

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 and there are also reports that speech and language may improve.

Sperm production is impaired and it is thought the semen of men with 49,XXXXY generally contains no sperm. Men may be sexually active, but even with testosterone therapy, it is thought they will be infertile.

Why did this happen?

Most parents of boys with 49,XXXXY syndrome have a normal number of chromosomes themselves. The extra chromosomes most likely come from unusual chromosome separation during the formation of the mother's egg cells (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 the X chromosomes do not separate as expected but it is not thought to be due to anything that parents did or did not do during or before pregnancy.

Can it happen again?

49,XXXXY syndrome 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.



Four years old

Parents say

Don't forget to enjoy your little guy, he is so special! Of course there are worries, but also happy moments. He will reach his milestones in his own time.

Try to keep in touch with other families, get in contact with a multidisciplinary team (speech therapist, physical or motor therapist, but also a behavioral therapist can be useful because the inability to speak can induce other behavior).

Inform Network Support

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When you are ready for more information, Unique can help. We can answer individual queries and we also publish a full leaflet about 49,XXXXY syndrome. This leaflet 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. The information is believed to be the best available at the time of publication and has been verified by Dr Martine Borghgraef, University of Leuven, Belgium, by Dr Gerard Conway, paediatric endocrinologist, the Middlesex Hospital, London 2004 and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick 2005. Version 1.1 2020 (AP)

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49,XXXXY syndrome



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 our DNA which is packaged into structures called chromosomes. Most of the cells in our body contain the same set of 46 chromosomes. Chromosomes come in pairs, the first 22 pairs are numbered 1 to 22 and the remaining pair are called the sex chromosomes: girls and women usually 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. 49,XXXXY syndrome was previously considered a variant of Klinefelter Syndrome (47,XXY) but it is now accepted as a separate syndrome.

Key features

These features 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, characteristics and experiences.

Most boys and men will have:

- a variable level of learning difficulty
- some speech difficulties
- incomplete natural 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 is thought to have 49,XXXXY syndrome. This means that most midwives, paediatricians and geneticists have never met a boy with 49,XXXXY syndrome before. Although it's estimated that there are thousands of boys in the world with 49,XXXXY, many will remain undiagnosed and only around 100 have been described in the medical literature. In 2020, *Unique* had 83 members with 49,XXXXY.

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 reaching an average or 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. Speech and language therapies are recommended.

■ **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 49,XXXXY 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. Many 49,XXXXY boys are easy going and wish to please, they are 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. Recent research suggests that frustration and anxiety may be related to speech and communication difficulties, that may improve with appropriate therapies.

■ **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. 49,XXXXY boys may benefit from therapies that help address social difficulties.

Medical concerns

Orthopaedics

'Musculoskeletal' features are common in boys with 49,XXXXY. 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 and ulna) may be fused (this is called radioulnar synostosis), making it impossible to twist the arm at the elbow or fully straighten it.

Some boys have hamstring tightness and others have an abnormal range of shoulder motion. Torticollis has also been reported (muscle tightness in the neck). Hip, knee or elbow dislocation can occur.

Some boys have curvature of the spine (either scoliosis or kyphosis) which may be related to muscle weakness (hypotonia).

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.