COL2A1 gene

collagen type II alpha 1 chain

Normal Function

The *COL2A1* gene provides instructions for making the basic component of type II collagen, called the alpha-1(II) chain. Type II collagen adds structure and strength to connective tissues and plays an important role in the normal development of joints, eyes, and the inner ear.

Type II collagen is found primarily in cartilage, a tough, flexible tissue that makes up much of the skeleton during early development. Most cartilage is later replaced by bone, except for the cartilage that covers and protects the ends of bones and the cartilage that is present in the nose and external ears. Type II collagen is particularly abundant in a form of cartilage known as hyaline cartilage, which is found in the developing skeleton, joints, and at the end of the long bones of the arms and legs where new bone is produced (growth plates). 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 alpha-1(II) chains twist together to form a procollagen molecule. Procollagen molecules are then processed by enzymes in the cell. Once processed, the modified collagen molecules leave the cell and arrange themselves into long, thin fibrils that attach (bind) to one another in a lattice pattern (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 hypochondrogenesis and a form of achondrogenesis called achondrogenesis type 2. These disorders are characterized by short bones in the arms and legs, a small chest with underdeveloped lungs (lung hypoplasia), and a lack of normal bone formation (ossification) in the spine. Affected individuals typically die before birth or shortly thereafter. Hypochondrogenesis was once believed to be a distinct condition but is now considered to be part of the same disease spectrum as achondrogenesis type 2.

Most of the variants that cause achondrogenesis type 2 and hypochondrogenesis change one of the protein building blocks (amino acids) used to make the alpha-1(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 characteristic features of achondrogenesis type 2 and hypochondrogenesis.

Kniest dysplasia

Multiple variants in the *COL2A1* gene have been found in individuals with Kniest dysplasia. This condition is a skeletal disorder that is characterized by short stature, short arms and legs, progressive curvature of the spine, joint disease, and problems with vision and hearing. Many of the variants that cause Kniest dysplasia change or delete one or more of the DNA building blocks (nucleotides) in the *COL2A1* gene. These variants lead to the production of abnormal alpha-1(II) chains, which then join with normal alpha-1(II) chains. This mismatch of alpha-1(II) chains results in an abnormal version of type II collagen, which cannot function properly. Without enough functional type II collagen, bones and other connective tissues cannot develop properly, which leads to the features seen in people with Kniest dysplasia.

Platyspondylic dysplasia, Torrance type

Multiple variants in the *COL2A1* gene have been identified in individuals with platyspondylic dysplasia, Torrance type. This severe disorder of bone growth is characterized by very short arms and legs, a small chest with short ribs, unusually short fingers and toes (brachydactyly), and flattened vertebrae (platyspondyly). Affected individuals often die before birth or shortly thereafter.

The variants that are associated with platyspondylic dysplasia, Torrance type often change a single amino acid in a region near the end of the alpha-1(II) chain called the C-propeptide domain. This region plays an important role in the formation of procollagen molecules. The variants that cause platyspondylic dysplasia, Torrance type cause the cell to produce an abnormal version of the alpha-1(II) chain that interferes with the formation of procollagen molecules. As a result, cells do not make as much mature type II collagen. In some instances, abnormal alpha-1(II) chains build up in cartilage-forming cells (chondrocytes). Without enough mature type II collagen, bones cannot develop properly, resulting in the severe skeletal abnormalities seen in infants with platyspondylic dysplasia, Torrance type.

Spondyloepiphyseal dysplasia with marked metaphyseal changes

Variants in the *COL2A1* gene have been found to cause spondyloepiphyseal dysplasia (SED) with marked metaphyseal changes, a group of rare skeletal disorders that affect the vertebrae and the long bones in the arms and legs. Many of the variants that cause SED with marked metaphyseal changes alter single amino acids in the alpha-1(II) chain. Specifically, glycine is replaced with a different amino acid at one of various positions in this collagen chain. These amino acid substitutions disrupt the formation of stable collagen molecules. This change in type II collagen prevents bones and other

connective tissues from developing properly, which causes the characteristic features of spondyloepiphyseal dysplasia with marked metaphyseal changes.

Spondyloepiphyseal dysplasia congenita

Several variants in the *COL2A1* gene have been found to cause spondyloepiphyseal dysplasia (SED) congenita, a disorder of bone development that causes short stature with short arms and legs and a particularly short torso. The parts of the body are not proportional to one another (disproportionate short stature) in people with this condition. People with SED congenita also have problems with vision and hearing. Some of the variants that cause SED congenita replace glycine with a different amino acid at one of various positions in this collagen chain. Other variants cause cells to produce an abnormally short alpha-1(II) chain. All of these changes interfere with the formation of mature type II collagen molecules. A lack of mature type II collagen prevents bones and other connective tissues from developing properly, which causes the specific signs and symptoms seen in people with SED congenita.

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 are typically of average height and have joint pain that begins in childhood or adolescence. Many people with this condition have short toes. The variant that causes SED with metatarsal shortening replaces the amino acid arginine at position 275 with the amino acid cysteine (written as Arg275Cys or R275C) in the alpha-1(II) chain. Researchers suspect that this change might interfere with the collagen chain's ability to form a procollagen molecule. A disruption in the production of type II collagen can impair bone and cartilage development, causing the signs and symptoms seen in people with SED with metatarsal shortening.

Spondyloperipheral dysplasia

Variants in the *COL2A1* gene have been found to cause spondyloperipheral dysplasia. This disorder of bone growth is characterized by disproportionate short stature, brachydactyly, platyspondyly, and other skeletal abnormalities.

The *COL2A1* gene variants that cause spondyloperipheral dysplasia typically affect the C-propeptide domain near the end of the alpha-1(II) chain. This region plays an important role in the formation of procollagen molecules. The variants that cause spondyloperipheral dysplasia lead to the production of an abnormal version of the alpha-1(II) chain that interferes with the production of procollagen molecules. As a result, cells do not make as much mature type II collagen. Without enough functional type II collagen, bones cannot develop properly, resulting in the skeletal abnormalities seen in people with spondyloperipheral dysplasia.

Stickler syndrome

Variants in the *COL2A1* gene are the most common cause of Stickler syndrome. People

with this condition are typically of average height and have a distinctive facial appearance, eye abnormalities, hearing loss, and joint problems. Several of the *COL2A1* gene variants that cause Stickler syndrome create a premature stop signal in the instructions for making the alpha-1(II) chain. This causes cells to produce only half the normal amount of this collagen chain, which reduces the amount of mature type II collagen fibers in cartilage and other tissues. A shortage of type II collagen causes the characteristic features of Stickler syndrome.

Variants in the *COL2A1* gene can also cause a form of Stickler syndrome that primarily affects the eyes. The features seen in people with the ocular form of Stickler syndrome may include severe nearsightedness (high myopia) and a tearing of the light-sensitive tissue at the back of the eye (retinal detachment). This ocular type of Stickler syndrome is caused by variants in a particular region of the *COL2A1* gene, which plays an important role in the normal development of the eye.

Other disorders

Variants in the *COL2A1* gene have been associated with a group of milder conditions called dysplasia of the proximal femoral epiphyses that are characterized by normal stature and joint problems. Signs and symptoms may appear similar to those seen in people with Legg-Calvé-Perthes disease, which typically begins in childhood.

Other Names for This Gene

- collagen of cartilage
- collagen, type II
- collagen, type II, alpha 1
- collagen, type II, alpha 1 (primary osteoarthritis, spondyloepiphyseal dysplasia, congenital)

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)

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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