

Important points

- **Klinefelter syndrome** (also called XXY syndrome) is one of the more common chromosomal conditions affecting males; they have two or more copies of the X chromosome instead of the usual one copy (47,XXY)
- Affects between 1 in 500 and 1 in 1000 males born each year in Australia
- The range and severity of symptoms depends on the number and distribution of cells containing the extra copy of the X chromosome
- In about 80% of cases, there is a 47,XXY chromosome complement in all of the cells of their body
- In some very rare cases, there are three or four extra copies of the X chromosome in all of the cells -48,XXXXY or 49,XXXXXY – which results in more exaggerated features of XXY syndrome
- When the extra copy of the X chromosome is only in **some** of the cells the chromosomes in the cells of their body, the cells may show two different patterns, ie. some cells with 46 chromosomes and some with 47: **mosaic XXY syndrome**
 - Affects about 6% of cases
 - More rarely boys may have 48,XXXXY or 49,XXXXXY in some cells or have other rearrangements of an X chromosome
 - Mosaic XXY syndrome occurs because of a mistake in cell division that occurs after conception
- In some cases, a diagnosis of XXY syndrome is not made until a boy approaches puberty and some men may never be diagnosed with the condition
- Some affected boys will have more features of the syndrome than others and there will be a difference in the degree of severity of the symptoms between affected boys.
- The most common features include learning difficulties and a tendency to grow at a slightly quicker rate than their peers so that their final height may be more than expected, but is usually within the normal range; reduction in body hair, beard growth and testicular size that can be treated with the male hormone testosterone; while sexuality is normal men with the syndrome may be infertile
- Having a son with XXY syndrome does not appear to be related to either the age of the mother or the father at the time of conception
- Those with 47,XXY in all their cells usually are infertile; assisted reproductive technology (ART) such as *in vitro* fertilisation (IVF) may be of assistance
- Screening and diagnostic testing (where indicated) is available in pregnancy
- Decisions regarding screening and testing during pregnancy should only be made on an informed basis following counselling (see Genetics Fact Sheet 3)

XXY syndrome (also called Klinefelter syndrome), was first described in 1942 by Dr Harry Klinefelter and is one of the more common chromosomal conditions affecting males. An additional X chromosome is found in the cells of these affected boys, giving them two X chromosomes instead of the usual one (see later). The condition affects between 1 in 500 and 1 in 1000 males born each year in Australia.

Characteristics of XXY syndrome

A syndrome is a condition distinguished by a number of features that often occur together. There are a number of features that can be present in XXY syndrome.

Some affected boys will have more features of the syndrome than others and there will be a difference in the degree of severity of the symptoms between affected boys. In some cases, a diagnosis of XXY syndrome is not made until a boy approaches puberty and some men may never be diagnosed with the condition.

Features include

- Learning difficulties which may be the greatest developmental challenge. IQ however, is in the normal range, although it may be 10-15 points lower than that of their siblings
- As children, affected boys are often quieter, less assertive and more passive than other boys and more so than their siblings.
- They may be slower to develop language, motor (movement) skills and emotional maturity than their peers. This does not mean that they will not achieve these things, but will do so at a slower rate.

- As boys with XXY syndrome grow older, shyness, unassertiveness and relative immaturity may persist
- Problems with language, speech and verbal skills generally are the major learning problems for these boys and they may need some remedial intervention at school
- There is a tendency to grow at a slightly quicker rate than their peers so that their final height may be more than expected, but is usually within the normal range
- In around 50% of boys there is some growth of breast tissue at puberty (*gynaecomastia*). This can be distressing and in about 10% of cases, the offer of corrective treatment by plastic surgery is taken up
- Body hair, beard growth and testicular size are all reduced in males with XXY syndrome. The use of the male hormone testosterone has been effective in increasing strength and developing a more masculine appearance. Treatment usually begins around the age of 11-12 years and can be given in the form of patches. Consultation with an endocrinologist (a hormone specialist) will provide further information about testosterone treatment
- Sexuality is normal although men with the syndrome may be infertile

Chromosomes

In each human cell, except the egg and sperm cells, there are 46 chromosomes, made up of 23 pairs (see Genetics Fact Sheet 1).

There are

- 22 pairs of chromosomes that have been numbered 1-22 according to their size from the largest to the smallest

When egg and sperm cells are formed, the chromosome pairs separate so that there is only one of each pair in these cells ie. 23 chromosomes instead of 46.

A baby is conceived when the egg from the mother and the sperm from the father come together. The baby would then have two copies of each chromosome (46 chromosomes in total) just like the parents.

One copy of each chromosome would have come from the mother and one copy from the father.

Sometimes, when the egg and sperm are forming, a mistake occurs so that the chromosome pairs do not separate in an ordered fashion. The result is an egg or sperm cell that has only 22 chromosomes while others have 24 chromosomes.

If an egg or sperm carrying 24 chromosomes combines with an egg or sperm carrying the usual 23 chromosomes, the result would be an individual with cells in which there are 47 chromosomes instead of the usual 46 (Figure 31.1).

Thus there would be three copies of a particular chromosome in the cells rather than the usual two copies (see Genetics Fact Sheet 6).

The chromosome pattern in XXY syndrome

In addition to 22 pairs of autosomes (chromosomes that are numbered 1-22), males usually have two **sex chromosomes**: one X chromosome copy that they receive from their mother and a Y chromosome copy that they receive from their father.

Every egg has an X chromosome and every sperm has either an X or a Y chromosome.

- If the sperm donates an X chromosome at conception, the baby will be a girl who will then have two X chromosomes, one from the mother and one from the father. The chromosome pattern is described as 46,XX
- If the sperm donates a Y chromosome, the baby will be a boy, with one X chromosome from the mother and a Y chromosome from the father. The chromosome pattern is described as 46,XY

XXY syndrome is the result of a mistake in cell division either at the time of conception or soon after.

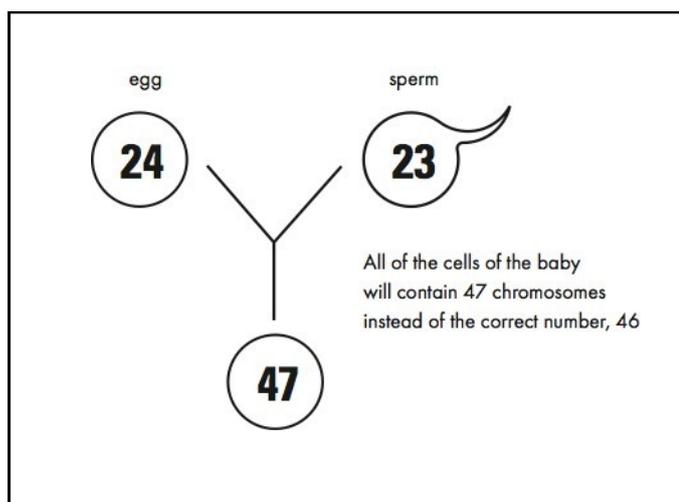


Figure 31.1: When the egg has 24 chromosomes, and the sperm has the usual 23, the baby's cells will contain 47 chromosomes instead of 46. This may also happen in the reverse situation so that the sperm contains 24 and the egg 23 chromosomes.

- Boys with XXY syndrome have a 47,XXY chromosome complement instead of the usual 46XY
 - About 80% of boys with XXY syndrome will have 47,XXY in all cells of the body
- Figure 31.2 shows a picture of the chromosomes from a male with XXY syndrome (47, XXY).

In some very rare cases, males may have three or four extra X chromosome copies: 48,XXX or 49,XXXXY.

Those boys who have one of these less common chromosome arrangements will show more exaggerated features of XXY syndrome and intellectual disability may be present.

When a mistake in cell division affecting the sex chromosomes occurs soon after conception, the chromosomes in the cells of the boys may show two different patterns. This is called **chromosomal mosaicism** and means that some boys who have XXY syndrome have some of their body cells containing 47 chromosomes because of an extra copy of the X chromosome, while other cells in their body have the usual 46 chromosomes. The boy is said to be mosaic for XXY syndrome (see Genetics Fact Sheet 13).

- About 6% of boys or men with XXY syndrome will be mosaic for XXY syndrome
- Rarely there is 48,XXX or 49,XXXXY or other rearrangements of an X chromosome

Who is at risk of having a boy with XXY syndrome?

XXY syndrome results from an error during the division of the sex chromosomes in either the egg or the sperm. Such an event is said to occur sporadically (spontaneously for unknown reasons) and it is highly unlikely to affect further children.

Having a son with XXY syndrome does not appear to be related to either the age of the mother or the father at the time of conception.

This is unlike other chromosomal conditions where there is an extra chromosome copy in the cells, eg. trisomy 21 (Down syndrome—see Genetics Fact Sheet 28), where the mother's age is a factor.

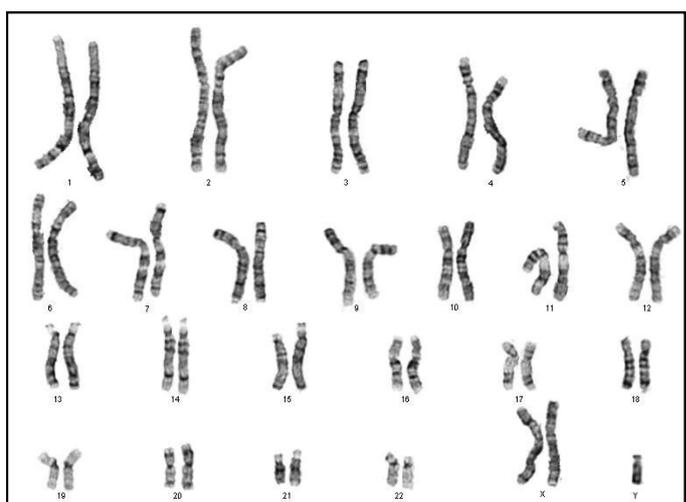


Figure 31.2: Chromosome picture (karyotype) from a male with XXY syndrome (SEALS Genetics, Prince of Wales Hospital, Randwick).

Can XXY syndrome be inherited?

Men with 47,XXY in all their cells are highly unlikely to ever have children naturally. Advances in assisted reproductive technologies (ART), however, are assisting in overcoming their fertility problems.

Those who are mosaic for XXY syndrome and have some cells with the usual 46,XY complement may be able to father children unassisted. Therefore it may be possible for a man with 47,XXY to have a child who also has 47,XXY, but this has not been recorded to date.

Is there any treatment for XXY syndrome?

There is no cure for XXY syndrome. There are, however, a number of treatments that are aimed at reducing the impact of the symptoms of the condition.

In XXY syndrome, the testes do not function normally so that the production of the male hormone called testosterone is reduced. This means that the bodily changes that occur at puberty are impacted. Treatment is with the administration of male hormones (*androgens*) that promote the development of the secondary sexual characteristics (*virilisation*). This treatment starts when the boy is around 11-12 years but does not restore function to the testes and infertility remains. The therapy continues until late adulthood.

The use of testosterone therapy has secondary benefits in helping to improve self-image and self-esteem.

This in turn will impact on a boy's performance at school and his ability to form friendships. Learning problems and language deficits can be helped with expert intervention following a thorough assessment.

Can XXY syndrome be diagnosed before birth?

There are several prenatal screening and diagnostic tests that can be done during pregnancy to determine if the baby is at risk of having, or definitely has XXY syndrome.

- Genetics Fact Sheet 17 provides a summary of the most common prenatal diagnostic and screening tests available
- The prenatal screening tests are detailed in Genetics Fact Sheet 17B and the prenatal diagnostic tests in Genetics Fact Sheet 17C

In addition, preimplantation genetic diagnosis (PGD) allows for testing for XXY syndrome on an embryo that has been created using assisted reproductive technology (ART) such as in vitro fertilisation (IVF). If the embryo does not have the condition, it is transferred to the uterus and allowed to develop normally (see Genetics Fact Sheet 18).

Any consideration of testing before or during pregnancy should only be made on an informed basis following appropriate counselling (see Genetics Fact Sheet 3).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 6, 13, 17, 17B, 17C, 18, 28