Inversions
What is an inversion?
An inversion in a chromosome occurs when a piece of the chromosome breaks out, turns round 180 degrees and reinserts itself into the chromosome.

Two sorts of inversion
There are two different sorts of inversion. Chromosomes have two arms, joined at a narrow point called a centromere. This is the point where the top (short, also known as p) arm ends and the bottom (long, also known as q) arm begins.

An inversion that does not include the centromere is called a paracentric inversion. Both breaks are in the same arm of the chromosome.

An inversion that includes the centromere is called a pericentric inversion. One break is in the short arm, and the other is in the long arm.
Do inversions cause any health or developmental problems?
Someone with an inversion is called a carrier. Carriers are not expected to have any health or development problems caused by the inversion. This would only occur if the inversion disrupted a gene, or there was loss of chromosomal material. All the carrier’s genetic material is present, though the DNA within the inverted piece is in reverse order. Apparently being in reverse order does not affect the way DNA works. The breaks and rejoining in most places also do not cause problems.

How common are inversions?
Some inversions are so common that geneticists consider that they are natural variants (see page 4). Apart from these natural variants, inversions are not found frequently. 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.
Many inversions are so common that they are considered to be natural variants. These include inversions of regions around the centromere which are inactive.

The chromosomes in each cell are numbered in pairs from 1 to 22, and in addition everyone has two sex chromosomes, two Xs for females and an X and a Y for males. Natural variant inversions of the inactive regions around the centromere are especially common in chromosomes 1; 9; 16 and the male Y chromosome.

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

Natural variant inversions are also commonly found in chromosome 2 between bands 2p11.2 and 2q13; in chromosome 3 between bands 3p11 and 3q11, bands 3p11 and 3q12 and bands 3p13 and 3q12; in chromosome 5 between bands 5p13 and 5q13; and in chromosome 10 between bands 10p11.2 and 10q21.2.

People with these variants can expect that their health and development will not be affected, and that they will not normally have difficulties when they want to have children.
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 problems would be expected due to a paracentric inversion. Some of the children would be expected to have the same inversion as their parent; other children would be expected to have standard chromosomes. No problems would normally be expected when one of the parents has one of the natural variant inversions listed on page 4.

Problems are more likely if one of the parents has any other type of pericentric inversion. There are usually four possible outcomes when a couple with a pericentric inversion tries for a baby. These will be more likely or less likely, depending on your particular inversion. Your genetics expert can help by saying which outcomes are more likely for you.

1: a child with standard chromosomes
2: a child with the same pericentric inversion as the parent
3: a delay in getting pregnant, or apparent fertility problems. These would be caused by the creation in the parent’s sperm or egg cells of a new chromosome with two copies of the end of one of the chromosome arms. Geneticists call a new chromosome of this type a recombinant chromosome.
4: an ongoing pregnancy which may not continue to term, or may lead to the birth of a child with physical and/or learning problems. This would be also be caused by the new chromosome with two copies of the end of one of the chromosome arms, a recombinant chromosome, in the pregnancy or baby.

The diagram (left) shows two possible new recombinant chromosomes. On the left is the parent’s chromosome with a pericentric inversion. In the middle is a new chromosome in the sperm or egg cell that has two copies of the end of the short arm. This new chromosome is also missing the end of the long arm. On the right is a new chromosome in the sperm or egg cell that has two copies of the end of the long arm. This chromosome is also missing the end of the short arm.

Generally, the closer the breaks are to the ends of the chromosomes, the greater the chances of a baby surviving to birth. This is because the missing and extra pieces of DNA will be smaller and include fewer genes.

Two possibilities
Parent’s pericentric inversion (left) can give rise to new (recombinant) chromosome with two short arms (middle) or two long arms (right).
Having children: a family with a pericentric inversion

Your geneticist can try to suggest which of these outcomes are more likely for your family. Parents contribute one chromosome from each pair.

1. One parent with a pericentric inversion
2. One parent with standard chromosomes
3. Either 
   - Same pericentric inversion as parent
   - Unbalanced: two ends of the long arm, no end of the short arm
4. Either 
   - Standard chromosomes
   - Unbalanced: two ends of the short arm, no end of the long arm

In this family, these two chromosome arrangements should not cause health problems or special learning needs.

These two arrangements with too much and too little chromosome material can lead to fertility problems and pregnancy loss. In most families only one of these two arrangements leads to the birth of a child with special needs and sometimes health problems.
A child with the same inversion as the parent: passing on an inversion

If you or your partner pass an inversion on to a 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: if the inversion is paracentric, they would not expect to have any difficulties having children. If the inversion is pericentric, they can have children with standard chromosomes; children with the same inversion as themselves; fertility problems or pregnancies in which the baby has unbalanced chromosomes.

The tests for unbalanced chromosomes are likely to be possible earlier in the pregnancy and more precise than when you were pregnant and generally waits for results will be shorter.

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.

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 had children with this form of Down’s syndrome; no men have.

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 this 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, it turns out that 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.

New, 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. If the inversion is pericentric, it may take longer for a pregnancy to be established because a proportion of their sperm or eggs have unbalanced chromosomes and any embryos may not survive.

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 the couple has a pericentric 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 - of a baby with standard chromosomes, a baby with the inherited inversion, or of a missed or failed pregnancy or a baby with an unbalanced (recombinant) chromosome.

If you have many 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 they may die soon after birth and if they survive how severely they will 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 (afterbirth). You will usually be given the results in three days to two to three weeks. The test itself may make it slightly (about 1 per cent) more likely that you will miscarry, and if this happens, it will occur within a few days of the test.

Your baby’s chromosomes can also be analysed from cells obtained at 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 per cent.

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 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 a full picture of how a baby with an unbalanced (recombinant) chromosome is affected can only be drawn 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 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.

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

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 as their brother or sister’s. 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.

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 rejoined don’t disrupt the smooth running of the genes.

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.

An inversion is found in a baby during pregnancy

Occasionally a baby is found to have an inversion at chorionic villus sampling or at 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 normal chromosomes, the baby’s inversion is a new one (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 the break points are not as clean as they appear. 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 any possible problems.

It is sometimes helpful to analyse the chromosomes again using a sensitive molecular or DNA technology that will show whether particular genes have been left out, added in or disrupted at the break points.
Support and Information

Rare Chromosome Disorder Support Group,
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Join Unique for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you are able to support our work in any way, however small, please make a donation via our website at www.rarechromo.org/html/MakingADonation.asp
Please help us to help you!

You can watch animated videos on paracentric and pericentric inversions prepared by the National Centre for Medical Genetics, Dublin, Ireland by visiting: https://goo.gl/3BBh30
and
https://goo.gl/pfgaqb

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. 2014 V1.1 (PM)

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