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 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.

Health Conditions Related to Genetic Changes

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.

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.

**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.

**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.

**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.
Platyspondylic lethal skeletal dysplasia, Torrance type

More than 10 mutations in the \textit{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 \textit{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.

Spondyloepimetaphyseal dysplasia, Strudwick type

At least six mutations in the \textit{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 \textit{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.

Spondyloepiphyseal dysplasia congenita

More than 40 mutations in the \textit{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.
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.

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.

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.

Chromosomal Location
Cytogenetic Location: 12q13.11, which is the long (q) arm of chromosome 12 at position 13.11
Molecular Location: base pairs 47,972,967 to 48,006,212 on chromosome 12 (Homo sapiens Updated Annotation Release 109.20200522, GRCh38.p13) (NCBI)

Credit: Genome Decoration Page/NCBI

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

Additional Information & Resources
Educational Resources
• Molecular Biology of the Cell (fourth edition, 2002): After Secretion, Fibrillar Procollagen Molecules Are Cleaved to Collagen Molecules, Which Assemble into Fibrils
  https://www.ncbi.nlm.nih.gov/books/NBK26810/#A3557
• Molecular Biology of the Cell (fourth edition, 2002): Collagens Are the Major Proteins of the Extracellular Matrix
  https://www.ncbi.nlm.nih.gov/books/NBK26810/#A3551
• Molecular Biology of the Cell (fourth edition, 2002): Some Types of Collagen and Their Properties
  https://www.ncbi.nlm.nih.gov/books/NBK26810/?rendertype=table&id=A3554
• Molecular Cell Biology (fourth edition, 2000): Collagen: The Fibrous Proteins of the Matrix
  https://www.ncbi.nlm.nih.gov/books/NBK21582/

Clinical Information from GeneReviews
• Stickler Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1302
• Type II Collagen Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK540447

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28COL2A1%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22+AND+%5Bdp%5D

Catalog of Genes and Diseases from OMIM
• AVASCULAR NECROSIS OF FEMORAL HEAD, PRIMARY, 1
  http://omim.org/entry/608805
• COLLAGEN, TYPE II, ALPHA-1
  http://omim.org/entry/120140
• OSTEOARTHRITIS SUSCEPTIBILITY 1
  http://omim.org/entry/165720

Research Resources
• Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_COL2A1.html
• ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=COL2A1%5Bgene%5D
• HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:2200
• Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:1280
• NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/1280
• UniProt
  https://www.uniprot.org/uniprot/P02458

Sources for This Summary

• Cheah KS, Stoker NG, Griffin JR, Grosveld FG, Solomon E. Identification and characterization of the human type II collagen gene (COL2A1). Proc Natl Acad Sci U S A. 1985 May;82(9):2555-9. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/3857598
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC397602/
• Donoso LA, Edwards AO, Frost AT, Ritter R 3rd, Ahmad N, Vrabec T, Rogers J, Meyer D, Parma S. Clinical variability of Stickler syndrome: role of exon 2 of the collagen COL2A1 gene. Surv Ophthalmol. 2003 Mar-Apr;48(2):191-203. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12686304
• Go SL, Maugeri A, Mulder JJ, van Driel MA, Cremers FP, Hoyng CB. Autosomal dominant rhegmatogenous retinal detachment associated with an Arg453Ter mutation in the COL2A1 gene. Invest Ophthalmol Vis Sci. 2003 Sep;44(9):4035-43. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12939326
• Hoornaert KP, Marik I, Kozlowski K, Cole T, Le Merrer M, Leroy JG, Coucke PJ, Sillence D, Mortier GR. Czech dysplasia metatarsal type: another type II collagen disorder. Eur J Hum Genet. 2007 Dec;15(12):1269-75. Epub 2007 Aug 29. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17726487
• Kannu P, Bateman J, Savarirayan R. Clinical phenotypes associated with type II collagen mutations. J Paediatr Child Health. 2012 Feb;48(2):E38-43. doi: 10.1111/j.1440-1754.2010.01979.x. Epub 2011 Feb 18. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21332586
• Kannu P, Bateman JF, Randle S, Cowie S, du Sart D, McGrath S, Edwards M, Savarirayan R. Premature arthritis is a distinct type II collagen phenotype. Arthritis Rheum. 2010 May;62(5):1421-30. doi: 10.1002/art.27354. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20131279
• Körkkö J, Cohn DH, Ala-Kokko L, Krakow D, Prockop DJ. Widely distributed mutations in the COL2A1 gene produce achondrogenesis type II/hypochondrogenesis. Am J Med Genet. 2000 May 15;92(2):95-100. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10797431
• Liu YF, Chen WM, Lin YF, Yang RC, Lin MW, Li LH, Chang YH, Jou YS, Lin PY, Su JS, Huang SF, Hsiao KJ, Fann CS, Hwang HW, Chen YT, Tsai SF. Type II collagen gene variants and inherited osteonecrosis of the femoral head. N Engl J Med. 2005 Jun 2;352(22):2294-301. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15930420
• Miyamoto Y, Matsuda T, Kitoh H, Haga N, Ohashi H, Nishimura G, Ikegawa S. A recurrent mutation in type II collagen gene causes Legg-Calvé-Perthes disease in a Japanese family. Hum Genet. 2007 Jun;121(5):625-9. Epub 2007 Mar 30. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17394019

page 7
• Mortier GR, Weis M, Nuytinck L, King LM, Wilkin DJ, De Paepe A, Lachman RS, Rimoin DL, Eyre DR, Cohn DH. Report of five novel and one recurrent COL2A1 mutations with analysis of genotype-phenotype correlation in patients with a lethal type II collagen disorder. J Med Genet. 2000 Apr; 37(4):263-71.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10745044
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1734564/

• Nishimura G, Haga N, Kitoh H, Tanaka Y, Sonoda T, Kitamura M, Shirahama S, Itoh T, Nakashima E, Ohashi H, Ikegawa S. The phenotypic spectrum of COL2A1 mutations. Hum Mutat. 2005 Jul; 26(1):36-43.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15895462

• Prockop DJ. Type II collagen and avascular necrosis of the femoral head. N Engl J Med. 2005 Jun 2;352(22):2268-70.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15930417

• Richards AJ, Baguley DM, Yates JR, Lane C, Nicol M, Harper PS, Scott JD, Snead MP. Variation in the vitreous phenotype of Stickler syndrome can be caused by different amino acid substitutions in the X position of the type II collagen Gly-X-Y triple helix. Am J Hum Genet. 2000 Nov;67(5):1083-94. Epub 2000 Sep 25.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11007540
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1288550/

• Richards AJ, Meredith S, Poulson A, Bearcroft P, Crossland G, Baguley DM, Scott JD, Snead MP. A novel mutation of COL2A1 resulting in dominantly inherited rhegmatogenous retinal detachment. Invest Ophthalmol Vis Sci. 2005 Feb;46(2):663-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15671297

• Su P, Li R, Liu S, Zhou Y, Wang X, Patil N, Mow CS, Mason JC, Huang D, Wang Y. Age at onset-dependent presentations of premature hip osteoarthritis, avascular necrosis of the femoral head, or Legg-Calvé-Perthes disease in a single family, consequent upon a p.Gly1170Ser mutation of COL2A1. Arthritis Rheum. 2008 Jun;58(6):1701-6. doi: 10.1002/art.23491.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18512791

• Tiller GE, Polumbo PA, Weis MA, Bogaert R, Lachman RS, Cohn DH, Rimoin DL, Eyre DR. Dominant mutations in the type II collagen gene, COL2A1, produce spondyloepimetaphyseal dysplasia, Strudwick type. Nat Genet. 1995 Sep;11(1):87-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/7550321

• Wilkin DJ, Artz AS, South S, Lachman RS, Rimoin DL, Wilcox WR, McKusick VA, Stratakis CA, Francomano CA, Cohn DH. Small deletions in the type II collagen triple helix produce kniest dysplasia. Am J Med Genet. 1999 Jul 16;85(2):105-12.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10406661

• Zabel B, Hilbert K, Stöss H, Superti-Furga A, Spranger J, Winterpacht A. A specific collagen type II gene (COL2A1) mutation presenting as spondyloperipheral dysplasia. Am J Med Genet. 1996 May 3;63(1):123-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8723097
Zankl A, Neumann L, Ignatius J, Nikkels P, Schrander-Stumpel C, Mortier G, Omran H, Wright M, Hilbert K, Bonafé L, Spranger J, Zabel B, Superti-Furga A. Dominant negative mutations in the C-propeptide of COL2A1 cause platyspondylic lethal skeletal dysplasia, torrance type, and define a novel subfamily within the type 2 collagenopathies. Am J Med Genet A. 2005 Feb 15;133A(1):61-7. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15643621

Zankl A, Zabel B, Hilbert K, Wildhardt G, Cuenot S, Xavier B, Ha-Vinh R, Bonafé L, Spranger J, Superti-Furga A. Spondyloperipheral dysplasia is caused by truncating mutations in the C-propeptide of COL2A1. Am J Med Genet A. 2004 Aug 30;129A(2):144-8. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15316962

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/COL2A1

Reviewed: March 2015
Published: August 17, 2020

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services