

## Support and Information



Understanding Chromosome & Gene Disorders

**Rare Chromosome Disorder Support Group,**  
The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK  
Tel: +44(0)1883 723356  
info@rarechromo.org | www.rarechromo.org

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You can watch animated videos on paracentric and pericentric inversions prepared by the National Centre for Medical Genetics, Dublin, Ireland by visiting:

<https://www.youtube.com/watch?v=THAjvn1cdDM> paracentric

<https://www.youtube.com/watch?v=QXU7XojaEOs> pericentric

<https://www.youtube.com/watch?v=62h7-AJP-bs> insertional translocation

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr Bronwyn Kerr, clinical geneticist, Manchester Centre for Genomic Medicine, Manchester, UK. This guide was updated by Unique (AP) and reviewed by Dr Sally Ann Lynch, senior clinical geneticist, and Zephra Adamson, senior clinical cytogeneticist at Our Lady's Children's Hospital, Crumlin, Dublin.

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# Inversions

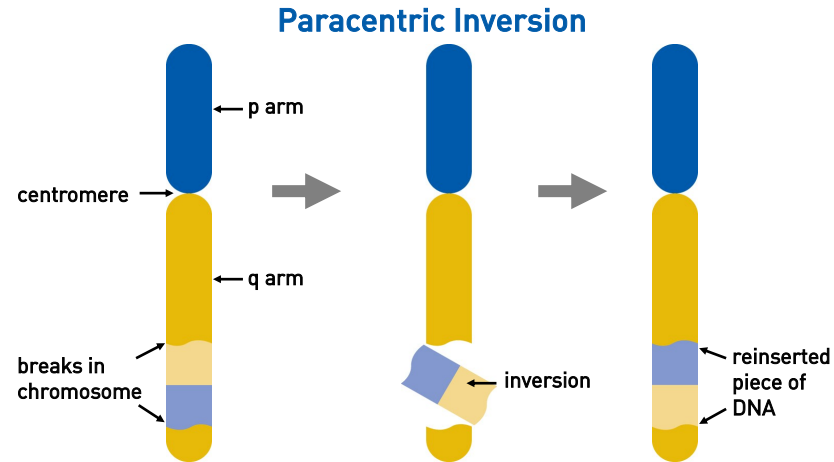
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## What is an inversion?

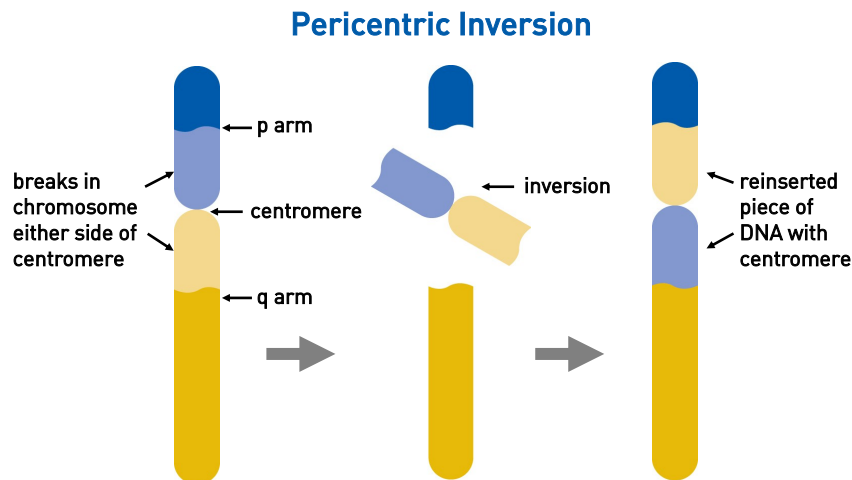
An inversion in a chromosome occurs when a piece of chromosome breaks off, turns round 180 degrees and reinserts itself back into the same chromosome.

### There are two basic types of inversion

Chromosomes have two arms, a short 'p' arm and a long 'q' arm, joined at a narrow point called a centromere. The two basic types of inversion depend on whether the centromere is involved: paracentric and pericentric as shown in the images below.



An inversion that does not include the centromere is called a **paracentric** (away from the centre) **inversion**. Both breaks are in the same arm of the chromosome.



An inversion that includes the centromere is called a **pericentric** (around the centre) **inversion**. One break is in the short 'p' arm, and the other is in the long 'q' arm.

## We have one child with special needs. If we have another child with special needs, will they be affected in the same way?

If you have more than one child with an unbalanced recombinant chromosome, it is very likely that each of them will have special needs. But their needs won't be exactly the same. Depending on your particular inversion, one child may have extra DNA from the short arm, and lose DNA from the long arm; the other may lose DNA from the short arm, and have extra DNA from the long arm. In most families, though, children with unbalanced chromosomes have the same recombinant chromosome. Even so, the effects can vary quite a lot - just as brothers and sisters with ordinary chromosomes are different from each other.

## What about my other children?

Your other children can have their chromosomes tested once they are old enough to decide that they want to know. If you feel strongly that you want to know their chromosome status but they are still too young to decide for themselves, talk it over with your genetics service. The guidance about when it is best to test and tell is flexible and intended to be in families' best interests. If your child is developing normally, it is most likely that they will either have normal chromosomes or the family balanced translocation. A normally developing girl or boy with the family balanced translocation can expect to be unaffected by it until they have children of their own.

## Why me? Is it my fault?

If you've been told you have a balanced inversion, you may wonder 'Why me?' Remember that the inversion probably arose by chance when the egg or sperm cell that was destined to create you was formed. At the very latest, it arose in the earliest days of your mother's pregnancy. So there is certainly nothing you can blame yourself for or feel guilty about. No environmental, diet, workplace or lifestyle factors are known to cause them. They affect men and women from all types of different backgrounds all over the world. They are not your fault and they are not the fault of anyone else in your family. Some people with a balanced inversion feel guilty. Some people who inherit a inversion find that the parent who passed it on feels guilty. There is absolutely no reason for anyone to feel guilty.

## Intracytoplasmic sperm injection (ICSI)

Where there are concerns over fertility, there are ways to select active, fast-moving sperm with sperm analysis and use them in intrauterine insemination or in intracytoplasmic injection (ICSI). In ICSI a single sperm is pre-selected. It is then injected directly into an egg that has been ripened and removed from the mother in the same way as if she was having in vitro fertilisation (IVF). This procedure can be combined with PGD to ensure that only embryos with balanced or normal chromosomes are transferred to the womb.

## Egg or sperm donation

Couples may consider egg or sperm donation if they are not successful in having a healthy child. Donated sperm can be given using intrauterine insemination (IUI) following a woman's natural cycles or after stimulating ovulation with medication. Donated sperm or eggs can come from someone you know or be supplied by a clinic. The donated egg is combined with the partner's fresh sperm and once the recipient's womb has been prepared with hormones, the embryo is transferred to the womb using a normal IVF procedure.

## Questions

### Can an inversion be corrected?

No, it can't. But an inversion of either sort – paracentric or pericentric - is very unlikely to cause any problems until the carrier wants to have children.

### Will my inversion affect my health?

For the great majority of the 2.6 million people with an inversion there is no effect on their own health. For any child who inherits the inversion there should also be no health problems caused by it. Inversions don't usually have any effect on health or development because in the great majority of cases the points in the genome where chromosomes have broken and re-joined don't disrupt the function of important genes.

### What happens if an inversion is found in my baby during pregnancy?

Occasionally a baby is found to have an inversion following chorionic villus sampling or amniocentesis. The parents' chromosomes should then be checked to see if the inversion is inherited. If it is inherited, and the parent has no problems from it, it's unlikely that the baby will have any problems either.

If both parents have standard chromosomes, the baby's inversion is new (de novo). In most cases, the baby will be unaffected but there is a risk that the chromosome breaks have disrupted important genes or that important genetic material has been deleted and/or duplicated. A more detailed chromosome array test could be done to check for loss (deletion) or gain (duplication) of genetic material in the region of the inversion. The mother should be offered high-level ultrasound scans to look for any physical abnormalities. Couples should also have very early access to genetic counselling to identify and discuss any possible problems.

## Do inversions affect health and developmental?

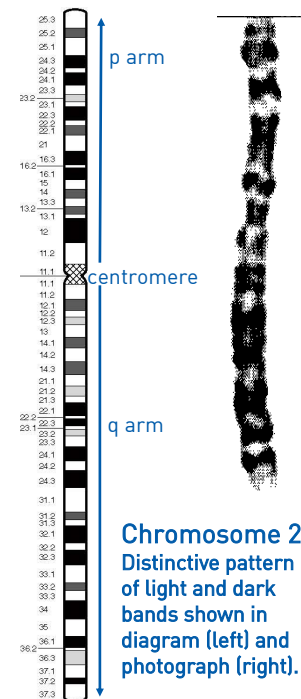
Many people have inversions and their health and developmental are not affected, these people are commonly called **carriers**. Health and development may be affected if an inversion disrupts an important gene, or chromosomal material has been lost. A lot of the time, carrier's do not have a loss of genetic material, they just have a piece of chromosome that is in reverse order. Being in reverse order does not affect the way that piece of chromosome works. The chromosome breaks and re-joining in most places also do not cause problems.

## How common are inversions?

Some inversions are so common that geneticists consider them as natural variants in the human genome (see below). Apart from these natural variants, inversions are not commonly identified. Paracentric inversions have been found in 10-50 in every 100,000 people. Pericentric inversions have been found in 12-70 per 100,000 people. This means that globally there are an estimated 2.6 million inversion carriers. In the US there would be more than 113,000 inversion carriers; in Australia there would be around 8370; and in the United Kingdom there would be more than 22,750. When this guide was written, Unique had members with inversions on virtually every chromosome.

## Natural variants

Common inversions that have no apparent affect are considered to be natural variants. They include inversions of inactive regions around the centromere.



Chromosomes are numbered from 1 to 22, and we each have two copies of these numbered chromosomes (usually one comes from our mother and one from our father). We also have two sex chromosomes, two X's if we are females and an X and a Y if we are male. Natural variant inversions of the inactive regions around the centromere are seen in chromosomes 1; 3; 5; 9; 10; 16 and the male Y chromosome. Most laboratories would not report these inversions as they are considered part of normal human variation.

The health and development of people with natural variants is not normally affected and they will not normally experience difficulties when they have children.

When chromosomes are stained and magnified under a microscope, a distinctive pattern of light and dark bands is revealed, as shown in the images to the left. These bands are numbered from the centromere outwards, so bands in the short arm have a number that starts with a p, and bands in the long arm have a number that starts with a q.

## What happens when an inversion carrier wants to have children?

What happens at conception (when a baby is made) depends on the type of inversion. No difficulties would normally be expected when one of the parents has a natural variant inversion (page 3).

There are usually five possible outcomes when a couple with a significant paracentric or pericentric inversion tries for a baby. These will be more likely or less likely, depending on each particular inversion. A genetics expert can help explain which outcomes are more likely for each family.

- a child will have standard chromosomes and be unaffected
- a child will have the same inversion as the parent and be unaffected
- there may be a delay in getting pregnant, or apparent fertility problems
- a pregnancy may not continue to term
- a child may be born with physical anomalies and/or learning difficulties

## Chromosomes

Most of the cells in our body have 46 chromosomes (see image below). They contain two of each chromosome numbered 1 to 22 (so 22 'pairs' of numbered chromosomes) and two 'sex' chromosomes (a sex chromosome 'pair') that establish biological sex (this is usually two X chromosomes in females and an X and a Y chromosome in males).



Example of a set of 46 chromosomes

The affect an inversion can have on fertility, pregnancy or a child depends on the chromosome present in each egg or sperm. Problems can arise during the chromosome crossing over stage of egg or sperm production and the outcome depends on the location and size of an inversion.

When sperm or eggs are made, matching chromosome pairs (1-22) line up and exchange genetic material. Two new and unique copies of each chromosome numbered 1 to 22 are formed and a single copy of each is placed into a sperm or egg together with either a single X or Y chromosome.

Each egg or sperm therefore contains a single copy of each chromosome i.e. 23 chromosomes. When an egg and sperm cell are united at conception, a total of 46 chromosomes is restored.

Your baby's chromosomes can also be analysed from cells obtained by amniocentesis. A fine needle removes fluid from the liquid surrounding the fetus. This is performed at about 16 weeks of pregnancy and you will usually have confirmation of the baby's chromosome make-up in 10-14 days. Amniocentesis is associated with a slightly raised possibility of miscarriage of about 0.5-1 %.

These tests can show whether your baby has too much or too little chromosome material, but they cannot tell you how your baby will be affected. A child with an unbalanced recombinant chromosome is likely to have special needs.

Scans, including an early dating scan at around 12 weeks, and an anomaly scan at 18-21 weeks, can help to show if the baby is likely to have major health concerns by revealing structural problems with the heart or other major organs. But further details of how a baby with an unbalanced recombinant chromosome is affected can only be assessed after birth.

You should have the opportunity to talk over what is involved in these tests with your midwife or obstetric doctor and they should refer you to a genetic counsellor or geneticist if you want more information about any abnormal results.

If these tests give an abnormal result, you will have the choice of continuing the pregnancy and preparing yourselves for the birth of a child with special needs or terminating the pregnancy. Many Unique members have faced these decisions.

## Other reproductive choices

You may want to look at other reproductive choices. What is available and whether you have to pay depends on what country you live in, but can include the following options.

## Pre-implantation genetic diagnosis (PGD)

Pre-implantation genetic diagnosis (PGD) gives the opportunity to select an embryo without an unbalanced recombinant chromosome that can be placed back in the womb. The procedure uses in vitro fertilisation (IVF) techniques, involves checking the chromosomes of 3-day-old embryos and only transferring those with standard chromosomes or inversion carriers back to the womb. The method used at the moment does not distinguish between embryos with standard chromosomes and inversion carriers.

Unique has members who have used PGD to have healthy children and are happy to share their experiences. The availability of PGD varies widely between countries and it is not available for chromosome inversions in all clinics offering PGD. Success rates vary between centres, but are around 20 per cent per cycle started and 30 per cent per embryo transferred (take home baby rate). In the UK the procedure is expensive but 85 per cent of couples get funding. Some people find it emotionally demanding, and counselling and support are vital before and throughout the process. If you want to find out more about your options for PGD, ask first for a referral to a genetics centre.

## Miscarriage and pregnancy loss

It's surprisingly common to miscarry, often even before a woman knows she is pregnant. When anyone discovers they are pregnant, there is a one in seven possibility that the pregnancy will end in miscarriage. Usually, no obvious reason is found - which is why doctors do not normally investigate until after the second or third loss.

When one member of a couple has an inversion, the possibility of losing the pregnancy, usually in the first three months but sometimes later, is higher. Miscarriages happen in this situation because the developing baby has an unbalanced (recombinant) chromosome - too much DNA from one arm of the inverted chromosome, and too little from the other arm. The further the break is from the end of the chromosome, the more likely it is that pregnancy will not be established in the first place or, if it is, it will be lost.

Each time a couple tries for a pregnancy, the possibilities are the same; conceiving a baby with standard chromosomes; a baby with the inherited inversion; a baby with an unbalanced (recombinant) chromosome resulting in pregnancy loss or birth of a child who may be special needs and/or have health problems.

If you have repeated miscarriages without any successful pregnancies, you may want to discuss this with your genetic counsellor or geneticist. Questions that you may want answered include:

- knowing whether a baby with an unbalanced chromosome can survive to birth
- whether the baby may die soon after birth
- if the baby survives how severely will they be affected mentally and physically

If you know that you have a family inversion inherited from one of your parents, you have reassuring proof that it is possible to have a healthy child.

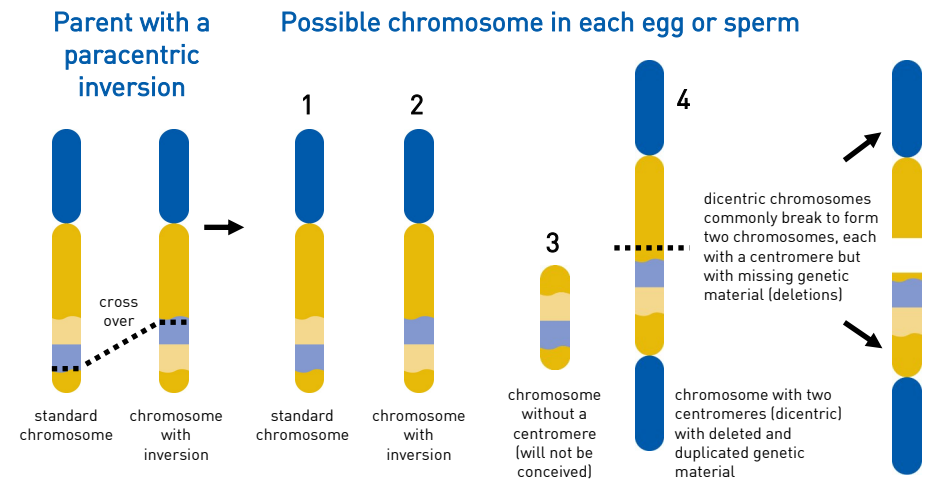
When you have a miscarriage you may be invited to send the 'products' for genetic testing. This is a hard decision to make at a traumatic time but it can help to build up a picture of what is going on, and can also help to further genetic knowledge.

## You're pregnant: how soon can you find out about the baby's chromosomes?

The earliest test that will currently show your baby's chromosome make-up during pregnancy is based on chorionic villus sampling (CVS) at about 11-13 weeks. A fine needle removes some tissue from the placenta. You will usually be given the results in three days to two to three weeks. The test itself may make it slightly (about 1 %) more likely that you will miscarry, and if this happens, it will occur within a few days of the test.

## Paracentric inversions

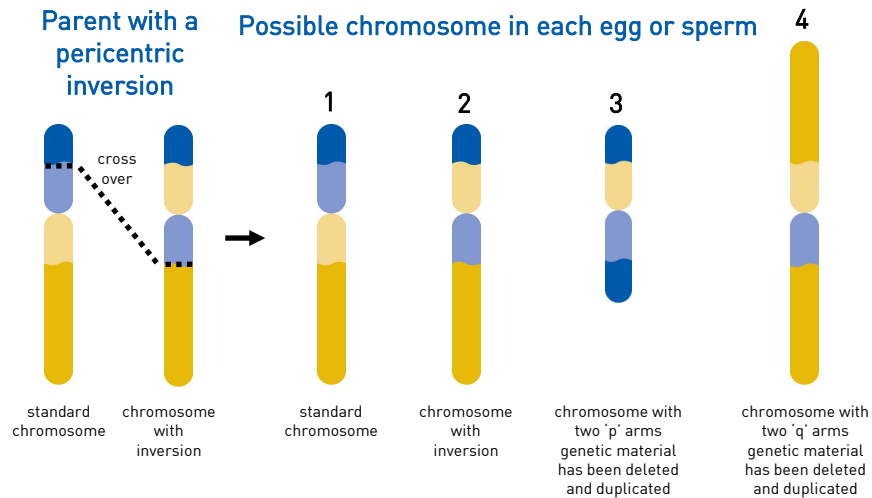
If a parent has a **paracentric inversion** on a numbered chromosome, the unique chromosomes that are made for each sperm or egg, for that chromosome, can be quite different if the chromosome with the inversion is not able to line up correctly with the other copy of the same chromosome. One of the chromosomes needs to form a loop at the site of the inversion in order to line up correctly with the same sections of the second chromosome. This is easier to visualise by watching the following video: <https://www.youtube.com/watch?v=THAjvn1cdDM>. Cross overs that occur outside of this loop are part of the natural process but if a cross over occurs within the loop, the wrong piece of chromosome can be crossed over. The possible chromosome cross over outcomes are shown below.



- 1. A standard chromosome will be packaged into an egg or sperm. The inversion will not be inherited from this cell.
- 2. The chromosome with the inversion will be packaged into an egg or sperm. A child conceived from this egg/sperm would carry the inversion, just like his/her parent but would not expect to experience any inversion related difficulties (unless experienced by the parent carrying the inversion).
- 3. The chromosome that lacks a centromere will not be conceived and therefore is not seen in a clinical setting. This may reduce the number of viable eggs or sperm which could present as reduced fertility.
- 4. The chromosome with two centromeres (dicentric) is usually broken at a random place to form two chromosomes that are packaged into separate eggs or sperm. This results in a smaller chromosome than expected in each sperm or egg with missing genetic material (a deletion). Since part of the chromosome is missing, it is referred to as unbalanced. These situations are very rare. Sometimes this unbalanced form can be identified from analysing a sample from a pregnancy that resulted in a miscarriage. Very rarely, a child is born with a large deletion or a dicentric chromosome, they are likely to have special needs and/or health problems.

## Pericentric inversions

If a parent has a **pericentric inversion** the unique chromosomes that are made for each sperm or egg can be quite different since the chromosomes are not able to line up correctly to cross over the matching genetic material. One of the chromosomes needs to form a loop at the site of the inversion. Cross overs that occur outside of this loop are part of the natural process but if a cross over occurs within the loop, the wrong piece of chromosome can be crossed over (see below and <https://www.youtube.com/watch?v=QXU7XojaEOs>). There are four chromosomal outcomes.



1. A standard chromosome will be packaged into an egg or sperm. The inversion will not be inherited from this cell.
2. The chromosome with the inversion will be packaged into an egg or sperm. A child conceived from this cell would carry the inversion, just like his/her parent but would not expect to experience any inversion related difficulties (unless experienced by the parent carrying the inversion).
3. An unbalanced chromosome (known as a recombinant chromosome) will form that consists of two short 'p' arms so has a duplication and deletion of genetic material (one of the p arms has genetic material from the q arm).
4. An unbalanced chromosome (recombinant chromosome) will form that consists of two long 'q' arms so has a duplication and deletion of genetic material (one of the q arms has genetic material from the p arm).

If a child is conceived from either of the two **recombinant** chromosomes, meaning those with deleted and duplicated genetic material, they may have special needs and/or health problems. These two types of chromosome may also lead to fertility problems and/or pregnancy loss.

## Passing on an inversion to your child

If you or your partner pass on the same inversion to your child, he or she should not have any new health problems or special needs caused by it.

When your children come to have their own children, they will be in the same position as you were: they can have children with standard chromosomes; children with the same inversion as themselves; fertility problems and/or pregnancy loss due to inheritance of a recombinant chromosome with missing and/or duplicated genetic material; birth of a child with special needs and/or health problems due to inheritance of a recombinant chromosome.

Anyone who carries an inversion can ask their GP to refer them to a genetics centre to find out what tests and services are available. You may also wish to read Unique's guide 'Planning your next child' (for families with rare chromosome or gene disorders).

### Questions:

#### Does it make any difference if it's the father who has the inversion or the mother?

In theory no. In practice it seems that women may be more likely to have eggs with a recombinant (unbalanced) chromosome than men to have recombinant sperm. There is a fairly common inversion of chromosome 21 that gives rise to a form of Down's syndrome; this is called the 21p12q21.1 inversion. Only women have passed on this chromosomal inversion to their children.

#### Could I have a child with the same inversion as myself, but who has special needs?

In a family with an inherited inversion, it would be very unusual to have a child with special needs caused by the same chromosome rearrangement. The more people there are in your family with the inversion and no special needs, the more confident you can be.

Very occasionally, an inversion thought to be balanced in fact includes an extra or missing piece of DNA that is too tiny to be seen under a microscope. In this extremely rare situation, the carrier may have some special needs.

More sensitive molecular ways of looking at chromosomes such as the technique called array CGH can help to detect tiny pieces of missing or extra DNA. As this technique is now in routine use, such tiny pieces can be specifically looked for and would be detected. However, this has never been reported in a family where a parent passed an inversion on to their child or children.

#### Will men and women with an inversion have fertility problems?

Most men and women with an inversion are able to have children. However, it may take longer for a pregnancy to be established because a proportion of sperm or eggs will have unbalanced chromosomes and some embryos may not survive.