COL11A1 Gene

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collagen type XI alpha 1 chain

genes

1. Normal Function

The *COL11A1* gene provides instructions for making a component of type XI collagen called the pro-alpha1(XI) chain. Collagens are molecules that provide structure and strength to the connective tissues that support the body's muscles, joints, organs, and skin. Type XI collagen is normally found 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 XI collagen is also part of the inner ear; the vitreous, which is the clear gel that fills the eyeball; and the nucleus pulposus, which is the center portion of the discs between the bones of the spine (vertebrae).

Collagens begin as rope-like procollagen molecules that are each made up of three chains. The pro-alpha1(XI) chain combines with two other collagen chains, pro-alpha2(XI) and pro-alpha1(II), to form a triple-stranded procollagen molecule. Then the ropelike procollagen is processed by enzymes to create mature collagen. Mature collagen molecules arrange themselves into long, thin fibrils that form stable interactions (cross-links) with one another in the spaces between cells (the extracellular matrix). The cross-links result in the formation of very strong type XI collagen fibers.

Type XI collagen also helps maintain the spacing and width (diameter) of another type of collagen molecule, type II collagen. Type II collagen is an important component of the vitreous and cartilage. The arrangement and size of type II collagen fibrils is essential for the normal structure of these tissues.

2. Health Conditions Related to Genetic Changes

2.1. Fibrochondrogenesis

At least seven mutations in the *COL11A1* gene have been identified in people with fibrochondrogenesis type 1, a disorder of bone growth characterized by severe skeletal abnormalities, hearing loss, and vision loss. Infants with fibrochondrogenesis type 1 have a very narrow chest that prevents the lungs from developing normally. Most

children with this condition are stillborn or die shortly after birth from respiratory failure, although some have lived into childhood.

Some cases of fibrochondrogenesis type 1 result from a combination of *COL11A1* gene mutations. Specifically, one copy of the gene has a mutation that prevents the production of any functional pro-alpha1(XI) chain, and the other copy has a mutation that results in an abnormal version of the pro-alpha1(XI) chain. When the abnormal chain is incorporated into collagen molecules, it creates defective type XI collagen. The abnormal collagen weakens connective tissues, impairing the formation of bones throughout the skeleton and causing changes in the eye and inner ear that lead to vision and hearing problems.

In at least two reported cases, fibrochondrogenesis type 1 has been caused by combinations of *COL11A1* gene mutations that completely eliminate the production of the pro-alpha1(XI) chain. Researchers speculate that a loss of this chain changes the structure of type XI collagen molecules and disrupts its ability to form cross-links. However, the effects of these mutations are still under study.

2.2. Stickler Syndrome

Mutations in the *COL11A1* gene account for 10 to 20 percent of all cases of Stickler syndrome. When Stickler syndrome results from *COL11A1* gene mutations, it is classified as type II. Signs and symptoms of this condition include a distinctive facial appearance, eye abnormalities, hearing loss, and joint problems. These signs and symptoms tend to be less severe than those of fibrochondrogenesis (described above). However, they vary widely among affected individuals.

More than two dozen *COL11A1* gene mutations have been found in people with Stickler syndrome. Some of these mutations change single protein building blocks (amino acids) or delete a small number of amino acids from the pro-alpha1(XI) chain. Other mutations cause segments of DNA to be skipped when the protein is made, resulting in an abnormally short pro-alpha1(XI) chain. All of these changes impair the production or assembly of type XI collagen molecules. Defective collagen disrupts the normal development of connective tissues in many different parts of the body, which leads to the varied signs and symptoms of Stickler syndrome.

Mutations in the *COL11A1* gene can also cause Marshall syndrome, a condition that is very similar to Stickler syndrome. Some researchers have classified Marshall syndrome as a variant of Stickler syndrome, while others consider it to be a separate disorder. Most of the mutations associated with Marshall syndrome cause a segment of DNA in the *COL11A1* gene to be skipped when the protein is made, resulting in an abnormally short pro-alpha1(XI) chain. This shortened protein impairs the formation of mature type XI collagen, which leads to the abnormal development of connective tissues and the signs and symptoms of Marshall syndrome.

2.3. Carpal Tunnel Syndrome

Carpal tunnel syndrome

2.4. Intervertebral Disc Disease

Intervertebral disc disease

2.5. Osteoarthritis

Osteoarthritis

2.6. Other Disorders

Several variations in the *COL11A1* gene may increase the risk of developing osteoarthritis, a common disease of the joints. Osteoarthritis is characterized by the breakdown of joint cartilage, which causes pain, stiffness, and restricted movement. The genetic changes associated with osteoarthritis are differences in single amino acids in the pro-alpha1(XI) chain of type XI collagen. Studies suggest that the altered pro-alpha1(XI) chain may weaken collagen fibers, which could contribute to the erosion of joint cartilage. Variations in the *COL11A1* gene are among many genetic and environmental factors that likely influence this complex disease.

3. Other Names for This Gene

- COBA1_HUMAN
- COLL6
- collagen type XI alpha 1
- collagen XI, alpha-1 polypeptide
- collagen, type XI, alpha 1
- STL2

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