Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones. The term "osteogenesis imperfecta" means imperfect bone formation. People with this condition have bones that break easily, often from mild trauma or with no apparent cause. Multiple fractures are common, and in severe cases, can occur even before birth. Milder cases may involve only a few fractures over a person’s lifetime.

There are at least eight recognized forms of osteogenesis imperfecta, designated type I through type VIII. The types can be distinguished by their signs and symptoms, although their characteristic features overlap. Type I is the mildest form of osteogenesis imperfecta and type II is the most severe; other types of this condition have signs and symptoms that fall somewhere between these two extremes. Increasingly, genetic factors are used to define the different forms of osteogenesis imperfecta.

The milder forms of osteogenesis imperfecta, including type I, are characterized by bone fractures during childhood and adolescence that often result from minor trauma. Fractures occur less frequently in adulthood. People with mild forms of the condition typically have a blue or grey tint to the part of the eye that is usually white (the sclera), and may develop hearing loss in adulthood. Affected individuals are usually of normal or near normal height.

Other types of osteogenesis imperfecta are more severe, causing frequent bone fractures that may begin before birth and result from little or no trauma. Additional features of these conditions can include blue sclerae, short stature, hearing loss, respiratory problems, and a disorder of tooth development called dentinogenesis imperfecta. The most severe forms of osteogenesis imperfecta, particularly type II, can include an abnormally small, fragile rib cage and underdeveloped lungs. Infants with these abnormalities have life-threatening problems with breathing and often die shortly after birth.

Frequency

This condition affects an estimated 6 to 7 per 100,000 people worldwide. Types I and IV are the most common forms of osteogenesis imperfecta, affecting 4 to 5 per 100,000 people.

Causes

Mutations in the COL1A1, COL1A2, CRTAP, and P3H1 genes cause osteogenesis imperfecta.

Mutations in the COL1A1 and COL1A2 genes are responsible for more than 90 percent of all cases of osteogenesis imperfecta. These genes provide instructions for making
proteins that are used to assemble type I collagen. This type of collagen is the most abundant protein in bone, skin, and other connective tissues that provide structure and strength to the body.

Most of the mutations that cause osteogenesis imperfecta type I occur in the \textit{COL1A1} gene. These genetic changes reduce the amount of type I collagen produced in the body, which causes bones to be brittle and to fracture easily. The mutations responsible for most cases of osteogenesis imperfecta types II, III, and IV occur in either the \textit{COL1A1} or \textit{COL1A2} gene. These mutations typically alter the structure of type I collagen molecules. A defect in the structure of type I collagen weakens connective tissues, particularly bone, resulting in the characteristic features of osteogenesis imperfecta.

Mutations in the \textit{CRTAP} and \textit{P3H1} genes are responsible for rare, often severe cases of osteogenesis imperfecta. Cases caused by \textit{CRTAP} mutations are usually classified as type VII; when \textit{P3H1} mutations underlie the condition, it is classified as type VIII. The proteins produced from these genes work together to process collagen into its mature form. Mutations in either gene disrupt the normal folding, assembly, and secretion of collagen molecules. These defects weaken connective tissues, leading to severe bone abnormalities and problems with growth.

In cases of osteogenesis imperfecta without identified mutations in one of the genes described above, the cause of the disorder is unknown. These cases include osteogenesis imperfecta types V and VI. Researchers are working to identify additional genes that may be responsible for these conditions.

**Inheritance Pattern**

Most cases of osteogenesis imperfecta have an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the condition. Many people with type I or type IV osteogenesis imperfecta inherit a mutation from a parent who has the disorder. Most infants with more severe forms of osteogenesis imperfecta (such as type II and type III) have no history of the condition in their family. In these infants, the condition is caused by new (sporadic) mutations in the \textit{COL1A1} or \textit{COL1A2} gene.

Less commonly, osteogenesis imperfecta has an autosomal recessive pattern of inheritance. Autosomal recessive inheritance means two copies of the gene in each cell are altered. The parents of a child with an autosomal recessive disorder typically are not affected, but each carry one copy of the altered gene. Some cases of osteogenesis imperfecta type III are autosomal recessive; these cases usually result from mutations in genes other than \textit{COL1A1} and \textit{COL1A2}. When osteogenesis imperfecta is caused by mutations in the \textit{CRTAP} or \textit{P3H1} gene, the condition also has an autosomal recessive pattern of inheritance.
Other Names for This Condition
- Brittle bone disease
- Fragilitas ossium
- OI
- Vrolik disease

Diagnosis & Management

Genetic Testing Information
- What is genetic testing?
- Genetic Testing Registry: Osteogenesis imperfecta
- Genetic Testing Registry: Osteogenesis imperfecta type 5
- Genetic Testing Registry: Osteogenesis imperfecta type 7
- Genetic Testing Registry: Osteogenesis imperfecta type 8
- Genetic Testing Registry: Osteogenesis imperfecta type 9
- Genetic Testing Registry: Osteogenesis imperfecta type 10
- Genetic Testing Registry: Osteogenesis imperfecta type 12
- Genetic Testing Registry: Osteogenesis imperfecta type I
- Genetic Testing Registry: Osteogenesis imperfecta type III
- Genetic Testing Registry: Osteogenesis imperfecta with normal sclerae, dominant form
- Genetic Testing Registry: Osteogenesis imperfecta, recessive perinatal lethal
- Genetic Testing Registry: Osteogenesis imperfecta, type XI
Research Studies from ClinicalTrials.gov
• ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=osteogenesis+imperfecta

Other Diagnosis and Management Resources
• GeneReview: COL1A1/2 Osteogenesis Imperfecta
  https://www.ncbi.nlm.nih.gov/books/NBK1295
• MedlinePlus Encyclopedia: Osteogenesis Imperfecta
  https://medlineplus.gov/ency/article/001573.htm

Additional Information & Resources
Health Information from MedlinePlus
• Encyclopedia: Osteogenesis Imperfecta
  https://medlineplus.gov/ency/article/001573.htm
• Health Topic: Osteogenesis Imperfecta
  https://medlineplus.gov/osteogenesisimperfecta.html

Genetic and Rare Diseases Information Center
• Dentinogenesis imperfecta
  https://rarediseases.info.nih.gov/diseases/6258/dentinogenesis-imperfecta
• Osteogenesis imperfecta
  https://rarediseases.info.nih.gov/diseases/1017/osteogenesis-imperfecta

Additional NIH Resources
• National Human Genome Research Institute
  https://www.genome.gov/Genetic-Disorders/Osteogenesis-Imperfecta
• National Institute of Arthritis and Musculoskeletal and Skin Diseases: Heritable Disorders of Connective Tissue
  https://www.niams.nih.gov/health-topics/heritable-disorders-connective-tissue
• National Institute of Arthritis and Musculoskeletal and Skin Diseases: Osteogenesis Imperfecta Overview
  https://www.bones.nih.gov/health-info/bone/osteogenesis-imperfecta

Educational Resources
• Boston Children's Hospital
  http://www.childrenshospital.org/conditions-and-treatments/conditions/o/osteogenesis-imperfecta
• Howard Hughes Medical Institute: Genetic Mutation Explains Form of Brittle Bone Disease (October 20, 2006)
• Kennedy Krieger Institute
  https://www.kennedykrieger.org/patient-care/conditions/osteogenesis-imperfecta-oi

• Lucile Packard Children's Hospital at Stanford

• MalaCards: osteogenesis imperfecta, type i
  https://www.malacards.org/card/osteogenesis_imperfecta_type_i_2

• MalaCards: osteogenesis imperfecta, type ii
  https://www.malacards.org/card/osteogenesis_imperfecta_type_ii

• MalaCards: osteogenesis imperfecta, type iii
  https://www.malacards.org/card/osteogenesis_imperfecta_type_iii_2

• MalaCards: osteogenesis imperfecta, type iv
  https://www.malacards.org/card/osteogenesis_imperfecta_type_iv

• Merck Manual Consumer Version

• Orphanet: Osteogenesis imperfecta
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=666

Patient Support and Advocacy Resources

• Little People of America (LPA)
  https://www.lpaonline.org/

• Little People UK
  https://littlepeopleuk.org/

• National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/osteogenesis-imperfecta/

• Osteogenesis Imperfecta Foundation
  https://oif.org/informationcenter/about-oi/

Clinical Information from GeneReviews

• COL1A1/2 Osteogenesis Imperfecta
  https://www.ncbi.nlm.nih.gov/books/NBK1295

Scientific Articles on PubMed

• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Osteogenesis+Imperfecta%5BMAJR%5D%29+AND+%28osteogenesis+imperfecta%5BTIAB%5D%29+AND+english%5BLa%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D
Catalog of Genes and Diseases from OMIM

- OSTEOGENESIS IMPERFECTA, TYPE I
  http://omim.org/entry/166200
- OSTEOGENESIS IMPERFECTA, TYPE II
  http://omim.org/entry/166210
- OSTEOGENESIS IMPERFECTA, TYPE III
  http://omim.org/entry/259420
- OSTEOGENESIS IMPERFECTA, TYPE IV
  http://omim.org/entry/166220
- OSTEOGENESIS IMPERFECTA, TYPE V
  http://omim.org/entry/610967
- OSTEOGENESIS IMPERFECTA, TYPE VII
  http://omim.org/entry/610682
- OSTEOGENESIS IMPERFECTA, TYPE VIII
  http://omim.org/entry/610915
- OSTEOGENESIS IMPERFECTA, TYPE XI
  http://omim.org/entry/610968

Medical Genetics Database from MedGen

- Osteogenesis imperfecta

Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301472

Reprinted from Genetics Home Reference:

Reviewed: April 2013
Published: November 12, 2019

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