COL2A1 Gene

Subjects: Genetics & Heredity
Contributor: Vicky Zhou

collagen type II alpha 1 chain

Keywords: genes

1. 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 converted to bone, except for the cartilage that continues to cover and protect the ends of bones and is present in the nose and external ears. Type II collagen is also part of the clear gel that fills the eyeball (the vitreous), the inner ear, and the center portion of the discs between the vertebrae in the spine (nucleus pulposus).

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.

2. Health Conditions Related to Genetic Changes

2.1. Achondrogenesis

At least 18 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 pelvis. Serious health problems result from these abnormalities, and infants with achondrogenesis usually die before or soon after birth.

The mutations 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 mutations prevent the normal production of mature type II collagen, which results in the severe skeletal abnormalities seen in this disorder.

2.2. Czech Dysplasia

A specific *COL2A1* gene mutation causes Czech dysplasia, a condition that affects joint function and bone development. This genetic change is inherited from a parent who has the condition. The mutation replaces the amino acid arginine with the amino acid cysteine (written as Arg275Cys or R275C) in the pro-alpha1(II) chain. The effect of the mutation is unknown, although researchers speculate that it 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 Czech dysplasia.

2.3. Hypochondrogenesis

At least 18 mutations 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 pelvis. Some mutations delete part of the *COL2A1* gene or lead to a pro-alpha1(II) chain that is missing critical segments. Other mutations 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. All of these mutations interfere with the formation of mature triple-stranded type II collagen molecules, which results in the features of hypochondrogenesis by affecting tissues that are rich in type II collagen.

2.4. Kniest Dysplasia

More than 20 mutations in the *COL2A1* gene have been found in people with Kniest dysplasia, a disorder of bone growth characterized by short stature (dwarfism) with other skeletal abnormalities and problems with vision and hearing. Most of the mutations that cause Kniest dysplasia delete one or more DNA building blocks (nucleotides) in the *COL2A1* gene. These mutations 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 abnormal 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.

2.5. Legg-Calvé-Perthes Disease

Mutations in the *COL2A1* gene can also cause the bone abnormalities 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 mutations involved in Legg-Calvé-Perthes disease change single amino acids in the pro-alpha1(II) chain of type II collagen. While the altered protein is still incorporated into collagen fibers, the fibers may be less stable than normal. Researchers speculate that the breakdown of bone characteristic of 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 specifically affected.

2.6. Platyspondylic Lethal Skeletal Dysplasia, Torrance Type

More than 10 mutations 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).

All of the mutations associated with this condition occur in a region of the pro-alpha1(II) chain called the C-propeptide domain. Most often, mutations change a single amino acid in the pro-alpha1(II) chain. These *COL2A1* gene mutations lead to the production of an abnormal version of the pro-alpha1(II) chain that cannot be incorporated into type II collagen fibers. As a result, a reduced amount of type II collagen is produced. 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 characteristic of platyspondylic lethal skeletal dysplasia, Torrance type.

2.7. Spondyloepimetaphyseal Dysplasia, Strudwick Type

At least six mutations 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 known *COL2A1* gene mutations that cause spondyloepimetaphyseal dysplasia, Strudwick type all change single amino acids in the pro-alpha1(II) chain of type II collagen. 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, triple-stranded, ropelike collagen molecules. This alteration in type II collagen prevents bones and other connective tissues from developing properly, which causes the signs and symptoms of spondyloepimetaphyseal dysplasia, Strudwick type.

2.8. Spondyloepiphyseal Dysplasia Congenita

More than 40 mutations 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 the known mutations 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 mutations result in the production of an abnormally short pro-alpha1(II) chain. All of these changes interfere with the formation of mature triple-stranded type II collagen molecules. This interference results in spondyloepiphyseal dysplasia congenita by affecting tissues that are rich in type II collagen.

2.9. Spondyloperipheral Dysplasia

At least four mutations 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. All of the *COL2A1* gene mutations associated with spondyloperipheral dysplasia occur in a region of the pro-alpha1(II) chain called 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. Mutations 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 that occur in spondyloperipheral dysplasia.

2.10. Stickler Syndrome

Almost 200 mutations 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 mutations 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 mutations create a premature stop signal in the instructions for making the pro-alpha1(II) chain. As a result of these *COL2A1* gene mutations, 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.

2.11. Other Disorders

Mutations in the *COL2A1* gene can sometimes result in a condition known as avascular necrosis of the femoral head, which is similar to Legg-Calvé-Perthes disease (described above) but 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 and deficient bone repair. It can lead to pain and limping and cause the legs to be of unequal length. One mutation known to be responsible for the inherited form of this disorder alters the sequence of amino acids in the pro-alpha1(II) chain of type II collagen. It is unknown exactly how irregular type II collagen affects the hip joints and results in this disorder.

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

3. Other Names for This Gene

- cartilage collagen
- CO2A1_HUMAN
- COL11A3
- collagen II, alpha-1 polypeptide
- collagen type II alpha 1
- collagen, type II, alpha 1
- collagen, type II, alpha 1 (primary osteoarthritis, spondyloepiphyseal dysplasia, congenital)
- STL1

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