



Genetics

(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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The Osteogenesis Imperfecta Foundation, Inc. is the only voluntary national health organization dedicated to helping people cope with the problems associated with osteogenesis imperfecta. The Foundation's mission is to improve the quality of life for people affected by OI through research to find treatments and a cure, education, awareness, and mutual support.

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.

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. **Most researchers now agree that recessive inheritance rarely causes osteogenesis imperfecta.**

OI in Families

There are essentially three scenarios that occur to cause a child to be born with OI.

1. *Direct Inheritance from a Parent.* A person with OI has two genes for type 1 collagen—one gene is faulty, the other is normal. Each time that person conceives a child, he or she passes on *one* of the two genes to the child. Therefore, there is a *50 percent chance* that his or her child will inherit the faulty gene. If the child inherits the faulty gene, he or she will have the same type of OI as the parent. However, the child may be affected in different ways than the parent (e.g., the child's number of fractures, level of mobility, stature, etc. may not be identical to his or her parent's).

If the parent with 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.* About 25 percent of children with OI are born into a family with no history of the disorder. That is, a child is born with a dominant genetic mutation that causes OI, yet neither parent has OI. This occurs when the child has a “new” or “spontaneous” dominant mutation. The gene spontaneously mutated in either the sperm or the egg before the child's conception. Now that the child has a dominant gene for OI, he or she has a 50 percent chance of passing the disorder on to his or her children, as explained above.

As far as we know, *nothing* the parents did caused a spontaneous mutation to occur. There are no known environmental, dietary, or behavioral triggers for this type of mutation.

In most cases, when a family with no history of OI has a child with OI, they are *not* at any greater risk than the general population for having a second child with OI. (For the exception to this rule, see “Mosaicism” below.) In addition, unaffected siblings of a person with OI are at no greater risk of having children with OI than the general population.

3. *Mosaicism.* In studies of families into which infants with OI Type II (the perinatal lethal form) were born, it was found that most of the babies had a new dominant mutation in a collagen gene. However, in some of these families, more than one infant was born with OI. Previously, researchers had seen this recurrence as evidence of recessive inheritance of this form of OI. More recently, however, researchers have concluded that the rare recurrence of OI in a previously unaffected family is more likely due to a phenomenon called *mosaicism*.

Studies suggested that the mutation, instead of occurring in an *individual* sperm or egg, occurred in a *percentage of the cells that give rise to a parent's multiple sperm or eggs*. Thus, although the parent is not affected by the disorder, the mutation present in a percentage of his or her reproductive cells can result in more than one affected child. It is estimated that 2 to 4 percent of families into which an infant with OI Type II is born are at risk of having another affected child because of this problem with sperm or eggs.

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.

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 who 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.

For more information about osteogenesis imperfecta contact:



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The National Resource Center is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases with contributions from the National Institute of Child Health and Human Development, National Institute of Dental and Craniofacial Research, National Institute of Environmental Health Sciences, NIH Office of Research on Women's Health, HHS Office on Women's Health, and the National Institute on Aging.

The Resource Center is operated by the National Osteoporosis Foundation, in collaboration with the Paget Foundation and the Osteogenesis Imperfecta Foundation.