Abnormal layering of these muscles may interfere with the muscle movements that move food through the digestive tract.

Deletions or duplications of genetic material can affect all or part of the *FLNA* gene, and may also include nearby genes on the X chromosome. Changes in these additional genes may account for some of the other signs and symptoms, such as neurological abnormalities and unusual facial features, that occur in some affected individuals.

2.3 Melnick-Needles Syndrome

At least 10 mutations in a region of the *FLNA* gene called exon 22 have been identified in people with Melnick-Needles syndrome. This condition is typically the most severe of the otopalatodigital spectrum disorders (described above). It involves abnormalities in skeletal development, causing short stature, abnormal curvature of the spine, partial dislocation of joints, and other health problems. The *FLNA* gene mutations associated with Melnick-Needles syndrome are described as "gain of function" because they appear to enhance the activity of the filamin A protein or give the protein a new, atypical function. Researchers believe that the mutations involved in Melnick-Needles syndrome may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of the condition.

2.4 Otopalatodigital Syndrome Type 1

At least five mutations in the *FLNA* gene have been found to cause otopalatodigital syndrome type 1. This condition is typically the mildest of the otopalatodigital spectrum disorders (described above). It is characterized by hearing loss caused by malformations in tiny bones in the ears (ossicles), an opening in the roof of the mouth (cleft palate), and skeletal abnormalities involving the fingers or toes (digits).

The *FLNA* gene mutations that cause otopalatodigital syndrome type 1 all result in changes to the filamin A protein in a region that binds to actin (known as the CH2 domain). Many of these mutations change single amino acids in the filamin A protein. These mutation are described as "gain-of-function" because they appear to lead to a protein with an increased ability to bind to actin. Researchers believe that the *FLNA* gene mutations impair the stability of the cytoskeleton and disrupt cellular processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of otopalatodigital syndrome type 1.

2.5 Otopalatodigital Syndrome Type 2

At least 16 mutations in the *FLNA* gene have been found to cause otopalatodigital syndrome type 2, which is part of the otopalatodigital spectrum (described above). This condition is similar to otopalatodigital syndrome type 1 (described above) and is characterized by hearing loss caused by malformations in the ossicles, a cleft palate, and skeletal abnormalities involving the digits. These abnormalities in skeletal development are typically more severe than in otopalatodigital syndrome type 1.

The *FLNA* gene mutations that cause otopalatodigital syndrome type 2 all result in changes to the filamin A protein in a region that binds to actin (known as the CH2 domain). Most of these mutations change single amino acids in the filamin A protein. These mutations are described as "gain-of-function" because they appear to lead to a protein with an increased ability to bind to actin. Researchers believe that the *FLNA* gene mutations impair the stability of the cytoskeleton and disrupt cellular processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of otopalatodigital syndrome type 2.

2.6 Periventricular Heterotopia

More than 130 *FLNA* gene mutations have been identified in individuals with periventricular heterotopia, a condition in which nerve cells (neurons) do not move (migrate) properly during the early development of the fetal brain leading to seizures and other neurological problems. Most of these mutations result in a protein that is too short and cannot perform its function, which makes the cytoskeleton disorganized and impairs the attachment (adhesion) of cells to one another. Impaired adhesion alters the lining of the fluid-filled cavities near the center of the brain (the ventricles), which is where neurons develop. Disruption of this lining prevents the movement of neurons to the surface of the brain. Neurons that do not migrate properly during development form clumps (nodules) around the ventricles, resulting in the signs and symptoms of periventricular heterotopia.

In some cases, mutations result in the substitution of one protein building block (amino acid) for another amino acid in the protein sequence. These mutations may result in the production of a partially functional protein, causing a milder form of the disorder.

2.7 Terminal Osseous Dysplasia

At least one mutation in the *FLNA* gene has been found to cause terminal osseous dysplasia, which is part of the otopalatodigital spectrum of disorders (described above). Terminal osseous dysplasia is characterized by skeletal

abnormalities in the hands and feet, noncancerous (benign) tumors on the fingers and toes (digits), and dark patches of skin on the face.

The *FLNA* gene mutation that causes terminal osseous dysplasia changes a single DNA building block (nucleotide) in the gene, substituting adenine for guanine at DNA position 5217 (written as 5217G>A). This DNA change alters the way the blueprint for making the filamin A protein is put together. The version of the protein made using this blueprint is abnormally short. Researchers suspect the altered protein may not be able to interact with other molecules normally. It is thought that the inability to bind to other proteins disrupts important processes involved in skeletal development and cell growth, leading to the bone and skin abnormalities characteristic of terminal osseous dysplasia.

2.8 X-Linked Cardiac Valvular Dysplasia

At least four mutations in the *FLNA* gene have been found to cause X-linked cardiac valvular dysplasia, a condition characterized by abnormally thick heart valves. Most of these mutations change single protein building blocks in the filamin A protein. These mutations likely alter the shape of the protein, impairing its ability to bind to actin and other proteins. As a result, the cell cytoskeleton is weakened and valve cells as well as the extracellular matrix are disorganized. The cells are not positioned properly within the valve, so the valve becomes malformed. In addition, the cells' decreased ability to change shape impairs the valves' ability to open and close when the heart pumps blood. It appears that excess proteins are produced in the abnormal extracellular matrix, causing the valves to become thickened and further impairing their ability to open and close normally.

It is unclear why the heart valves are the only tissue affected by these *FLNA* gene mutations. The mutations that cause X-linked cardiac valvular dysplasia occur in a different part of the gene than those that cause other disorders (described above). It has been suggested that the region of the filamin A protein affected by these mutations is necessary for binding to other proteins that play a significant role in heart development.

2.9 FG Syndrome

2.10 Other Disorders

Mutations in the *FLNA* gene are a rare cause of a large group of conditions that affect children's lungs called childhood interstitial lung disease (chILD). The signs and symptoms of chILD can include shortness of breath (dyspnea), rapid breathing (tachypnea), frequent coughing or wheezing, frequent bouts of pneumonia or other lung infections, and slow growth.

The signs and symptoms of chILD caused by *FLNA* gene mutations can be life-threatening. Individuals with chILD typically experience complication that include overinflation of the lungs due to air being trapped and not exhaled (hyperinflation), narrowing of the blood vessels in the lungs (pulmonary vascular attenuation), and high blood pressure in the vessels that carry blood from the heart to the lungs (pulmonary hypertension).

The role of the filamin A protein in the lungs is unclear, but it is thought to be involved in the development of small air sacs (alveoli) in the lungs before birth. Changes in the *FLNA* gene that cause chILD are "loss-of-function" mutations; they reduce levels of the filamin A protein or impair its function. A shortage of functioning filamin A likely prevents the normal development of the lungs, leading to the signs and symptoms of chILD in affected individuals.

3. Other Names for This Gene

- ABP-280
- ABPX
- actin-binding protein 280
- DKFZp434P031
- filamin 1
- filamin A, alpha
- filamin A, alpha (actin binding protein 280)
- FLN
- FLN1
- FLNA_HUMAN

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