ACAN gene

aggrecan

Normal Function

The *ACAN* gene provides instructions for making the aggrecan protein. Aggrecan is a type of protein known as a proteoglycan, which means it has several sugar molecules attached to it. It is the most abundant proteoglycan in cartilage, a tough, flexible tissue that makes up much of the skeleton during early development. Most cartilage is later converted to bone (a process called ossification), except for the cartilage that continues to cover and protect the ends of bones and is present in the nose, airways, and external ears.

Aggrecan attaches to the other components of cartilage, organizing the network of molecules that gives cartilage its strength. These interactions occur at a specific region of the aggrecan protein called the C-type lectin domain (CLD). Because of the attached sugars, aggrecan attracts water molecules and gives cartilage its gel-like structure. This feature enables the cartilage to resist compression, protecting bones and joints. Although its role is unclear, aggrecan affects bone development.

Health Conditions Related to Genetic Changes

Familial osteochondritis dissecans

At least one variant (also known as a mutation) in the *ACAN* gene has been found to cause familial osteochondritis dissecans. This condition is characterized by areas of bone damage (lesions) caused by the detachment of cartilage and some of the underlying bone from the end of the bone at a joint. People with familial osteochondritis dissecans have multiple lesions that affect the knees, elbows, hips, or ankles. Other common features are short stature and early development of a painful joint disorder called osteoarthritis.

The *ACAN* gene variant associated with this condition changes a single protein building block (amino acid) in the CLD of the aggrecan protein. Specifically, the amino acid valine is replaced by the amino acid methionine at protein position 2303 (written as Val2303Met or V2303M). The abnormal aggrecan protein is unable to attach to other components of cartilage. As a result, the cartilage is disorganized and weak. It is unclear how the abnormal cartilage is involved in the development of the lesions and osteoarthritis characteristic of familial osteochondritis dissecans. Researchers have

suggested that a disorganized cartilage network in growing bones impairs their growth, leading to short stature.

Intervertebral disc disease

MedlinePlus Genetics provides information about Intervertebral disc disease

Other disorders

Two other conditions associated with short stature, called spondyloepimetaphyseal dysplasia, aggrecan type and spondyloepiphyseal dysplasia, Kimberley type, are caused by variants in the *ACAN* gene. People with spondyloepimetaphyseal dysplasia, aggrecan type have extremely short stature, short fingers and toes, and distinctive facial features. This condition is caused by a variant that changes the amino acid at position 2267 in the aggrecan protein from aspartic acid to asparagine (written as Asp2267Asn or D2267N). The amino acid change, which occurs in the CLD, alters aggrecan's interaction with at least one component of the cartilage network. It is unclear how this change leads to the particular signs and symptoms of spondyloepimetaphyseal dysplasia, aggrecan type.

Spondyloepiphyseal dysplasia, Kimberley type is characterized by short stature and early development of osteoarthritis, particularly in the knees, ankles, and hips. This condition is caused by a variant in which a single DNA building block is inserted into the *ACAN* gene, which could disrupt the gene's instructions and lead to the production of an abnormally short aggrecan protein that is missing the CLD. It is unknown if the abnormal protein is produced or what effects it might have. It is unclear what role this gene variant plays in the development of the specific features of spondyloepiphyseal dysplasia, Kimberley type.

Other Names for This Gene

- AGC1
- AGCAN
- aggrecan core protein
- cartilage-specific proteoglycan core protein
- chondroitin sulfate proteoglycan core protein 1
- CSPG1
- CSPGCP
- large aggregating proteoglycan
- MSK16
- SEDK

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ACAN (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=176[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28ACAN%5BTI%5D%29+OR+%28aggrecan%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- AGGRECAN; ACAN (https://omim.org/entry/155760)
- SPONDYLOEPIPHYSEAL DYSPLASIA, KIMBERLEY TYPE; SEDK (https://omim.org/entry/608361)
- SPONDYLOEPIMETAPHYSEAL DYSPLASIA, AGGRECAN TYPE; SEMDAG (https://omim.org/entry/612813)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/176)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ACAN[gene])

References

- Aspberg A, Adam S, Kostka G, Timpl R, Heinegard D. Fibulin-1 is a ligand forthe C-type lectin domains of aggrecan and versican. J Biol Chem. 1999 Jul16;274(29): 20444-9. doi: 10.1074/jbc.274.29.20444. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/10400671)
- Gentili C, Cancedda R. Cartilage and bone extracellular matrix. Curr PharmDes. 2009;15(12):1334-48. doi: 10.2174/138161209787846739. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19355972)
- Gleghorn L, Ramesar R, Beighton P, Wallis G. A mutation in the variable repeatregion of the aggrecan gene (AGC1) causes a form of spondyloepiphyseal dysplasiaassociated with severe, premature osteoarthritis. Am J Hum Genet. 2005Sep;77(3):484-90. doi: 10.1086/444401. Epub 2005 Jul 22. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16080123) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1226213/)
- Olin AI, Morgelin M, Sasaki T, Timpl R, Heinegard D, Aspberg A. Theproteoglycans aggrecan and Versican form networks with fibulin-2 through theirlectin domain

binding. J Biol Chem. 2001 Jan 12;276(2):1253-61. doi:10.1074/jbc.M006783200. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11038354)

- Stattin EL, Wiklund F, Lindblom K, Onnerfjord P, Jonsson BA, Tegner Y, SasakiT, Struglics A, Lohmander S, Dahl N, Heinegard D, Aspberg A. A missense mutationin the aggrecan C-type lectin domain disrupts extracellular matrix interactionsand causes dominant familial osteochondritis dissecans. Am J Hum Genet. 2010 Feb12; 86(2):126-37. doi: 10.1016/j.ajhg.2009.12.018. Epub 2010 Feb 4. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20137779) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2820178/)
- Tompson SW, Merriman B, Funari VA, Fresquet M, Lachman RS, Rimoin DL, NelsonSF, Briggs MD, Cohn DH, Krakow D. A recessive skeletal dysplasia, SEMD aggrecantype, results from a missense mutation affecting the C-type lectin domain ofaggrecan. Am J Hum Genet. 2009 Jan;84(1):72-9. doi: 10.1016/j.ajhg.2008.12.001. Epub 2008 Dec 24. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19110214) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668039/)

Genomic Location

The *ACAN* gene is found on chromosome 15 (https://medlineplus.gov/genetics/chromosome/15/).

Last updated October 1, 2012