

## Fast Facts on Osteogenesis Imperfecta

### 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

While 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. In dominant (classical) OI, a person has too little type I collagen or a poor quality of type I collagen due to a mutation in one of the type I collagen genes. Collagen is the major protein of the body's connective tissue. It is part of the framework that bones are formed around. In recessive OI, mutations in other genes interfere with collagen production. The result in all cases is fragile bones that break easily. It is often, though not always, possible to diagnose OI based solely on clinical features. Clinical geneticists can also 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 DNA test are thought to detect almost 90% of all type I collagen mutations.

A positive type I collagen study confirms the diagnosis of dominant OI, but a negative result could mean that either a collagen type I mutation is present but was not detected or the patient has a form of the disorder that is not associated with type 1 collagen mutations or the patient has a recessive form of OI. Therefore, a negative type I collagen study does not rule out OI. When a type I collagen mutation is not found, other DNA tests to check for recessive forms are available.

### 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 cases of OI (possibly 85-90 %) are caused by a dominant mutation in a gene coding for type I collagen (Types I, II, III, and IV in the following list). Types VII and VIII are newly identified forms that are inherited in a recessive manner. The genes causing these two types have been identified. Types V and VI do not have a type 1 collagen mutation, but the genes causing them have not yet been identified. The general features of each known type of OI are as follows:

#### *Type I*

- Most common and mildest type of OI.
- Bones fracture easily. Most fractures occur before puberty.
- Normal or near-normal stature.
- Loose joints and muscle weakness.
- Sclera (whites of the eyes) usually have a blue, purple, or gray tint.
- Triangular face.
- Tendency toward spinal curvature.
- Bone deformity absent or minimal.
- Brittle teeth possible.
- Hearing loss possible, often beginning in early 20s or 30s.
- Collagen structure is normal, but the amount is less than normal.

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### **Type II**

- Most severe form.
- Frequently lethal at or shortly after birth, often due to respiratory problems.
- Numerous fractures and severe bone deformity.
- Small stature with underdeveloped lungs.
- Tinted sclera.
- Collagen improperly formed.

### **Type III**

- Bones fracture easily. Fractures often present at birth, and x-rays may reveal healed fractures that occurred before birth.
- Short stature.
- Sclera have a blue, purple, or gray tint.
- Loose joints and poor muscle development in arms and legs.
- Barrel-shaped rib cage.
- Triangular face.
- Spinal curvature.
- Respiratory problems possible.
- Bone deformity, often severe.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen improperly formed.

### **Type IV**

- Between Type I and Type III in severity.
- Bones fracture easily. Most fractures occur before puberty.
- Shorter than average stature.
- Sclera are white or near-white (i.e. normal in color).
- Mild to moderate bone deformity.
- Tendency toward spinal curvature.
- Barrel-shaped rib cage.
- Triangular face.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen improperly formed.

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 that groups had other features in common. They named these groups Types V and 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 I collagen genes.**

### **Type V**

- Clinically similar to Type IV in appearance and symptoms of OI.
- A dense band seen on x-rays adjacent to the growth plate of the long bones.
- Unusually large calluses (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). This leads to restriction of forearm rotation.
- White sclera.
- Normal teeth.
- Bone has a “mesh-like” appearance when viewed under the microscope.
- Dominant inheritance pattern

### **Type VI**

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

### **Recessive Forms of OI**

After years of research, two forms of OI that are inherited in a recessive manner were discovered in 2006. Both types are caused by genes that affect collagen formation. These forms provide information for people who have severe or moderately severe OI but who do not have a primary collagen mutation.

### **Type VII**

- The first described cases resemble Type IV OI in many aspects of appearance and symptoms.
- In other instances the appearance and symptoms are similar to Type II lethal OI, except infants had white sclera, a small head and a round face.
- Short stature.
- Short humerus (arm bone) and short femur (upper leg bone).
- Coxa vera is common (the acutely angled femur head affects the hip socket).
- Results from recessive inheritance of a mutation to the CRTAP (cartilage-associated protein) gene. Partial function of CRTAP leads to moderate symptoms while total absence of CRTAP was lethal in all 4 identified cases.

### **Type VIII**

- Resembles lethal Type II or Type III OI in appearance and symptoms except that infants have white sclera.
- Severe growth deficiency.
- Extreme skeletal under mineralization.
- Caused by a deficiency of P3H1 (Prolyl 3-hydroxylase 1) due to a mutation to the LEPRE1 gene.

***For a detailed list of OI Types including clinical signs, degrees of severity and mutation, please see the OI Foundation Website.***

### **Inheritance Factors**

Most cases of OI (85-90%) 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. Children who have the dominant form of OI have either inherited it from a parent or, when the parent does not have OI, as a spontaneous mutation.

Approximately 10-15 percent of cases of OI 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.

When a child has recessive OI, there is a 25 percent chance per pregnancy that the parents will have another child with OI. Siblings of a person with a recessive form of 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.

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. 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 their inheritance from the other parent. Genetic counselors can help people with OI and their family members further

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understand OI genetics and the possibility of recurrence, and assist in prenatal diagnosis for those who wish to exercise that option. For more information on OI inheritance, see the OI Foundation fact sheet titled “Genetics.”

### **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.

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 physician and/or physical therapist to discuss appropriate and safe exercise.

Children and adults with OI will also 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 make bones more fragile. For more information on nutrition, see the OI Foundation fact sheet titled “Nutrition.”

A surgical procedure called “rodding” is frequently considered for people with OI. This treatment involves inserting metal rods through the length of the long bones to strengthen them and prevent and/or correct deformities. For more information, see the OI Foundation’s fact sheet on “Rodding Surgery.”

Several medications and other treatments are being explored for their potential use to treat OI. These include growth hormone treatment, treatment with intravenous and oral drugs called bisphosphonates, an injected drug called teriparatide (for adults only) and gene therapies. It is not clear if people with recessive OI will respond in the same manner as people with dominant OI to these treatments. The OI Foundation provides current information on research studies, as well as information about participating in clinical trials.

### **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 physical activity, and short 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.