ACTA1 Gene

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actin, alpha 1, skeletal muscle

genes

1. Normal Function

The *ACTA1* gene provides instructions for making a protein called skeletal alpha (α)-actin, which is part of the actin protein family. Actin proteins are important for cell movement and the tensing of muscle fibers (muscle contraction). These proteins also help maintain the cytoskeleton, which is the structural framework that determines cell shape and organizes cell contents.

Skeletal α-actin plays an important role in skeletal muscles, which are muscles that the body uses for movement. Within skeletal muscle cells, skeletal α-actin is an essential component of structures called sarcomeres. Sarcomeres are composed of thin filaments made up of actin and thick filaments made up of another protein called myosin. Attachment (binding) and release of the overlapping thick and thin filaments allows them to move relative to each other so that the muscles can contract.

2. Health Conditions Related to Genetic Changes

2.1 Actin-accumulation myopathy

At least nine mutations in the *ACTA1* gene have been identified in people with actin-accumulation myopathy. Most of these mutations change single protein building blocks (amino acids) in the skeletal α-actin protein sequence.

Researchers suggest that *ACTA1* gene mutations that cause actin-accumulation myopathy may affect the way the actin binds to ATP. ATP is a molecule that supplies energy for cells' activities and is important in the formation of thin filaments from individual actin molecules. Dysfunctional actin-ATP binding may result in abnormal thin filament formation and impair muscle contraction, leading to muscle weakness and the other signs and symptoms of actin-accumulation myopathy.

2.2 Cap myopathy

At least one *ACTA1* gene mutation has been identified as a cause of cap myopathy. The mutation replaces the amino acid methionine with the amino acid valine at position 47 in the protein sequence, written as Met47Val or

M47V. The resulting abnormal protein may interfere with the proper assembly of thin filaments. Cap myopathy is characterized by the presence of cap-like structures in muscle cells, and these structures are composed of disorganized thin filaments. The abnormal filament structure likely impairs the ability of skeletal muscles to contract, resulting in muscle weakness and the other signs and symptoms of cap myopathy.

2.3 Congenital fiber-type disproportion

At least seven mutations in the *ACTA1* gene have been found to cause congenital fiber-type disproportion, a disorder that causes general muscle weakness that typically does not worsen over time. The mutations that cause this condition change single amino acids in skeletal α-actin. These mutations lead to the production of an abnormal actin protein, which interferes with the function of normal actin proteins in the sarcomere. As a result, the function of the sarcomere is impaired, which disrupts muscle contraction. Inefficient muscle contraction leads to muscle weakness in people with congenital fiber-type disproportion.

2.4 Intranuclear rod myopathy

At least 13 mutations in the *ACTA1* gene have been identified in people with intranuclear rod myopathy. These mutations change single amino acids in the skeletal α-actin protein sequence.

ACTA1 gene mutations that cause intranuclear rod myopathy result in rod-shaped accumulations of actin in the nucleus of muscle cells. Normally, most actin is found in the fluid surrounding the nucleus (the cytoplasm), with small amounts in the nucleus itself. Researchers suggest that the *ACTA1* gene mutations that cause intranuclear rod myopathy may interfere with the normal transport of actin between the nucleus and the cytoplasm, resulting in the accumulation of actin in the nucleus and the formation of intranuclear rods. Abnormal accumulation of actin in the nucleus of muscle cells and a corresponding reduction of available actin in muscle fibers may impair muscle contraction and lead to the muscle weakness seen in intranuclear rod myopathy.

A few *ACTA1* gene mutations that have been identified in people with intranuclear rod myopathy have also been found in people with actin-accumulation myopathy. It is unclear how the same mutation can cause two different conditions.

2.5 Nemaline myopathy

More than 170 mutations in the *ACTA1* gene have been found to cause nemaline myopathy. Nemaline myopathy is the most common muscle disorder associated with *ACTA1* gene mutations. Some of the mutations that cause this disorder alter the structure or function of skeletal α-actin, causing the protein to cluster together and form clumps (aggregates). These aggregates interfere with the normal functioning of muscle cells. Other *ACTA1* gene mutations prevent the production of any skeletal α-actin, impairing the muscle cells' ability to contract. *ACTA1* gene mutations that cause nemaline myopathy impair muscle contraction, causing weakness and the other features of this condition.

3. Other Names for This Gene

- ACTA
- ACTS_HUMAN
- alpha skeletal muscle actin
- ASMA

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