COL1A1 Gene

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collagen type I alpha 1 chain

genes

1. Normal Function

The *COL1A1* gene provides instructions for making part of a large molecule called type I collagen. Collagens are a family of proteins that strengthen and support many tissues in the body, including cartilage, bone, tendon, skin, and the white part of the eye (the sclera). Type I collagen is the most abundant form of collagen in the human body.

A component of type I collagen called the pro-α1(I) chain is produced from the *COL1A1* gene. Collagens begin as rope-like procollagen molecules that are each made up of three chains. Type I collagen is composed of two pro-α1(I) chains and one pro-α2(I) chain (which is produced from the *COL1A2* gene).

The triple-stranded procollagen molecules are processed by enzymes in a series of steps inside and outside the cell to create mature collagen. The collagen molecules then arrange themselves into long, thin fibrils that form stable interactions (cross-links) with one another in the spaces between cells. The cross-links result in the formation of very strong type I collagen fibers.

2. Health Conditions Related to Genetic Changes

2.1. Caffey Disease

A particular mutation in the *COL1A1* gene causes infantile cortical hyperostosis, commonly known as Caffey disease. The signs and symptoms of Caffey disease are usually apparent by the time an infant is 5 months old. This condition is characterized by swelling of soft tissues (muscles, for example), pain, and excessive new bone formation (hyperostosis). The bone abnormalities mainly affect the jawbone, collarbones (clavicles), and the shafts (diaphyses) of long bones in the arms and legs. For unknown reasons, the pain and swelling associated with Caffey disease typically go away within a few months. Through a normal process called bone remodeling, which replaces old bone tissue with new bone, the excess bone is usually reabsorbed by the body and undetectable on x-ray images by the age of 2.

The mutation that causes this condition occurs in one copy of the *COL1A1* gene in each cell. It alters a single protein building block (amino acid), replacing the amino acid arginine with the amino acid cysteine at protein position 836 (written as Arg836Cys or R836C). This mutation results in the production of type I collagen fibrils that are variable in size and shape, but it is unknown how these changes lead to the signs and symptoms of Caffey disease.

2.2. Ehlers-Danlos Syndrome

Mutations in the *COL1A1* gene have been found to cause several forms of Ehlers-Danlos syndrome, a group of disorders that affect the connective tissues supporting the skin, bones, blood vessels, and many other organs and tissues. These mutations occur in one copy of the *COL1A1* gene in each cell.

At least five mutations in the *COL1A1* gene can result in the arthrochalasia type of Ehlers-Danlos syndrome, which is characterized by an unusually large range of joint movement (hypermobility) and dislocations of both hips at birth. The genetic changes that cause this form of the disorder lead to the production of a pro-α1(I) chain that is missing a critical segment. The absence of this segment interferes with the assembly and processing of pro-α1(I) chains into mature type I collagen molecules. Tissues that are rich in type I collagen, such as the skin, bones, and tendons, are most affected by this change.

COL1A1 gene mutations are also a very rare cause of the classical and vascular types of Ehlers-Danlos syndrome. (In most cases, these types result from mutations in other genes.) The classical type is characterized by skin that is soft, highly stretchy (elastic), and fragile; abnormal scarring; and joint hypermobility. Additionally, people with classical Ehlers-Danlos syndrome resulting from a *COL1A1* gene mutation are prone to tearing (rupture) of major arteries in adulthood. The vascular type is associated with rupture of blood vessels, intestines, and other organs. One *COL1A1* gene mutation that has been associated with both the classical and vascular types of Ehlers-Danlos syndrome replaces the amino acid arginine with the amino acid cysteine at position 312 in the pro-α1(I) chain (written as Arg312Cys or R312C). The altered pro-α1(I) chain interferes with other collagen-building proteins, disrupting the structure of type I collagen fibrils and trapping collagen in the cell. These changes in collagen increase the risk of blood vessel and organ rupture, and the other abnormalities that can occur with the classical and vascular types of Ehlers-Danlos syndrome.

2.3. Osteogenesis Imperfecta

Osteogenesis imperfecta is the most common disorder caused by mutations in the *COL1A1* gene. People with this condition have bones that break easily, often from mild trauma or with no apparent cause. In addition, affected individuals can have a blue or grey tint to the part of the eye that is usually white (the sclera), short stature, hearing loss, respiratory problems, and a disorder of tooth development called dentinogenesis imperfecta. Hundreds of *COL1A1* gene mutations that cause osteogenesis imperfecta have been identified. Most of the mutations that are responsible for osteogenesis imperfecta type I, the mildest form of this disorder, reduce the production of pro-α1(I) chains. With fewer pro-α1(I) chains available, cells can make only half the normal amount of type I collagen. A

shortage of this critical protein underlies the bone fragility and other characteristic features of osteogenesis imperfecta type I.

Several kinds of mutations in the *COL1A1* gene cause the more severe forms of osteogenesis imperfecta, including types II, III, and IV. Some of these mutations delete segments of DNA from the *COL1A1* gene, resulting in an abnormally shortened pro-α1(I) chain. Other genetic changes alter the sequence of amino acids in the pro-α1(I) chain, usually replacing the amino acid glycine with a different amino acid. In some cases, amino acid substitutions alter one end of the protein chain (called the C-terminus or C-propeptide), which interferes with the assembly of collagen molecules. These *COL1A1* gene mutations lead to the production of abnormal versions of type I collagen. When this abnormal collagen is incorporated into developing bones and other connective tissues, it causes the serious health problems associated with severe forms of osteogenesis imperfecta.

2.4. Carpal Tunnel Syndrome

Carpal tunnel syndrome

2.5. Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans, a rare type of cancer that causes a tumor in the deep layers of the skin, is characterized by a noninherited (somatic) mutation involving the *COL1A1* gene. Somatic mutations are acquired during a person's lifetime and are present only in certain cells, in this case cells in the skin from which the cancer arises. Dermatofibrosarcoma protuberans is associated with a rearrangement (translocation) of genetic material between chromosomes 17 and 22. This translocation, written as t(17;22), fuses part of the *COL1A1* gene on chromosome 17 with part of a gene on chromosome 22 called *PDGFB*. This translocation is found on one or more extra chromosomes that can be either the normal linear shape or circular.

The fused *COL1A1-PDGFB* gene provides instructions for making a combined (fusion) protein that researchers believe ultimately functions like the active PDGFB protein. In the translocation, the *PDGFB* gene loses the part of its DNA that limits its activity, and production of the COL1A1-PDGFB fusion protein is controlled by *COL1A1* gene sequences. As a result, the gene fusion leads to the production of a larger amount of active PDGFB protein than normal. Active PDGFB protein signals for cell growth and division (proliferation) and maturation (differentiation). Excess PDGFB protein abnormally stimulates cells to proliferate and differentiate, leading to tumor formation in dermatofibrosarcoma protuberans.

2.6. Intervertebral Disc Disease

Intervertebral disc disease

2.7. Other Disorders

People with certain *COL1A1* mutations exhibit the signs and symptoms of both osteogenesis imperfecta and Ehlers-Danlos syndrome (described above). These mutations usually replace the amino acid glycine with a different amino acid in the pro-α1(I) chain, which interferes with the assembly and processing of pro-α1(I) chains into mature type I collagen molecules. The resulting abnormal type I collagen fibrils weaken connective tissue, causing the signs and symptoms associated with these two conditions.

A common variation in the *COL1A1* gene (called a polymorphism) appears to increase the risk of developing osteoporosis. Osteoporosis is a condition that makes bones progressively more brittle and prone to fracture. This polymorphism, which occurs in a control (regulatory) region of the *COL1A1* gene, likely affects the production of type I collagen but not the molecule's structure. Several studies have shown that women with this genetic change are more likely to have signs of osteoporosis, particularly low bone density and bone fractures, than are women without the change. This variation is only one of many factors that can increase the risk of osteoporosis.

3. Other Names for This Gene

- alpha 1 type I collagen preproprotein
- CO1A1_HUMAN
- COL1A1 protein
- collagen I, alpha-1 polypeptide
- collagen of skin, tendon and bone, alpha-1 chain
- collagen type I alpha 1
- collagen, type I, alpha 1
- type I collagen alpha 1

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