COL2A1 gene

collagen type II alpha 1 chain

Normal Function

The *COL2A1* gene provides instructions for making one component of type II collagen, called the pro-alpha1(II) chain. Type II collagen adds structure and strength to the connective tissues that support the body's muscles, joints, organs, and skin. Type II collagen is found primarily in cartilage, a tough but flexible tissue that makes up much of the skeleton during early development. Most cartilage is later replaced by bone, except for the cartilage that continues to cover and protect the ends of bones and the cartilage that is present in the nose and external ears. Type II collagen is also part of the inner ear, the clear gel that fills the eyeball (the vitreous), and the center portion (nucleus pulposus) of the discs between the bones of the spine (vertebrae).

To construct type II collagen, three pro-alpha1(II) chains twist together to form a triple-stranded, rope-like procollagen molecule. Procollagen molecules are then processed by enzymes in the cell. Once processed, the molecules leave the cell and arrange themselves into long, thin fibrils that link to one another (cross-link) in the spaces around cells. The cross-linkages result in the formation of very strong, mature type II collagen fibers.

Health Conditions Related to Genetic Changes

Achondrogenesis

Several variants (also called mutations) in the *COL2A1* gene have been found to cause a form of achondrogenesis known as type 2 or the Langer-Saldino type. This rare disorder of bone development is characterized by short arms and legs, a narrow chest with short ribs, underdeveloped lungs, and a lack of normal bone formation (ossification) in the spine and hips. These abnormalities cause serious health problems, and infants with achondrogenesis usually die before or soon after birth.

The variants that cause achondrogenesis type 2 change one of the protein building blocks (amino acids) used to make the pro-alpha1(II) chain. Specifically, the amino acid glycine is replaced with a different amino acid at one of various positions in this collagen chain. All of these variants prevent the normal production of mature type II collagen, which results in the severe skeletal abnormalities seen in people with this disorder.

Spondyloepiphyseal dysplasia with metatarsal shortening

A specific *COL2A1* gene variant causes spondyloepiphyseal dysplasia (SED) with metatarsal shortening, a condition that affects joint function and bone development. Affected individuals typically inherit this genetic change from a parent who also has the condition. The variant replaces the amino acid arginine with the amino acid cysteine (written as Arg275Cys or R275C) in the pro-alpha1(II) chain. Researchers suspect that this change might interfere with the collagen chain's ability to form a procollagen molecule. Procollagen molecules are needed to produce mature type II collagen. A disruption in the production of type II collagen can impair bone and cartilage development, causing the signs and symptoms of SED with metatarsal shortening.

Hypochondrogenesis

Several variants in the *COL2A1* gene have been found to cause hypochondrogenesis, a severe disorder of bone growth characterized by a small body, short limbs, and abnormal bone formation in the spine and hips. Some variants change one of the amino acids used to make the pro-alpha1(II) chain. Specifically, the amino acid glycine is replaced with a different amino acid at one of various positions in this collagen chain. These variants interfere with the formation of mature type II collagen molecules, which causes the features of hypochondrogenesis.

Kniest dysplasia

Multiple variants in the *COL2A1* gene have been found in people with Kniest dysplasia, a disorder of bone growth characterized by short stature (dwarfism), other skeletal abnormalities, and problems with vision and hearing. Most of the variants that cause Kniest dysplasia delete one or more of the DNA building blocks (nucleotides) in the *COL2A1* gene. These variants lead to the production of abnormally short pro-alpha1(II) chains, which then join with normal-length chains. The mismatch of normal and short pro-alpha1(II) chains results in type II collagen molecules that are shorter than usual. This abnormal type II collagen prevents bones and other connective tissues from developing properly, which leads to the features of Kniest dysplasia.

Legg-Calvé-Perthes disease

Variants in the *COL2A1* gene can also cause the bone abnormalities that are characteristic of Legg-Calvé-Perthes disease. This disorder begins in childhood and is characterized by the breakdown of the upper end of the thigh bone at the hip joint (called the femoral head), leading to hip pain and limping. The gene variants involved in Legg-Calvé-Perthes disease change single amino acids in the pro-alpha1(II) chain. This altered protein may make collagen fibers less stable than normal. Researchers speculate that the breakdown of bone seen in people with Legg-Calvé-Perthes disease is caused by impaired blood flow to the femoral head, which leads to death of the bone tissue (osteonecrosis). However, it is unclear how abnormal type II collagen is involved in this process or why the hips are affected.

Platyspondylic lethal skeletal dysplasia, Torrance type

Multiple variants in the *COL2A1* gene have been identified in people with platyspondylic lethal skeletal dysplasia, Torrance type. This severe disorder of bone growth is characterized by very short arms and legs, a small chest with short ribs, underdeveloped pelvic bones, unusually short fingers and toes (brachydactyly), flattened spinal bones (platyspondyly), and an exaggerated curvature of the lower back (lordosis).

The variants associated with platyspondylic lethal skeletal dysplasia, Torrance type occur in a region of the pro-alpha1(II) chain called the C-propeptide domain. Most often, these variants change a single amino acid in the pro-alpha1(II) chain. These *COL2A1* gene variants lead to the production of an abnormal version of the pro-alpha1(II) chain that cannot be incorporated into type II collagen fibers. Instead of forming collagen molecules, the abnormal pro-alpha1(II) chains build up in cartilage-forming cells (chondrocytes). These changes disrupt normal bone development, resulting in the skeletal abnormalities seen in people with platyspondylic lethal skeletal dysplasia, Torrance type.

Spondyloepimetaphyseal dysplasia, Strudwick type

Variants in the *COL2A1* gene have been found to cause spondyloepimetaphyseal dysplasia, Strudwick type. This disorder of bone growth is characterized by dwarfism, skeletal abnormalities, and problems with vision. The *COL2A1* gene variants that cause spondyloepimetaphyseal dysplasia, Strudwick type all change single amino acids in the pro-alpha1(II) chain. Specifically, the amino acid glycine is replaced with a different amino acid at one of various positions in this collagen chain. These amino acid substitutions inhibit the formation of stable collagen molecules. This change in type II collagen prevents bones and other connective tissues from developing properly, which causes the signs and symptoms of spondyloepimetaphyseal dysplasia, Strudwick type.

Spondyloepiphyseal dysplasia congenita

Several variants in the *COL2A1* gene have been found to cause spondyloepiphyseal dysplasia congenita, another disorder of bone growth that causes dwarfism, skeletal abnormalities, and problems with vision and hearing. Some of these variants change a single amino acid in the pro-alpha1(II) chain. Specifically, the amino acid glycine is replaced with a different amino acid at one of various positions in this collagen chain. Other variants cause the production of an abnormally short pro-alpha1(II) chain. All of these changes interfere with the formation of mature type II collagen molecules. This interference causes spondyloepiphyseal dysplasia congenita by affecting tissues that contain many type II collagen molecules.

Spondyloperipheral dysplasia

Variants in the *COL2A1* gene have been found to cause spondyloperipheral dysplasia. This disorder of bone growth is characterized by platyspondyly, brachydactyly, short stature, and other skeletal abnormalities. The *COL2A1* gene variants associated with spondyloperipheral dysplasia typically occur in the C-propeptide domain. The C-propeptide domain is necessary for the pro-alpha1(II) chains to attach (bind) to one

another to form type II collagen. These variants lead to the production of an abnormally short pro-alpha1(II) chain that cannot be incorporated into type II collagen fibers. As a result, cells make a reduced amount of type II collagen. Instead of forming collagen molecules, the abnormal pro-alpha1(II) chains build up in chondrocytes. These changes disrupt normal bone development, resulting in the skeletal abnormalities seen in people with spondyloperipheral dysplasia.

Stickler syndrome

Hundreds of variants in the *COL2A1* gene have been found to cause the most common form of Stickler syndrome, designated as type I. This condition is characterized by a distinctive facial appearance, eye abnormalities, hearing loss, and joint problems. Several of the *COL2A1* gene variants that cause this condition result in the production of an abnormally short pro-alpha1(II) chain that cannot be incorporated into a type II collagen fiber. Other variants create a premature stop signal in the instructions for making the pro-alpha1(II) chain. As a result of these *COL2A1* gene variants, cells produce only half the normal amount of this collagen chain, which reduces the amount of type II collagen in cartilage and other tissues. A shortage of type II collagen underlies the signs and symptoms of Stickler syndrome type I.

Other disorders

Variants in the *COL2A1* gene can sometimes result in a condition known as avascular necrosis of the femoral head. This condition is similar to Legg-Calvé-Perthes disease, but it begins in adulthood. Both conditions can occur in the same family. Like Legg-Calvé-Perthes disease, avascular necrosis of the femoral head causes the upper ends of the thigh bones (femurs) to break down due to an inadequate blood supply. It can lead to pain and limping and cause the legs to be of unequal length. One variant known to be responsible for the inherited form of this disorder alters the sequence of amino acids in the pro-alpha1(II) chain. It is unknown exactly how irregular type II collagen affects the hip joints and results in this disorder.

Variants in the *COL2A1* gene can also cause a condition called autosomal dominant rhegmatogenous retinal detachment. Rhegmatogenous retinal detachment occurs when the retina (the specialized light-sensitive tissue in the eye) tears and becomes detached from the back of the eye, leading to vision difficulties and sometimes blindness. Variants that result in the production of abnormal type II collagen affect the development and function of the eye.

Variants in the *COL2A1* gene can also cause mild spondyloepiphyseal dysplasia (SED) due to *COL2A1* mutation with early-onset osteoarthritis. Individuals with this disorder have joint pain and stiffness in the hips, knees, shoulders, wrists, and hands. Symptoms can begin in childhood. Affected individuals may be shorter than their siblings.

Another condition caused by variants in the *COL2A1* gene is spondyloepiphyseal dysplasia, Stanescu type (SEDSTN). This condition is characterized by the tightening of tissues around joints (contractures) and a premature wearing down (degeneration) of the cartilage in the knees, hips, and fingers. Individuals with spondyloepiphyseal

dysplasia, Stanescu type typically have joint pain and difficulties walking. Additional features seen on medical imaging can include platyspondyly; small pelvic bones; and coxa valga, which is a change in the position of the femoral head. Coxa valga can cause pain and limit hip movement. The variants that cause spondyloepiphyseal dysplasia, Stanescu type typically change a single amino acid in the pro-alpha1(II) chain.

Other Names for This Gene

- ANFH
- AOM
- COL11A3
- collagen of cartilage
- collagen, type II
- collagen, type II, alpha 1
- collagen, type II, alpha 1 (primary osteoarthritis, spondyloepiphyseal dysplasia, congenital)
- SEDC
- STL1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of COL2A1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=1280[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28COL2A1%5BTIAB%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+1440+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- COLLAGEN, TYPE II, ALPHA-1; COL2A1 (https://omim.org/entry/120140)
- OSTEOARTHRITIS SUSCEPTIBILITY 1; OS1 (https://omim.org/entry/165720)
- AVASCULAR NECROSIS OF FEMORAL HEAD, PRIMARY, 1; ANFH1 (https://omim.org/entry/608805)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/1280)

- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=COL2A1[gene])

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Genomic Location

The *COL2A1* gene is found on chromosome 12 (https://medlineplus.gov/genetics/chromosome/12/).

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