ACTA1 gene

actin alpha 1, skeletal muscle

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.

Health Conditions Related to Genetic Changes

Actin-accumulation myopathy

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

Researchers suggest that *ACTA1* gene variants 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.

Cap myopathy

At least one *ACTA1* gene variant has been identified as a cause of cap myopathy. The variant 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.

Congenital fiber-type disproportion

At least seven variants 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 variants that cause this condition change single amino acids in skeletal α-actin. These variants 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.

Intranuclear rod myopathy

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

ACTA1 gene variants 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 variants 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 variants that have been identified in people with intranuclear rod myopathy have also been found in people with actin-accumulation myopathy (described above). It is unclear how the same variants can cause two different conditions.

Nemaline myopathy

More than 170 variants in the *ACTA1* gene have been found to cause nemaline myopathy. Nemaline myopathy is the most common muscle disorder associated with *ACTA1* gene variants. Some of the variants 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 variants prevent the production of any skeletal α-actin, impairing the muscle cells' ability to contract. *ACTA1* gene variants that cause nemaline myopathy impair muscle contraction, causing weakness and the other features of this condition.

Other Names for This Gene

- ACTA
- ACTS_HUMAN
- alpha skeletal muscle actin
- ASMA

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ACTA1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=58[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28ACTA1%5BTI%5D%29+OR+%28alpha+skeletal+muscle+actin%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- ACTIN, ALPHA-1, SKELETAL MUSCLE; ACTA1 (https://omim.org/entry/102610)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/58)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ACTA1[gene])

References

- Agrawal PB, Strickland CD, Midgett C, Morales A, Newburger DE, Poulos MA, Tomczak KK, Ryan MM, Iannaccone ST, Crawford TO, Laing NG, Beggs AH. Heterogeneity of nemaline myopathy cases with skeletal muscle alpha-actin genemutations. Ann Neurol. 2004 Jul;56(1):86-96. doi: 10.1002/ana.20157. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15236405)
- Castiglioni C, Cassandrini D, Fattori F, Bellacchio E, D'Amico A, Alvarez K, Gejman R, Diaz J, Santorelli FM, Romero NB, Bertini E, Bevilacqua JA. Musclemagnetic resonance imaging and histopathology in ACTA1-related congenitalnemaline myopathy. Muscle Nerve. 2014 Dec;50(6):1011-6. doi: 10.1002/mus.24353.Epub 2014 Oct 30. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25088345)

- Clarke NF, Ilkovski B, Cooper S, Valova VA, Robinson PJ, Nonaka I, Feng JJ, Marston S, North K. The pathogenesis of ACTA1-related congenital fiber typedisproportion. Ann Neurol. 2007 Jun;61(6):552-61. doi: 10.1002/ana.21112. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17387733)
- Feng JJ, Marston S. Genotype-phenotype correlations in ACTA1 mutations thatcause congenital myopathies. Neuromuscul Disord. 2009 Jan;19(1):6-16. doi:10.1016/j.nmd.2008.09.005. Epub 2008 Oct 30. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18976909)
- Hung RM, Yoon G, Hawkins CE, Halliday W, Biggar D, Vajsar J. Cap myopathycaused by a mutation of the skeletal alpha-actin gene ACTA1. Neuromuscul Disord.2010 Apr;20(4):238-40. doi: 10.1016/j.nmd.2010.01.011. Epub 2010 Mar 19. ErratumIn: Neuromuscul Disord.2010 Aug;20(8):567. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20303757)
- Ilkovski B, Clement S, Sewry C, North KN, Cooper ST. Defining alpha-skeletaland alpha-cardiac actin expression in human heart and skeletal muscle explainsthe absence of cardiac involvement in ACTA1 nemaline myopathy. NeuromusculDisord. 2005 Dec;15(12):829-35. doi: 10.1016/j.nmd.2005.08.004. Epub 2005 Nov 8. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16288873)
- Kaimaktchiev V, Goebel H, Laing N, Narus M, Weeks D, Nixon R. Intranuclearnemaline rod myopathy. Muscle Nerve. 2006 Sep;34(3):369-72. doi:10.1002/mus.20521. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16477620)
- Koy A, Ilkovski B, Laing N, North K, Weis J, Neuen-Jacob E, Mayatepek E, VoitT. Nemaline myopathy with exclusively intranuclear rods and a novel mutation inACTA1 (Q139H). Neuropediatrics. 2007 Dec;38(6):282-6. doi:10.1055/s-2008-1065356. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18461503)
- Laing NG, Clarke NF, Dye DE, Liyanage K, Walker KR, Kobayashi Y, Shimakawa S, Hagiwara T, Ouvrier R, Sparrow JC, Nishino I, North KN, Nonaka I. Actin mutationsare one cause of congenital fibre type disproportion. Ann Neurol. 2004Nov;56(5):689-94. doi: 10.1002/ana.20260. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15468086)
- Laing NG, Dye DE, Wallgren-Pettersson C, Richard G, Monnier N, Lillis S,Winder TL, Lochmuller H, Graziano C, Mitrani-Rosenbaum S, Twomey D, Sparrow JC, Beggs AH, Nowak KJ. Mutations and polymorphisms of the skeletal musclealpha-actin gene (ACTA1). Hum Mutat. 2009 Sep;30(9):1267-77. doi:10.1002/humu.21059. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19562689) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2784950/)
- Nowak KJ, Sewry CA, Navarro C, Squier W, Reina C, Ricoy JR, Jayawant SS, Childs AM, Dobbie JA, Appleton RE, Mountford RC, Walker KR, Clement S, Barois A,Muntoni F, Romero NB, Laing NG. Nemaline myopathy caused by absence ofalpha-skeletal muscle actin. Ann Neurol. 2007 Feb;61(2):175-84. doi:10.1002/ana.21035. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17187373)
- Ochala J. Thin filament proteins mutations associated with skeletalmyopathies: defective regulation of muscle contraction. J Mol Med (Berl). 2008Nov;86(11):1197-204. doi: 10.1007/s00109-008-0380-9. Epub 2008 Jun 24. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18574571)

- Schroder JM, Durling H, Laing N. Actin myopathy with nemaline bodies,intranuclear rods, and a heterozygous mutation in ACTA1 (Asp154Asn). ActaNeuropathol. 2004 Sep;108(3):250-6. doi: 10.1007/s00401-004-0888-1. Epub 2004 Jun24. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15221331)
- Sparrow JC, Nowak KJ, Durling HJ, Beggs AH, Wallgren-Pettersson C, Romero N, Nonaka I, Laing NG. Muscle disease caused by mutations in the skeletal musclealpha-actin gene (ACTA1). Neuromuscul Disord. 2003 Sep;13(7-8):519-31. doi:10.1016/s0960-8966(03)00101-9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12921789)
- Wallefeld W, Krause S, Nowak KJ, Dye D, Horvath R, Molnar Z, Szabo M, Hashimoto K, Reina C, De Carlos J, Rosell J, Cabello A, Navarro C, Nishino I, Lochmuller H, Laing NG. Severe nemaline myopathy caused by mutations of the stopcodon of the skeletal muscle alpha actin gene (ACTA1). Neuromuscul Disord. 2006Oct;16(9-10):541-7. doi: 10.1016/j.nmd.2006.07.018. Epub 2006 Sep 1. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16945536)

Genomic Location

The *ACTA1* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

Last updated May 1, 2016