



Genetics in Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a genetic condition characterised by bones that break easily, often from little or no apparent cause. The condition can vary in severity from person to person depending on the underlying genetic cause. For example, a person may have just a few or as many as several hundred fractures in a lifetime.

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Genetic Cause

OI is most commonly the result of a spelling mistake referred to as 'variant' or 'mutation' in one of two genes that carry instructions for making type 1 collagen (a major protein in bone and skin) referred to as COL1A/COL1A2. This may result in either a change in the structure of type 1 collagen, or in the amount of collagen made. Either of these changes results in weak bones that fracture easily. This accounts for about 85% of individuals with OI. Other genes known to be involved in the processing and/or secretion of type 1 collagen accounts for the remainder with a small proportion of individuals not having an identifiable genetic cause for their bone fragility.



What are genes?

Genes are the unique set of instructions inside our bodies which make each of us an individual. There are approximately 20,000 pairs of genes, each carrying a different instruction. All genes come in pairs as we inherit one copy from mother and one copy from father. If there is a spelling mistake in a gene, it can cause a genetic condition or disease. This gene alteration is sometimes known as a variant or mutation. It is important to remember that we all carry spelling mistakes within our genes that do not matter and there are only certain types of spelling mistakes that result in a genetic condition depending on how it alters the instruction i.e protein produced.

Where does OI come from?

Autosomal Dominant Inheritance

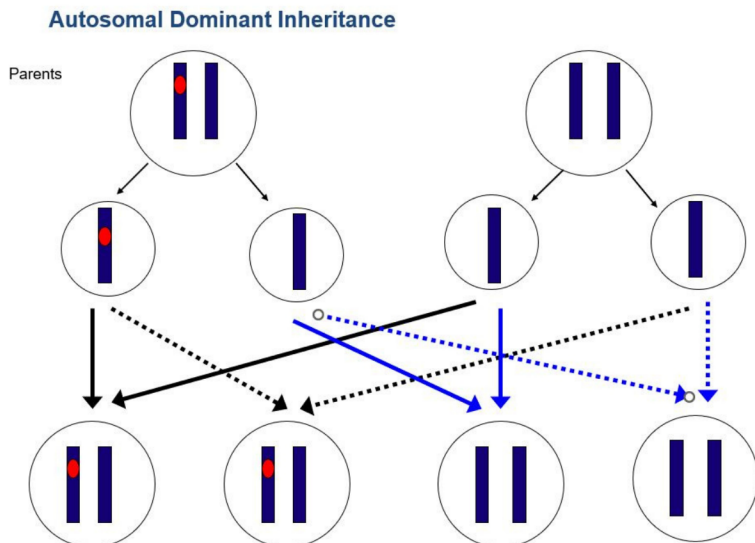
Most OI is inherited in an autosomal dominant manner. This is caused by a spelling mistake in one copy of a gene which dominates over the other normal copy of the gene. A person with OI who has inherited the dominant, faulty copy of the gene will have a 50% or 1 in 2 chance of passing on this copy to any children they have, causing them to also have OI. This would be regardless of the birth order or the sex of the child and the risk would be the same for each pregnancy.

New Dominant Variant/de novo mutation

Around 25% of children with OI are born into a family where there is no family history of the condition. This occurs when the child has a "new" or "spontaneous" dominant variant sometimes referred to as 'de novo mutation.'

When a couple have a child with OI with no other family history i.e. due to a de novo mutation, there is a chance that this can happen again in a future pregnancy as there is a risk of the genetic variation being present in the sperm or egg without being present in the rest of the parent. This is commonly referred to as 'gonadal mosaicism'. The risk in

this situation may likely be in the region of up to 7% and it would be important to seek genetic counselling to explore this further. A person who has OI as a result of a new dominant mutation will have a 50% or 1 in 2 chance of passing on the gene change to their children.



Autosomal Recessive Inheritance

Rarely OI is inherited in an autosomal recessive manner. In recessive conditions, individuals who have only one altered copy of a gene are completely healthy. They are known as healthy carriers, because they carry only one altered copy of a gene. Their normal copy of the gene keeps them healthy and compensates for the altered copy of the gene.



If both healthy parents carry the same altered recessive gene, then each child they have has a 25% (1 in 4) risk of inheriting the altered gene from both parents and therefore being affected. This would be regardless of the birth order or sex of the child and the risk would be the same for each pregnancy. Recessive pattern of inheritance accounts for some of the more severe clinical presentations in OI.

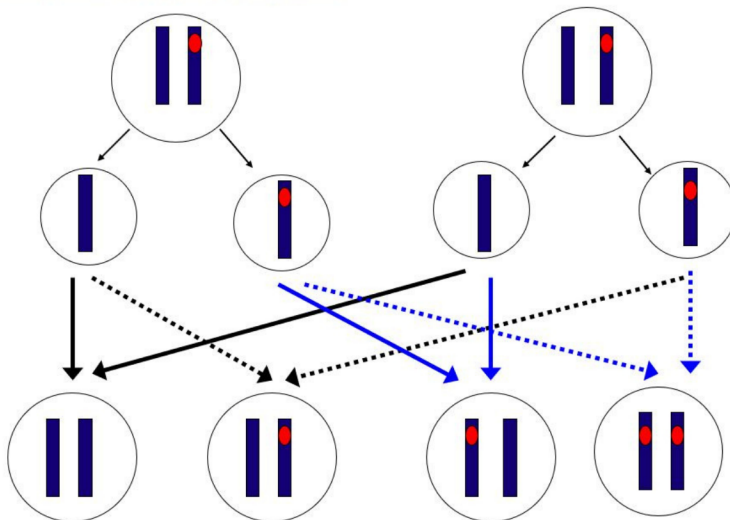
Children of couples who are both carriers of the same altered recessive gene have a 2 in 3 chance of inheriting one copy of the altered gene from one of their parents. If this happens, they are healthy carriers themselves.

It is therefore important that if there is a recessive form of OI in your family, you seek genetic advice prior to starting a family.

There are more rarer patterns of inheritance such as X-linked which causes bone fragility in boys and caused due to a fault on genes that sit within the X chromosome (as boys have only one copy of X), they manifest features whilst a woman who has 2 copies of X chromosome tends to be mildly affected or a healthy carrier'.

You can seek further genetic advice if you would like to pursue this through a referral from your GP/ clinician looking after you/your child.

Autosomal Recessive Inheritance



Further Information and Family Planning

If you or a member of your family have OI and you are concerned about other family members or have questions about recurrence risk and options in a future pregnancy, you can access information, genetic counselling and, in appropriate circumstances, genetic testing from your regional Clinical Genetics service.

To access the service go to your GP, tell them your concerns and ask for referral to the Clinical Genetics Service.

A directory of the regional Clinical Genetics Services in the UK can be found on our website.

Notes

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to the BBS

If you found our factsheet helpful and would like to support the BBS in continuing to provide resources, you can donate by scanning our QR Code



Compiled by the Brittle Bone Society in collaboration with BBS Medical Advisory Board and POINT (Paediatric Osteogenesis Imperfecta National Team). The information in this leaflet is correct as at 31st July 2021 but we cannot guarantee that it will be accurate and current at any given time. This leaflet is not intended in any way to replace the advice of your doctor or other medical professional. Leaflets are available online at www.brittlebone.org. This information is available in accessible formats on request.

The Brittle Bone Society (BBS) is a registered charity in Scotland (SCO50854) and company limited by guarantee (SC677346), supporting the OI community throughout the United Kingdom and in Ireland.