Why did this happen?
Most parents of boys with 49,XXXXY Syndrome have a normal number of chromosomes themselves. The cause of the extra chromosomes is most likely to be a mistake that occurred during the formation of the mother’s egg cells. When egg or sperm cells are forming, the two members of each pair of chromosomes usually separate so that each egg or sperm contains 23 chromosomes instead of 46. Not uncommonly, one pair of chromosomes fails to separate. This is called non-disjunction. Non-disjunction is more common in older mothers, but there is no evidence of this among the parents of boys and men with 49,XXXXY. It is not known why their X chromosomes failed to separate properly but it is generally accepted that it is not due to anything that parents did or did not do during or before pregnancy.

Can it happen again?
49,XXXXY is not hereditary and the chances of having another child with a chromosome disorder are not thought to be higher than for anyone else in the general population.

Sexual development
The testicles normally produce the male sex hormone testosterone but among boys with 49,XXXXY, the hormonal function of the testes can vary from nearly normal to severely deficient, for reasons that are not well understood. Where there is testosterone deficiency, the extra X chromosomes are responsible. Some boys are born with small genitals and small, undescended testicles. Commonly, puberty is delayed or remains incomplete. If secondary sex characteristics (growth in penis size, male hair distribution) do not develop, testosterone replacement therapy can be given by implant, injection or gel. Testosterone may have a positive effect on behaviour by boosting activity levels. The additional X chromosomes impair sperm production and so far as is known the semen of men with XXXXY generally contains no sperm. Men may be sexually active, but even with testosterone therapy none has been reported to be fertile.
What is 49,XXXXY Syndrome?

49,XXXXY Syndrome is a rare sex chromosome variation. It only affects boys and men.

Our genetic information is contained in each cell in our body. The genetic material that contains this information is the DNA, tightly coiled and forming 46 rod-like structures called chromosomes. These 46 chromosomes occur as 23 pairs. The first 22 pairs are numbered 1 to 22. The remaining pair are the sex chromosomes: girls and women have two X chromosomes (XX) and boys and men usually have one X and one Y chromosome (XY).

Boys and men with 49,XXXXY have three extra X chromosomes. Until recently, 49,XXXXY Syndrome was considered a variant of Klinefelter Syndrome (47,XXY) but it is now accepted that it has distinctive features.

Key features

These characteristics are shared to a greater or lesser degree but boys and men with 49,XXXXY are first and foremost individuals with their own unique combination of genes and experiences.

Most boys and men will have:

- a variable level of learning difficulty
- some speech difficulties
- incomplete sexual development so that sexual maturation does not develop fully at puberty. Boys may be born with small genitalia
- low muscle tone, causing floppiness
- a characteristic body shape that includes narrow shoulders and chest, long, thin legs and flat feet

How common is 49,XXXXY?

One boy in 85,000 to 100,000 has 49,XXXXY. This means that most midwives, paediatricians and geneticists have never met a boy with 49,XXXXY Syndrome before.

Development

- **Growth**
  Babies usually start out small and thin but in Unique’s experience, once feeding problems have been sorted out, boys usually grow normally and eventually show catch-up growth in childhood or puberty, reaching an above average adult height.
- **Learning**
  The extent of any effect on learning is very variable. In general it is important to have reasonable expectations that your son’s early intervention workers and teachers will help to suggest. Generally, boys with 49,XXXXY chromosomes do better at visual and construction tasks than at tasks that require verbal fluency.
- **Speech**
  Most boys show a delay in speaking that is disproportionate to their learning ability and some have difficulties with articulation. Until speech emerges, families find that signing is a helpful aid to expression. Occasionally boys do not develop speech but this appears to be the exception.
- **Sitting, walking …**
  Boys typically take longer than other children to roll, sit and walk. Once mobile, many boys go on to become physically active and accomplished although some remain floppy (hypotonic) and others lack stamina. One boy has been a special Olympic swimming medallist.
- **Behaviour**
  Babies are typically placid and undemanding but as boys become mobile and interact with their environment their personality starts to emerge. The average boy is easy going and wishes to please and is most at ease in a familiar environment. Episodes of irritability may start to show around toddler age and boys may have a low frustration tolerance. Consistent behaviour management is usually effective.
- **Social skills**
  Despite being sociable, some boys do not take social initiatives and are very shy. They usually need considerable family support and can be prone to anxiety. However, the picture is variable and all boys do not conform to this model.

Medical concerns

- **Orthopaedics**
  Many boys have lax joints and at first need support for walking in the form of insoles, splints or custom-made boots. Some boys have flat feet, causing the ankles to turn in and the knees to meet. Elbow abnormalities are common and many boys have double-jointed or prominent elbows. The two long bones of the forearm (radius, ulna) may be fused, making it impossible to twist the arm at the elbow or fully straighten it.
- **Teeth**
  Dental concerns are common and regular preventative treatment is usually needed. Teeth may emerge late and may be unusually large, small, discoloured or incorrectly aligned.
- **Heart**
  Most boys with 49,XXXXY have a healthy heart and circulatory system but 15 - 20 % are born with a structural heart defect. In some cases, no treatment is needed, while other boys need surgery to correct the fault. Boys usually thrive after surgery.
- **Respiratory infections**
  Chest infections in babies and toddlers are common and can be severe. Some boys outgrow this tendency by mid-childhood as they become more mobile, in others the infections become less severe, but in some the respiratory infections continue into adult life.
- **Seizures**
  Seizures are not a specific feature but are more common than in the general population. They are usually well controlled with medication.