

Inheritance Patterns-How OI Occurs in Families

Background. In general, we have two copies of each gene. One copy we inherited from our father and one we inherited from our mother. Some genetic conditions occur because one copy of one of these genes is altered (this is called a dominant condition) and in others they occur because there are two altered copies of the gene, one from each parent (this is called a recessive condition). The alteration and the process of alteration are both referred to as "mutation". OI can occur in both patterns.

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 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.

Thank you to Dr. Peter Byers, University of Washington in Seattle for reviewing this document. February 2015