

## Genetics

Osteogenesis imperfecta (OI) is the result of a mutation in one of the two genes that carry instructions for making type 1 collagen (the major protein in bone and skin). The mutation may result in either a change in the structure of type 1 collagen molecules, or in the number of collagen molecules made. Either of these changes results in weak bones that fracture easily. In recent years, researchers have studied skin cells, the collagen molecules they make, and the genes themselves from individuals with different forms of OI.

**Results of these studies show that the great majority of people with OI, even those who are the only affected person in a family, have dominantly inherited forms of the disorder. Recessive inheritance probably causes osteogenesis imperfect only about 10% of the time.**

### How Genes Work

Genes are units of hereditary material (DNA) that tell the cells in our bodies how to function. We receive two copies of each gene—one from each parent. Most of the time genes function the way they are supposed to. However, genes can sometimes be altered by a *mutation*, in which there is a change in the structure of the gene's DNA. When a mutation occurs, it can disrupt the normal function of a gene.

### Dominant Inheritance

Most cases of osteogenesis imperfecta involve a *dominant* mutation. When a gene with a dominant mutation is paired with a normal gene, the faulty gene “dominates” the normal gene. In OI, a dominant genetic defect causes one of two things to occur:

1. The dominant altered gene directs cells to make an altered collagen protein. Even though the normal gene directs cells to make normal collagen, the presence of altered collagen causes Type II, III, or IV OI. These types result from a problem with the *quality* of collagen.
2. The dominant altered gene fails to direct cells to make any collagen protein. Although some collagen is produced by instructions from the normal gene, there is an overall decrease in the total amount of collagen produced, resulting in Type I OI. This type results from a problem with the *quantity* of collagen. When a mutation is dominant, a person only has to receive *one* faulty gene to have a genetic disorder. This is the case with most people who have OI: they have one faulty gene for type 1 collagen, and one normal gene for type 1 collagen.

### Recessive Inheritance

With recessive inheritance, *both* copies of a gene must be defective for a person to have a genetic disorder. This occurs when both parents carry a single altered copy of the gene. The parents do not have the genetic disorder, because they have only one faulty gene, but they are *carriers* of the disorder. With each pregnancy, there is a 25 percent chance that the child will receive two altered genes, one from each parent. In this case, the child would have the genetic disorder. There is a 50 percent chance that the child will receive only one altered gene, in which case he or she will be a carrier (like his or her parents), but not have the disorder.

### OI in Families

There are four scenarios that cause a child to be born with OI. About 60% of people diagnosed with OI each year inherited OI from a parent and the condition is described as dominantly inherited. In about 20-30% of people diagnosed with OI each year the mutation is new in them and there is only one copy of the gene affected. This is referred to as a “new” dominant mutation. Recessive inheritance accounts for about 5% of people with OI and mosaicism (a special subset of dominant inheritance) is another rare explanation.

**1. A Dominant Mutation Inherited from an Affected Parent.** A person with dominant OI has a mutation in one copy of a gene for type I collagen, and a normal sequence in the second copy of that gene. The presence of the altered copy of the gene is enough to result in OI. Each time the affected person conceives a child he or she transmits only *one* of the two gene copies, but cannot choose which one. Therefore, there is a *50 % chance with*

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each pregnancy that the child will inherit the altered gene and develop OI. The severity of the OI in the child (e.g., number of fractures, level of mobility, stature) may not be identical to those of the parent, but is frequently in the same severity range. If the parent with dominant OI passes on his or her normal gene to a child, that child will *not* have OI and *cannot* pass on the disorder to his or her own children.

**2. A New Dominant Mutation.** Most children with OI who are born into a family with no history of the disorder have a new dominant mutation. The new mutation occurred before conception in either the one specific sperm or egg that contributed to the pregnancy. This process occurs in the normal course of copying genes every time a cell divides and there are no known environmental, dietary, or behavioral triggers for the mutations that cause OI.

In most instances when a child is born with a new mutation the parents are *not* at any greater risk than the general population to have a second (or subsequent) child with OI because the mutation occurred in only the single sperm or egg that gave rise to that child. The affected child who has the new dominant gene for OI has a 50 % chance to pass the disorder on to each of his or her children. In addition, unaffected siblings of a person whose dominant OI is caused by a spontaneous mutation have the same risk of having an OI child as the general population.

**3. Parental Mosaicism.** There is a small group of families in which the mutation occurred in cells that could give rise to eggs or sperm and so more than a single sperm or egg can be generated. This is a special instance of dominant inheritance in which the person who has only some cells with the mutation are not affected with OI but can have multiple affected children, each of whom would have only the one affected copy of the gene.

**4. Recessive Inheritance.** Recessive inheritance is the other possibility to consider when unaffected parents have more than one child with OI. In recessive OI, both copies of a particular gene received by the child are altered (have a mutation). Each parent of the affected child is a carrier of one copy of the altered gene, but neither parent is affected.

When both parents are each carriers for recessive OI, there is a 25% chance that each child will receive an altered copy of the gene from both parents and be affected. On average there is a 50% chance that the child will receive a normal gene copy from one parent and an altered copy from the other parent, and like the parent be a carrier. There is a 25% chance that a child will inherit both normal gene copies. An unaffected sibling of a child with recessive for of OI has a 2/3 (67%) chance to be a carrier. If a carrier sibling has a partner who is also a carrier (this may occur in instances where marriages within large families are preferred), the couple then may have children who are affected with severe OI. The carrier status of each child can be determined by genetic testing if the mutation is known in the affected child.

### **When Both Parents Have OI**

If two people with OI have a child, there is a 75 percent chance that the child will inherit one or both OI genes, as follows: There is a 25 percent chance the child will inherit only the mother's OI gene (and the father's unaffected gene), a 25 percent chance the child will inherit only the father's OI gene (and the mother's unaffected gene), and a 25 percent chance the child will inherit both parents' OI genes. Because this situation has been uncommon, the outcome of a child inheriting two OI genes is hard to predict. It is likely (even if both parents have mild OI) that the child would have a severe, possibly lethal, form of the disorder.

### **Prenatal Diagnosis**

Testing is available to help families further understand what type of OI someone has, provide some insight into the natural history of the condition (i.e., what the family can expect), and assist in prenatal diagnosis for families who wish to exercise that option. One of these tests examines collagen proteins to look for the quantitative or qualitative collagen defects that lead to OI. A second test is done directly on DNA from a blood sample, and looks for a genetic mutation that causes OI. Because of the relatively small 2 to 4 percent risk of recurrence of Type II OI in a family, many genetic centers now recommend very early ultrasound studies to determine if a developing fetus has the disorder. Women with OI who become pregnant, or women who conceive a child with a man who has OI, may also want to explore prenatal diagnosis. Undergoing prenatal diagnosis does not obligate parents to elect pregnancy termination, and the information obtained may be useful in managing pregnancy and delivery.

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- **Ultrasound** is the least invasive procedure for prenatal diagnosis, and therefore carries the least risk. Using ultrasound, a doctor can examine the fetus' skeleton for bowing (bending of the leg or arm bones), fractures, shortening, or other bone abnormalities that may indicate OI. Type II OI is usually identifiable by 14 to 16 weeks gestation and Type III by 16 to 18 weeks gestation. Though ultrasound has been used occasionally to diagnose milder forms of OI, mild OI is often not detected until late in the pregnancy, if at all. There are different levels of ultrasound, some of which are more useful than others for detecting OI in a fetus. Even when ultrasound is performed by a highly qualified ultrasonographer, it may be difficult to accurately pinpoint the type of OI before birth.
- **Chorionic villus sampling (CVS)** examines placental cells, and, under some circumstances, can be used to detect abnormal collagen proteins or a genetic mutation that indicates that the fetus has OI. CVS can be performed at 10 to 14 weeks gestation. There is a 1 percent risk of miscarriage associated with CVS.
- **Amniocentesis** examines fetal cells shed into the amniotic fluid. Because these cells carry all the genes that a fetus has inherited, amniocentesis can be used to look for a genetic mutation that causes OI. This technique is most useful when the mutation causing OI in a particular family has been identified through previous genetic testing of affected family members, including previous pregnancies involving a baby with OI. Amniocentesis is performed at 15 to 18 weeks gestation, and there is a 1 in 200 risk of miscarriage associated with the procedure.

Various circumstances affect the usefulness and accuracy of these tests. Not all types of tests are available in all geographic areas. When CVS or amniocentesis are used to attempt prenatal diagnosis of a fetus that has a parent with OI, it is helpful for the affected parent to have the results of his or her own collagen or DNA test available. Families are encouraged to discuss these techniques with their physician, as well as a geneticist and/or genetic counselor, to learn more about which techniques are appropriate for their situation.

*Note: The information in this fact sheet is of a general nature. Families should seek counseling from a qualified physician or genetics clinic.*

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