



**National Institutes of Health
Osteoporosis and Related
Bone Diseases ~
National Resource Center**

2 AMS Circle
Bethesda, MD 20892-3676

Phone: 202-223-0344
Toll free: 800-624-BONE
Fax: 202-293-2356
TTY: 202-466-4315

Email: NIAMSBoneInfo@
mail.nih.gov

Web site: www.niams.nih.gov/bone

The NIH Osteoporosis and Related Bone Diseases ~ National Resource Center is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases with contributions from the National Institute on Aging, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the NIH Office of Research on Women's Health, and the HHS Office on Women's Health.

The National Institutes of Health (NIH) is a component of the U.S. Department of Health and Human Services (HHS).



Osteogenesis Imperfecta Overview

Definition

Osteogenesis imperfecta (OI) is a genetic disorder characterized by bones that break easily, often from little or no apparent cause. A classification system of different types of OI is commonly used to help describe how severely a person with OI is affected. For example, a person may have just a few or as many as several hundred fractures in a lifetime.

Prevalence

Although the number of people affected with OI in the United States is unknown, the best estimate suggests a minimum of 20,000 and possibly as many as 50,000.

Diagnosis

OI is caused by genetic defects that affect the body's ability to make strong bones. Collagen is the major protein of the body's connective tissue and can be likened to the framework around which a building is constructed. In dominant (classical) OI, a person has either too little type 1 collagen or a poor quality of type 1 collagen caused by a mutation in one of the type 1 collagen genes. In recessive OI, mutations in other genes interfere with collagen production. The result in all cases is weak bones that break easily.

It is often possible to diagnose OI based solely on clinical features. Clinical geneticists can perform biochemical (collagen) or molecular (DNA) tests that can help confirm a diagnosis of OI in some situations.

These tests generally require several weeks before results are known. Both the collagen biopsy test and the DNA test are thought to detect nearly 90 percent of all type 1 collagen mutations.

A positive collagen type 1 test confirms the diagnosis of dominant OI, but a negative result leaves open the possibility that:

- A type 1 collagen mutation is present but was not detected.
- The patient has a form of the disorder that is not associated with type 1 collagen mutations.
- The patient has a recessive form of OI.

Therefore, a negative type 1 collagen study does not rule out OI. When a type 1 collagen mutation is not found, other DNA tests can check for recessive forms.

Clinical Features

The characteristic features of OI vary greatly from person to person, even among people with the same type of OI and even within the same family. Not all characteristics are evident in each case. The majority of OI cases (possibly 85 to 90 percent) are caused by a dominant mutation in a gene coding for type 1 collagen (Types I, II, III, and IV in the following list). Types V and VI do not have a type 1 collagen mutation, but the genes causing them have not yet been identified. Types VII and VIII are newly discovered forms that are inherited in a recessive manner, and the genes causing these two types have been identified. The general features of each of the known types of OI, which vary in characteristics and severity, are as follows:

Type I OI

- most common and mildest type of OI
- bones predisposed to fracture (most fractures occur before puberty)
- normal or near-normal stature
- loose joints and muscle weakness
- blue, purple, or gray tint to sclera (whites of the eyes)
- triangular face
- tendency toward spinal curvature
- absent or minimal bone deformity
- possible brittle teeth
- possible hearing loss, often beginning in early twenties or thirties
- normal collagen structure, but less than normal amount

Type II OI

- most severe form of OI
- frequently causes death at birth or shortly after, because of respiratory problems
- numerous fractures and severe bone deformity
- small stature with underdeveloped lungs
- blue, purple, or gray tinted sclera
- improperly formed collagen

Type III OI

- easily fractured bones (Fractures often present at birth, and x rays may reveal healed fractures that occurred before birth.)
- small stature
- blue, purple, or gray tinted sclera
- loose joints and poor muscle development in arms and legs
- barrel-shaped rib cage
- triangular face
- spinal curvature
- possible respiratory problems
- often severe bone deformity
- possible brittle teeth
- possible hearing loss
- improperly formed collagen

Type IV OI

- between Type I and Type III OI in severity
- bones easily fractured (most fractures occur before puberty)
- smaller than average stature
- sclera normal in color (i.e., white or near-white)
- mild to moderate bone deformity
- tendency toward spinal curvature
- barrel-shaped rib cage
- triangular face
- possible brittle teeth
- possible hearing loss
- improperly formed collagen

By studying the appearance of OI bone under the microscope, investigators noticed that some people who are clinically within the Type IV group had a distinct pattern to their bone. When they reviewed the full medical history of these

people, they found the groups had other features in common. They named these groups Type V and Type VI OI. The mutations causing these forms of OI have not been identified, but people in these two groups do not have mutations in the type 1 collagen genes.

Type V OI

- clinically similar to Type IV OI in appearance and symptoms
- a dense band seen on x rays adjacent to the growth plate of the long bones
- unusually large calluses, called hypertrophic calluses, at the sites of fractures or surgical procedures (A callus is an area of new bone that is laid down at the fracture site as part of the healing process.)
- calcification of the membrane between the radius and ulna (the bones of the forearm), which leads to restriction of forearm rotation
- sclera normal in color (i.e., white or near-white)
- normal teeth
- “mesh-like” appearance to bone when viewed under the microscope
- dominant inheritance pattern

Type VI OI

- clinically similar to Type IV OI in appearance and symptoms
- slightly elevated activity level of alkaline phosphatase (an enzyme linked to bone formation), which can be determined by a blood test
- distinctive “fish-scale” appearance to bone when viewed under the microscope
- diagnosed by bone biopsy
- unknown whether this form is inherited in a dominant or recessive manner, but researchers believe the mode of inheritance is most likely recessive
- Eight people identified with this type of OI to date

New Recessive Forms of OI

After years of research, in 2006, scientists discovered two forms of OI that are inherited in a recessive manner. Genes that affect collagen formation cause both types. The discovery of these new forms of OI provides information for people who have severe or moderately severe OI but do not have a primary collagen mutation.

Type VII OI

- resembles Type IV OI in many aspects of appearance and symptoms in the first described cases
- in other instances, similar appearance and symptoms to Type II lethal OI, except infants had white sclera, a small head, and a round face
- small stature

- short humerus (arm bone) and short femur (upper leg bone)
- coxa vara (a deformed hip joint in which the neck of the femur is bent downward) is common; the acutely angled femur head affects the hip socket.
- results from recessive inheritance of a mutation in the CRTAP gene. Partial (10 percent) expression of CRTAP leads to moderate bone dysplasia. Total absence of the cartilage-associated protein has been lethal in all identified cases.

Type VIII OI

- resembles lethal Type II or Type III OI in appearance and symptoms, except infants have white sclera
- severe growth deficiency
- extreme skeletal undermineralization
- caused by absence or severe deficiency of prolyl 3-hydroxylase activity due to mutations in the LEPRE1 gene

Inheritance Factors

Most cases of OI (85 to 90 percent) are caused by a dominant genetic defect. This means that only one copy of the mutation-carrying gene is necessary for the child to have OI. A person with a form of OI caused by a dominant mutation has a 50 percent chance of passing on the disorder to each of his or her children.

Some children who have the dominant form of OI inherit the disorder from a parent. Other children are born with the dominant form of OI even though there is no family history of the disorder. In these children, the genetic defect occurred as a spontaneous mutation.

Approximately 10 to 15 percent of OI cases are the result of a recessive mutation. In this situation, the parents do not have OI, but both carry the mutation in their genes. To inherit recessive OI, the child must receive a copy of the mutation from both parents.

The parents of a child with recessive OI have a 25-percent chance per pregnancy of having another child with OI. Siblings of a person with recessive OI have a 50-percent chance of being a carrier of the recessive gene. DNA testing is available to help parents and siblings determine if they are carriers of this type of gene mutation.

If one parent has OI because of a recessive mutation, 100 percent of their children will be carriers of the recessive OI mutation. Whether any of these children will have OI will depend on the genes inherited from the other parent. Genetic counselors can help people with OI and their family members understand OI

genetics and the possibility of recurrence, and they can assist in prenatal diagnosis for those who wish to exercise that option. For more information on OI inheritance, see the fact sheet, *Genetics*, from the Osteogenesis Imperfecta Foundation.

Treatment

There is not yet a cure for OI. Treatment is directed toward preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Care of fractures, extensive surgical and dental procedures, and physical therapy are often recommended for people with OI. Use of wheelchairs, braces, and other mobility aids is common, particularly (although not exclusively) among people with more severe types of OI.

Doctors frequently consider a surgical procedure called “rodding” for people with OI. This treatment involves inserting metal rods through the length of the long bones to strengthen them. The treatment also prevents or corrects deformities. For more information, see the Osteogenesis Imperfecta Foundation’s fact sheet, *Rodding Surgery*.

Scientists are exploring several medications and other treatments for their potential use to treat OI. These include growth hormone treatment, intravenous and oral drugs called bisphosphonates, an injected drug called teriparatide (for adults only), and gene therapies. It is not clear whether people with recessive OI and those with dominant OI will respond to these treatments in the same manner. The OI Foundation can provide current information on research studies and experimental treatments to help individuals with OI decide whether to participate in clinical trials.

People with OI are encouraged to exercise as much as possible to promote muscle and bone strength, which can help prevent fractures. Swimming and water therapy are common exercise choices for people with OI, as water allows independent movement with little risk of fracture. For those who are able, walking (with or without mobility aids) is excellent exercise. People with OI should consult their doctor or physical therapist to discuss appropriate and safe exercise.

Children and adults with OI also will benefit from maintaining a healthy weight, eating a nutritious diet, and avoiding activities such as smoking, excessive alcohol and caffeine consumption, and taking steroid medications—all of which may deplete bone and exacerbate bone fragility. For more information on nutrition, see the Osteogenesis Imperfecta Foundation’s fact sheet, *Nutrition*.

Prognosis

The prognosis for a person with OI varies greatly depending on the number and severity of symptoms. Respiratory failure is the most frequent cause of death for people with OI, followed by accidental trauma. Despite numerous fractures, restricted activity, and small stature, most adults and children with OI lead productive and successful lives. They attend school, develop friendships and other relationships, have careers, raise families, participate in sports and other recreational activities, and are active members of their communities.

Resource

For more information about osteogenesis imperfecta, contact:

Osteogenesis Imperfecta Foundation
804 West Diamond Avenue, Suite 210
Gaithersburg, MD 20878
Telephone: 301-947-0083
Toll free: 1-800-891-BONE
Fax: 301-947-0456
Email: bonelink@oif.org
Web site: www.oif.org

*The National Resource Center acknowledges the assistance of the
Osteogenesis Imperfecta Foundation in the preparation of this publication.*

Reviewed May 2009

For Your Information

This fact sheet contains information about medications used to treat the health condition discussed here. When this fact sheet was printed, we included the most up-to-date (accurate) information available. Occasionally, new information on medications is released.

For updates and for any questions about any medications you are taking, please contact the U.S. Food and Drug Administration at 888-INFO-FDA (888-463-6332, a toll-free call) or visit its Web site at www.fda.gov.

For updates and questions about statistics, please contact the Centers for Disease Control and Prevention's National Center for Health Statistics toll free at 800-232-4636 or visit its Web site at www.cdc.gov/nchs.

Recognizing the National Bone and Joint Decade 2002–2011