

XXYY syndrome



The XYY Syndrome, also known as 48,XYY, is a relatively uncommon sex chromosome variation. Only boys are affected and all of them have two extra sex chromosomes, one extra X and an extra Y. Most typically, boys have the extra chromosomes in every cell in their body, but a few have some cells with a different number of sex chromosomes. This is known as mosaicism and depending on the chromosomal make-up of the other cells will lessen or intensify the effects of the 48,XYY cells.

You might imagine that additional X and Y chromosomes would cancel each other out. In fact, the effects of the extra chromosomes are generally additive. Boys and men show features that are similar to people with a 47,XYY make-up (Klinefelter Syndrome) as well as some of the effects of the 47,XYY constitution.

Until recently, XYY Syndrome was considered as a variant of the Klinefelter Syndrome but families and doctors have become aware that it has distinctive features. A systematic study of XYY had not been undertaken until 2004 but one is now under way in the US under Dr Nicole Tartaglia and Dr Randi Hagerman in the Developmental-Behavioural Pediatrics Departments at the UC-Davis MIND Institute in Sacramento, California. For more information about the project, please contact info@xyysyndrome.org (Borgaonkar 1970; Parker 1970; Grammatico 1990).

The information in this booklet is drawn from published medical studies and from a postal survey of Unique's 34 member families in 2004. References are grouped for ease of reading at the end of paragraphs with references to the *Unique* survey marked (*Unique*).

Main features

Boys and men with 48,XYY share certain characteristics. However, the features are not obvious in everyone and do not affect everyone to the same extent. Many of the typical characteristics are also found in boys and men with Klinefelter Syndrome but in general the effects on learning, behaviour and height in boys with XYY are more marked.

- Vulnerability to social and behaviour difficulties. This varies between individuals, but some boys may be immature, shy, insecure and lack emotional judgement. They may also be prone to outbursts of temper.
- Incomplete sexual development. This may be apparent at birth in boys born with small genitalia and/or undescended testes. It may become noticeable at puberty when signs of sexual maturation fail to develop fully. Many boys, but not all, have a low level of testosterone, the male sex hormone.
- Tall compared with other family members, with long limbs.
- Delay in speech development.
- Some degree of learning difficulty, although this can be quite variable.

Other features

- General developmental delay. This ranges from mild to severe delays. Some boys have problems with fine motor skills while others have more difficulty with development of gross motor skills. Many boys have low muscle tone (hypotonia) in the early years.
- Boys have an increased risk of fractures as a result of osteoporosis unless treated with testosterone.
- Minor anomalies of the skeleton are fairly common, including fusion of the two bones in the forearm (radioulnar synostosis) and a curved fifth finger (clinodactyly).
- Large teeth and other dental anomalies.
- Intermittent puffiness (oedema) of the lower limbs, with a risk of developing ulcers.
- Lassitude and lack of energy.

Other conditions that appear to be more common in boys and men with XXY include heart conditions and neurological disorders, including a hand tremor.



Wayne, with UK comedian Ronnie Corbett.
Men with XXY have a tendency to be tall, but usually not exceptionally so.

What are boys & men with XYY Syndrome good at?

With their strong visuo-spatial abilities and sometimes good memory skills, boys with XYY are relatively good at activities like board & computer games and direction finding. Some have a talent for chess. Among the activities that they enjoy, computer games and television are favourites, closely followed among younger boys and adolescents by sports activities including cycling, walking, swimming, fishing, many ball games including soccer, basketball and baseball, cricket and water sports.

As a group they are also affectionate, friendly and non-judgemental and can be generous with their time, making themselves available to help others in need. They can also be caring, particularly to people with special needs (Visootsak 2007; U).

How common is XYY Syndrome?

No-one really knows how common XYY Syndrome is, but your son's doctors will probably not have met another case before. Although the syndrome seems very rare, it has been described in the medical literature with over 100 boys and men reported. Reported incidence among newborn boys varies between one in 17,000 and one in 50,000, but it is likely that many boys remain undiagnosed or are incorrectly diagnosed. Families affected by the syndrome are not, however, alone. In addition to the information and support that you can receive from *Unique*, there is a dedicated and active email support group for families at:

<http://groups.yahoo.com/group/xyyparentnetwork> and a website at www.xyyysyndrome.org.

As a result of similarities with Klinefelter Syndrome (47,XXY) which is very much more common, some support is also available from Klinefelter organisations and websites.

Why do some boys and men with XYY differ so much from each other?

This is not fully understood but most of the differences are genetic in origin. The unique combination of genes on the other chromosomes plays an important role. Also, it is possible that various genes on the X and Y chromosomes are expressed at different levels in each individual with XYY. The main effect in boys with XYY is assumed to come from the extra X chromosome as the Y chromosome contains relatively few genes and boys with XYY tend to be more obviously affected than boys with XY. Studies so far show that the extra X chromosome has always come from the father, so a boy with XYY has one X chromosome from his mother and the additional XY from his father. In any person with two X chromosomes, only one is switched on in every cell in the body; usually, in half the cells of the body, the X from the father is switched on and in the other half, the X from the mother. Studies so far show that in at least some boys with XYY, this 50:50 distribution is upset and up to 90% of cells have an active X chromosome from either the mother or the father. This could influence the effects of the extra chromosomes on an individual boy (Iitsuka 2001; Zelante 2003).

Diagnosis

XYY pregnancies are usually completely normal so most boys are not diagnosed until after birth and often not until they reach late puberty or adulthood. XYY Syndrome can be

diagnosed during pregnancy by examining the chromosomes from the chorionic villi (the developing placenta) or amniotic fluid. After birth, a sample of blood is taken for chromosome analysis and for FISH tests (analysis using molecular techniques) (Borgaonkar 1970; Nyberg 1994; *Unique*).

First suspicions

Most babies identified in pregnancy are found by chance when an older mother has an amniocentesis. Occasionally a pregnancy serum screening test may show a raised level of alpha fetoprotein (a protein made by the baby that may occur at high levels with certain abnormalities), an early dating scan may show increased nuchal translucency (an increase in thickness and transparency of the skin at the back of the neck) or a mid-pregnancy ultrasound scan may reveal something apparently wrong with the baby.

At birth, some boys have a small penis, undescended testicles or occasionally ambiguous genitals. They may also have other features that suggest a non-specific chromosome abnormality, such as an incurved fifth finger or a single palm crease. In childhood, the first signs that anything may be amiss are usually non-specific, such as speech or learning delay or turbulent behaviour.

Among 21 boys in the *Unique* series, a small number were diagnosed as newborn babies, a further small number as toddlers and two only received their XYY diagnosis as adults. Over half the boys were identified in the early school years between the ages of four and 12.

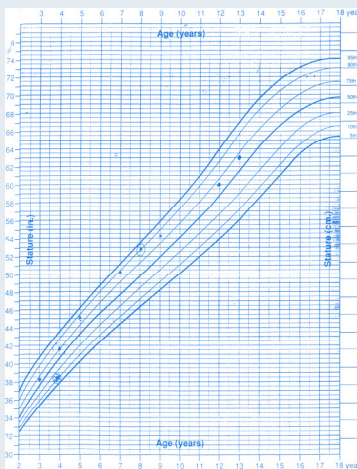
Will a boy look different from other boys?

Most boys with XYY Syndrome look no different from other boys in their family or school. They have a tendency to be tall, but not exceptionally so. If testosterone deficiency develops around puberty their body shape may take on feminine proportions, with narrow shoulders and increased weight around the hips and thighs. This often improves if they are treated with testosterone replacement.

What about growth?

At birth boys with XYY Syndrome come within the normal range of weight and length. Among boys born at term, the range of birth weights in the *Unique* series was 2600g (5lb 12oz) to 3855g (8lb 8oz). Birth length was close to the average at full term of 51cm (20") except for one boy who was 61cm (23.8") long at birth. However, from an early age boys grow noticeably tall and the extra height is most obvious in their long limbs. Boys with shorter than average parents may not be obviously tall but will still exceed their family norm. Most boys reach at least six foot (183cm) and some exceed seven foot (210cm).

Many boys will have their bone age assessed and will be given a predicted range of adult height. Once puberty starts, a constant amount of height (30 cm, 12") is added. Extra testosterone (either naturally around puberty, or given as treatment) hastens the closure of the growing ends of the bones (epiphyses). However, the extra height in XYY boys is not only due to low levels of testosterone but also to genes on the extra X chromosome and possibly also on the extra Y chromosome.



A growth chart to age 13 for a boy with XYYY Syndrome, showing above average height but well within the normal range.

The additional height can cause difficulties for boys who have hypotonia (low muscle tone) as it intensifies the apparent floppiness of movement. It also creates difficulties when buying clothes and once adult height is reached, beds and bedding as well. Some boys also have extremely large feet and need to have special shoes made (Borgaonkar 1970; Linden 1995). In boys with XYYY Syndrome, giving testosterone also increases muscle bulk.

Sex hormones

The key effect of the extra X chromosome is to interfere with production of the male sex hormone testosterone. In embryonic development, a single Y chromosome is enough to ensure maleness. Until around the sixth week of embryonic life, there is no visible sexual differentiation between a developing fetus with XX chromosomes

and one with XY. Around the sixth week, the SRY gene on the short arm of chromosome Y triggers a cascade of events and activates genes on other chromosomes that cause the until then sexless reproductive organ to develop into a testis rather than an ovary. In a 46,XY male, once the testes are mature enough, cells in the spaces between the tubules (Leydig cells) start to secrete testosterone. This causes the penis and scrotum to grow and the testes to descend into the scrotum.

In boys with an extra X chromosome the testicles become fibrous for reasons that are unclear, and in some cases the Leydig cells that make the testosterone are destroyed. The range of testosterone levels varies from very low to normal.

Signs that testosterone production has been low before birth are a small penis and undescended and/or small testes. During childhood or puberty, other signs may emerge: boys may grow breast tissue, the long bones in the arms and legs may grow disproportionately long, and muscles may be less developed than other boys'.

The amount of testosterone in the body is measured from a blood test. In 46,XY males, testosterone is usually produced in response to rising levels of two pituitary hormones, luteinising hormone (LH) and follicle stimulating hormone (FSH). In males with 48,XXYY, levels of these hormones may be high as the pituitary tries to stimulate testosterone production, but levels of testosterone are usually low. This state is called hypergonadotrophic hypogonadism. A protein called SHBG is also measured as testosterone can bind to it and become inactive. If SHBG levels are low, then free testosterone levels may be reasonably high.

A boy with XYYY chromosomes should be under the care of an endocrinologist who will tailor any hormone therapy to his own natural levels of testosterone and its effects on his development.

Testosterone therapy

Testosterone replacement is used not only to allow puberty to be completed but also to prevent some consequences of deficiency, such as osteoporosis and muscle wasting. Treatment has also led to increased physical activity levels in some adolescents. As levels of cholesterol and of red blood cells may rise when testosterone is given, they are usually monitored (Heuser 1999).

How is testosterone given and when?

Before puberty, testosterone levels in boys with XYY are usually normal. It is assumed that boys with a small penis or undescended testes at birth have experienced testosterone shortage before birth, but even this is not certain. This uncertainty means that there is no established protocol for when to start testosterone treatment in boys with XYY Syndrome. Some endocrinologists start all XYY boys on testosterone replacement at a certain age, others base their treatment on symptoms, and others treat boys according to the levels of testosterone, follicle stimulating hormone and luteinising hormone found in their blood. Some endocrinologists will treat XYY males with a short penis with small doses of testosterone in infancy to increase penile length.

Boys with 46,XY chromosomes typically experience a 'mini-puberty' at around 3 months of age. Some endocrinologists treat all babies with an extra X chromosome with three low-dose injections of testosterone in infancy to reproduce this 'mini-puberty'. This practice is controversial because the positive effects are unclear, and the importance of the 'mini-puberty' is also unclear. There are also possible harmful effects on the prostate (Tartaglia, personal communication).

Bones

Bones contain minerals such as calcium to make them dense and strong. To maintain density, the body needs a supply of minerals and hormones, including testosterone in males. If the body cannot regulate the mineral content of bones, they become less dense and more liable to fracture. All boys with XYY can expect to have a bone density scan and if testosterone levels remain low or replacement therapy is not used, the scan may be repeated regularly.

To maintain bone density, boys should take plenty of exercise (weight-bearing exercise three times a week for 30-60 minutes,

Families say ...

" He has started testosterone therapy as monthly injections given by his mum. Puberty started almost immediately, his penis grew, pubic hair appeared and his voice broke. He has become more confident but can be quite up and down, dependent on where we are in the month - age 12.

" Testosterone every three weeks as injections. This helps his mood but he can be up one minute and down the next - adult.

" No treatment as his testosterone was within the normal range. Levels are dropping now so he may soon need some - adult in his thirties.

Puberty

In some boys, puberty develops at a normal time and pace. In quite a few boys, however, puberty is delayed or more typically it starts and then remains incomplete because not enough testosterone is produced.

Occasionally, it starts early. If secondary sex characteristics (growth in penis size, male hair distribution) do not develop or if puberty remains incomplete, testosterone replacement therapy can be given by implant, injection or gel.

The Unique series shows that treatment typically is given from the age of 11 or 12 years and the dose of testosterone is slowly increased to mimic natural puberty. This has not been shown to lead to any increase in aggressive behaviour (Heuser 1999; Tartaglia, personal communication).

starting in adolescence) and eat a healthy diet that provides enough calcium and vitamin D. Children and adolescents get most of their vitamin D from breakfast cereals, meat and butter-type spreads, as well as from oily fish.

How can 48,XXYY affect learning?

The spectrum of effects of sex chromosome variations on children's ability to learn is extremely broad. There is a rule of thumb that with each extra X chromosome, overall IQ falls by 10-15 points – a difference that is quite standard between brothers and sisters with no chromosome abnormality. Many boys with XXY or XYY chromosomes have no discernible learning disability. Others encounter specific problems, particularly in the early years of education and while acquiring the language-based skills of reading and writing. Other boys find it hard to meet the behavioural expectations of a school setting. Boys with 48,XXYY have features of boys with either 47,XXY or 47,XYY and as a group show more difficulties with learning. Overall, around 10 per cent of boys have an IQ within the normal to above-average range, while most have a mild learning difficulty (Fryns 1995; Linden 1995; Tartaglia, personal communication).

A recent study comparing 11 boys and men with 48,XXYY with others with 48,XXXYY or 49,XXXXYY concluded that boys should be offered a comprehensive psychoeducational assessment to discover their strengths and any difficulties. A language-based communication component in their education plan was strongly recommended to address inherent communication problems (Visootsak 2007).

The XXYY Project states that 48,XXYY boys are visual learners who frequently have difficulties processing auditory information. The experience of the *Unique* series supports this, showing that boys are usually better at decoding words than understanding them and that they learn best from visual repetition and strategies to help them to organise their thoughts and ideas. Psychological testing shows that performance IQ is typically higher than verbal IQ, although this is not universally true. Particularly where boys have problems with expressive or receptive language, it is important that visual aids and other non-verbal strategies are chosen.

In general boys achieve more if tasks are broken down into manageable components. Many boys appear to be prone to sensory overload and respond well to a clear learning structure with small group and individual teaching. Most boys are sociable and their wish to please is helpful in an educational setting as is their characteristic determination and strong will. Memory skills

are highly variable but some boys have strong visual memories for skills like route finding.

Although many boys have difficulties that suggest an autistic spectrum disorder (ASD), only a minority are diagnosed with ASD.

Some boys have a hand tremor when they write or try to perform a purposeful task, making handwriting difficult and messy. From an early age they benefit from access to a keyboard and other alternatives to writing.

For more information on learning difficulties in boys with XXY, see the Education section of the Klinefelter Syndrome Association UK website at www.ksa-uk.co.uk.

For information on the learning difficulties of boys with XYY chromosomes, see the *Unique XYY* factsheet.

What about schooling?

The best schooling for your son depends on his abilities and what is on offer locally. Many boys start their education in mainstream (regular) schools, and profit from one to one support being available when needed. They may need to be withdrawn for language activities. As the curriculum becomes more demanding, most boys transfer to a special education setting where their individual needs can be met better. In the *Unique* series, out of 13 families with a son in secondary education or beyond, four were in mainstream schooling, usually with a dedicated resource teacher. All other boys were at a special school or an attached learning centre. The XXY Project is currently developing a model individual education plan for XYY.



With Joanna Lumley

Families

say ...

“ W reads words in newspapers and can write his name & address. He can count money and give correct change if allowed enough time - age 34.

“ C is most keenly motivated to read about sport because it interests him and learns because he wants to be like other boys. His memory is good, he has a good sense of direction and visual learning strategies are most helpful - age 19.

“ A has an extremely hard time writing because by the time he thinks about grammar, spelling and the words, he has forgotten what his sentence was. However, he is working at grade level in mathematics - age 13.

Families say ...

“Max still occasionally finds it difficult to find the right word. His vocabulary is not very advanced and he often used to transpose letters at beginnings and ends of words. Writing things down rather than giving verbal instructions and getting full attention before giving even brief verbal instructions was helpful - adult.

“S speaks very well now. He does not use long sentences but he speaks very clearly and appears to understand at a 10-11 year old level. He has had speech therapy throughout his schooling and it has been very important for his progress - age 17.

“Russell uses long and complex sentences, understands most things and can express himself very well, although his speech is very nasal - age 15.

A recent study recommends that school placement should be decided individually but boys should have contact with normally-developing boys in order to enhance their social skills and to allow imitation and modelling (Visootsak 2007).

How can XXY Syndrome affect speech?

Some boys with either 47,XXY or 47,XYY have a specific speech delay and this is also evident in boys with 48,XXYY. The *Unique* series shows that first words typically emerge between the ages of 2 and 4 but in some boys speech may develop much later than this. Speech therapy should be available through portage, pre-school or early interventions and some boys will benefit from learning to sign until their speech becomes fluent enough for them to communicate their needs and wishes. While a significant minority of boys have a delay in comprehension, most boys show a marked difference between understanding and expression. The typical auditory processing disorder impacts on understanding, so that concepts and instructions need to be delivered singly and possibly reinforced by visual prompts and boys need to be allowed time to process the information they have heard.

Specific difficulties have been recorded in **word retrieval, short term memory, sentence structure, volume, articulation leading to dysarthria** (unclear pronunciation), **dysphasia** (failure to arrange words in proper order) and **dyslexia**. The evidence from the *Unique* series is that while the extent of speech delay is highly variable (first words from 15 months to 14 years), all boys have some speech problems. As adults, men in the *Unique* series were able to express themselves but might prefer to use short phrases, choose from a limited vocabulary and continue to have difficulties with understanding.

Their problems with speaking and auditory processing lay them open to learning difficulties, emotional difficulties and problems with adjustment at school and in social situations. They should receive early and ongoing speech and language therapy, with specific therapies as needed to address oral motor planning deficits and developmental verbal apraxia. Their vocabulary should be built up and their ability to understand stories and sentences of increasing complexity enhanced. They need to be taught how to express their feelings to relieve their frustrations. They may need to be

taught how to interpret social cues, as part of a social skills training programme.

Recent recommendations include that problems with speaking and auditory processing lay boys open to learning difficulties, emotional difficulties and problems with adjustment at school and in social situations. They should therefore receive early and ongoing speech and language therapy, with specific therapies as needed to address oral motor planning deficits and developmental verbal apraxia. Their vocabulary should be built up and their ability to understand stories and sentences of increasing complexity enhanced. They need to be taught how to express their feelings to relieve their frustrations. They may need to be taught how to interpret social cues, as part of a social skills training programme (Visootsak 2007).

How can XXY affect motor skills?

Muscle tone, balance and co-ordination are often affected and may delay the average age at which boys reach their motor skill milestones. In addition, lack of muscle mass can lessen strength and stamina. Hypotonia (low muscle tone) is most significant in infancy and childhood and may improve with exercise and maturity. Hypotonia may persist into adulthood. Occupational therapy and physiotherapy help to improve muscle tone and to advance skills in movement.

While some boys have more severe motor delays, many boys develop into agile movers, but co-ordination problems affect activities such as football and other ball games. In general, adolescents and adults with XXY can stay fit with activities such as walking, cycling, and swimming.

Exercise is important to XXY boys who probably share with 47,XXY boys a tendency to put on weight around the midriff and potentially to develop type II (usually non insulin dependent) diabetes. Regular exercise also helps to build up muscle mass and to preserve bone density which can be compromised by the low testosterone levels. A common problem is that boys tend to tire quickly and may need frequent rests.

The *Unique* series shows that boys:

- rolled over as babies between 3 and 10 months
- sat up without support between 6 and 10 months
- crawled between 9 and 18 months
- walked independently between 12 and 27 months.

Families say ...

“ He dislikes swimming and team sports but enjoyed cycling and walking until his late teens. He’s mobile and active when motivated - adult.

“ Always at the extreme of normal for gross motor skills. He is very mobile and active but runs with a funny gait and is a bit clumsy, unco-ordinated and inflexible - age 15.

“ Fully mobile but tires more easily than other children and lacks shoulder and hand strength and still has difficulty opening packages - age 12.

“ He was late to crawl, walk and sit and slow learning to swim but now has very good football skills, and is an accomplished gymnast - age 11.

Families say ...

“ Alec has been diagnosed with a tic disorder. It’s usually worse when he’s nervous. He has had several different tics throughout the years like obsessively smelling his hands, twirling his hair, biting his nails, leaving his hand on top of his head and pulling his hair out - age 12.

“ It is very difficult to get a blood sample from Thomas’ hands or feet - age 11.

Medical concerns

Boys and young men with XYY are generally healthy. A minority are prone to the medical conditions described below. This does not mean that your son will ever develop any of these, rather that your son’s paediatrician and you can be alert and act promptly if any signs develop.

■ Asthma and allergies

The rate of asthma and allergies in the small *Unique* series is raised, with 6 out of 13 families reporting this as a significant problem. It is not known whether this is a direct or secondary effect of the condition or a chance observation.

Preliminary results of the current ongoing XYY research project show an increased prevalence of both atopy (a tendency to develop allergic conditions) and asthma. Asthma in babies and young children may persist into adolescence, although it appears to be generally well controlled with anti-inflammatory inhaler medication.

It is unclear whether respiratory infections are more common but some boys appear to be prone to chest infections in the winter and these can be severe and need hospital treatment. In some boys, preventive antibiotics have been prescribed to reduce the number of infections. This vulnerability means that all boys should be fully immunised (Tartaglia, personal communication; *Unique*).

■ Orthopaedics

Among boys the most frequent problem is flat feet, which affect 5/13 boys in the *Unique* series. Severity varies and while some boys outgrow their stance, some need orthopaedic insoles and others require special footwear. All boys should have a physiotherapy assessment for this as it may affect the age at which they start to walk and their mobility. In addition, some boys have particular features, including an unusual curvature of the feet and toes. Within the *Unique* series, this was always manageable with manipulation and no boys required surgery.

Radioulnar synostosis (a fusion of the two bones in the forearm, making it impossible to twist the arm and limiting elbow movements) has also been observed and some boys have contracted elbow joints. A variety of different orthopaedic problems has been observed in older men with XYY, including joint stiffness, dislocation of the knees and spinal curvature. This suggests that everyone with XYY should have a regular orthopaedic review (Fryns 1995).

■ Neurological

A few boys with XYYY have signs of neurological involvement. Some have an intentional tremor (their hands tremble when they try to perform a purposeful task) or a general tremor; a few have a repetitive tic; many have difficulties with fine motor skills and co-ordination; and some have seizures (Fryns 1995; *Unique*).

Intentional tremor affects half the boys in the *Unique* series, especially when they are performing intricate tasks or writing. One family has observed that the tremor is worse when their son is taking methylphenidate for attention deficit or hyperactivity (*Unique*).

Seizures are not universal among boys with XYYY, but they are more common than in the general population. Within the *Unique* series there is no typical seizure pattern and it is not known whether seizures are a chance finding. In two out of 34 boys on the *Unique* database, seizures are persistent; one boy experienced a single seizure episode.

In a few individuals, imaging has revealed structural abnormalities in the brain and the fluid surrounding it, but this needs to be further investigated. Agenesis of the corpus callosum (failure of proper development of the broad band of nervous tissue that connects the two hemispheres of the brain) has been observed both in the medical literature and in the *Unique* series (Nyberg 1994; *Unique*).

■ Heart and circulation

All boys with XYYY can expect to have a cardiac review followed by an echocardiogram (investigation and display of activity of the beating heart by ultrasound) should a heart murmur or abnormal heart sounds be found. Overall around eight per cent of boys are believed to have a heart condition (Meschede 1995).

Among the heart conditions that have been found are:

- pulmonary stenosis (narrowing of the artery that takes blood to the lungs)
- persistent holes in the heart, typically small and usually resolving without surgery
- tetralogy of Fallot, where a hole between the pumping chambers of the heart occurs together with pulmonary stenosis, an unusually narrow entrance to the artery that takes the blood to the lungs, and a hypoplastic (underdeveloped) left heart
- thickened heart valves
- mitral valve prolapse (a condition in which the valve between the upper and lower chambers of the left side of the heart allows blood to leak back into the upper chamber). Generally, this is a mild problem and it often produces no symptoms (Meschede 1995; Zelante 2003).

As dental or other surgery carries a small risk that bacteria released during treatment might move into the bloodstream and infect the heart, boys with heart conditions are usually given protective antibiotics before surgery.

Circulatory disorders are seen in many boys and men. Peripheral circulation may be poor, typically and most obviously affecting the lower extremities. One study revealed

Men with XYY describe their behaviour ...

“ Happy and friendly until I get in a temper – Jekyll and Hyde. When things go wrong or I don’t get my own way, I shout and thump my knuckles on whatever is available.

“ Pretty much happy, definitely friendly, sad sometimes, helpful sometimes, moody at times. Get angry at people bossing me around – walk off, slam doors, play loud music, throw things, swear.

“ I am moody, sometimes helpful, sometimes a bit aggressive but mainly towards myself.

a marked restriction and limitation of the capillary network in the lower limbs. This can make taking blood samples difficult especially from the hands or feet. In older men, this has been shown to contribute to ulcers, so careful foot care is imperative. Testosterone treatment has been used to improve the peripheral circulation (Parker 1970; Campbell & Price 1981; Grammatico 1990; Izumi 2000; *Unique*)

■ Autoimmune disorders

There is evidence that boys and men with XYY Klinefelter Syndrome are vulnerable to type II diabetes and to thyroiditis, an inflammation of the thyroid gland. It is not known for certain whether boys with XYY chromosomes are also vulnerable, but they are recommended to have regular thyroid screening. Vulnerability to type II diabetes can be partly managed by weight control.

■ Dental care

Most boys will have an unusual pattern of dental development. In the *Unique* series, 8 out of 13 families reported either missing or extra teeth (especially adult molars), severely decayed teeth or taurodontism, a condition in which the teeth have very large pulp chambers and long roots and where the teeth appear very large. Boys should have regular dental reviews and fluoride protection if their family wishes. They are more than usually likely to need dental surgery and may need antibiotic protection for this (see Heart and Circulation, page 13) (*Unique*).

What support services are boys likely to need?

There are no established programmes yet for boys with XYY Syndrome, but they should have a full evaluation by a developmental paediatrician. Early intervention programmes should be encouraged, to include speech therapy, occupational therapy, physiotherapy, behaviour therapy and early pre-school programmes. Many boys with XYY will not need the full range of therapies, but it is important to have a detailed evaluation of their needs.

Early intervention is known to improve the speech and language outcomes of boys with XYY and may also help with any social and behavioural concerns.

Can XYY Syndrome affect behaviour?

Boys with XYY chromosomes are vulnerable to behaviour difficulties although not all of them will develop problems. Even allowing for ascertainment bias – the families that doctors see and report on tend to cluster at the severe end of the spectrum – the extra chromosomes do commonly appear to impact on behaviour, affecting 11 out of 12 boys in one series and the great majority of *Unique* families. The behaviour difficulties are attributed either to the additional Y chromosome, because they are not seen typically in boys and men with XXY chromosomes, or to the fact that there are two extra chromosomes.

The evidence from *Unique* and from the medical literature suggests that typically, as babies, boys are easy-going and if anything passive. Passivity can become a problem if it continues into childhood and adolescence so that boys need to be strongly encouraged to perform tasks like washing and cleaning their teeth.

As toddlers, boys often seem eager to please, but are easily frustrated, especially when they cannot communicate their needs and wishes, when they face problems they cannot deal with, or when they are thwarted. By early to mid-childhood, a personality unfolds that is typically sweet and loving and among older boys and men a disposition that is happy, friendly, helpful and kind.

Easily frustrated and impulsive, however, boys are prone to mood swings and temper outbursts that can be extreme. They can challenge authority and when swept up in an outburst, boys may be extremely aggressive, destructive, verbally offensive and violent or unmanageable within a conventional educational or social setting. In this context, they may self harm.

Among adults with XYY in the *Unique* series, the extreme tantrums may persist in a milder and more manageable form as men gain greater understanding of their own behaviour and acquire greater verbal fluency. The XYY Project has also found that impulsivity and atypical social interactions are common, although they can be treated with behaviour therapy and medication if needed (Borghgraef 1991; Fryns 1995; *Unique*; Tartaglia, personal communication).

Parents should be prepared for this by learning behaviour management techniques when their son is still young. Parents and their paediatricians may want to seek out parenting classes and behaviour therapy to establish strong skills early before problems emerge.

Behaviour management strategies

- Seek behaviour support at the earliest signs of disturbance. Persist until you find an understanding and competent therapist.
- Clear routines, a calm and supportive environment.
- Music therapy for tantrums.
- Medication. Stimulant and antipsychotic medications can be helpful in controlling extreme behaviours but these medications have side effects and you should have a chance to discuss the pros and cons in detail with your child's psychiatrist or paediatrician.



Certificates of achievement

Outcomes are very dependent on the intervention received and the timing of the intervention. Boys who have received early intervention and appropriate medical treatment have generally done better in their language development and their social development than boys who have a late diagnosis or who do not receive the appropriate hormonal and psycho-pharmacological treatments.

A number of boys show features of Asperger's syndrome or an autistic spectrum disorder. Their behaviour includes a need for routine and inflexibility in adaptation, repetitive behaviours and obsessions with objects. Some boys have lied or fabricated the truth and others have repeatedly run away and need close supervision as they may not understand danger. It is important that caretakers understand the behavioural problems in XYY Syndrome and provide a stable home environment and consistent parenting and guidance.

Some boys have a short attention span, although hyperactivity is not universal. Some boys also have tics or repetitive actions and many have a tendency to chew objects (*Unique*).

A small, recent study that compared the behaviour and personality of 11 adults and adolescents with 48,XYY with 13 others with either 48,XXXY or 49,XXXXY found that boys and men with 48,XYY had better daily living skills, social and communication skills than the other groups. However, men and boys with XYY were especially vulnerable to becoming withdrawn or anxious or by contrast to becoming aggressive.

The researchers suggest that a possible reason for this is that men and boys with 48,XYY have greater opportunities to interact socially because of their more normal cognitive functioning and may find themselves challenged in more complex social settings because of their deficits in communication and social skills. They appear to be vulnerable to obstacles in social situations (Visootsak 2007).

How do boys function socially?

The evidence from *Unique* is that while a minority of boys and men are shy and reserved, most are well adjusted. After early socialising difficulties and immaturity in childhood, some adults with XXY have adapted well and acquired the self assurance for normal adult functioning.

In childhood, many boys do show awkward and immature social skills and may interact better with people older or younger than themselves. As a group, they are sociable and want social contact but may have difficulties initiating and managing it with their peers. They may show poor judgement of other people's feelings and fail to pick up on social cues. They act as if they were some years younger than their actual age and may be introverted at school.

Boys benefit from early social skills training and from active social management, ensuring that they learn to interact with their peers in controlled contexts such as out of school or activity clubs. Within the school setting, they benefit from one to one and group work and are helped by learning skills such as self defence to boost their confidence.

Boys and men with XXY may thrive best in a highly structured environment that appeals to their sense of order. They need to be warned before transitions to lessen any sense of frustration.

As they are typically helpful young men, assigning household tasks may build their self-confidence and daily living skills. Volunteer work placements may raise their sense of self worth and allow them to interact socially in a positive way (Visootsak 2007).

Mental health

Some adolescents and men with XXY develop mental health problems, and specifically bipolar disorder, in which periods of excitement and activity alternate with spells of passivity and depression. It is not known whether mental health problems are caused by the syndrome or whether it is a chance association. Some cases have been described in the medical literature and in the *Unique* series, which also shows that families may have difficulty in getting support and treatment. One family was only given support after their adult son ran away and was found on a motorway on his bicycle. Overall, bipolar disorder is rare in XXY syndrome (Borghgraef 1991; Fryns 1995; *Unique*).

What about food and eating?

Feeding problems may occur but the *Unique* evidence suggests that they are mild and do not affect all boys. Some babies are slow to latch on and suck and those with hypotonia may also be affected by gastro-oesophageal reflux (bringing their feeds back readily). Occasionally boys have difficulty co-ordinating breathing, sucking and swallowing and a small number of boys require feeding by naso-gastric tube for a short while.

Some boys and men are reluctant to chew or find it very difficult and prefer to be fed soft foods. Reluctance to chew has been said to result from a sensory integration problem. Although sensory integration disorders - where children over- or under-respond to sensory stimuli - have not yet been formally documented in XXY, they

Families say ...

“ Terrible sleep patterns. Goes to sleep at 3 or 4 am and is then unable to get up until noon - adult.

“ Obstructive airway disease, sleep apnoea - age 19.

“ Sleeps fitfully, talks and walks in sleep - age 15.

“ A restless sleeper and medication has made it harder for him. He has always an early riser. He listens to classical music in the night and we try to give daily stimulant medication as early as possible - age 12.

“ Terrible problems getting to sleep and staying asleep - age 11.

have been diagnosed in a few individuals with XXY Syndrome (Tartaglia, personal communication). Some occupational therapists have specific techniques which address sensory integration issues and this should be encouraged for XXY boys with sensory issues. This diagnosis is still slightly controversial and trials on the effectiveness of sensory integration therapies are still in progress. Discuss this with your son's paediatrician who may encourage you to use conventional approaches such as speech therapy and traditional occupational therapy in addition to sensory integration therapies.

Many boys and men will have significant constipation. Anticipating this by drinking plenty of water and fruit juice and eating a high-fibre diet will help cope with this problem, but some boys will need medication to soften their stools and to stimulate bowel action (Tartaglia personal communication, *Unique*).

Any sleep disorders?

Sleep disorders have not been systematically studied, but they are believed to be more common in XXY boys.

The *Unique* series suggests that a minority of boys have severe sleep difficulties. These may develop in childhood but more typically progress in adolescence, with many families of adults with XXY reporting that their sons stay up half the night and then are impossible to rouse in the morning. Evidence from the XXY Project also suggests this, with evidence of boys with narcolepsy (episodes of sleep during normal waking hours) as well as excessive sleep talking, sleep apnoea (breathing stops), problems falling asleep or a very rapid descent into sleep (short sleep latency).

Firm, consistent sleep routines from babyhood are helpful but some families will need specialist sleep training and for others medication will provide much needed relief.

Will he ever live independently?

Evidence from the *Unique* series shows adult men living at home and working part-time either as paid workers or on a voluntary basis or mixing work with college training. Favourite occupations include horticulture, agriculture and animal care, but some men have held down jobs in retail or in an office.

They have a varied degree of independence, and most need some level of supervision with their finances. One has a licence to drive a tractor, one had his own driving licence and another was working towards one. In general families reported that their sons are capable of carrying out all the activities needed for personal care but need to be prompted to do so.

Fertility

The additional X chromosome impairs sperm production and the semen of men with 48,XXYY generally contains no sperm and fertility has not been reported with XXYY Syndrome. Testosterone treatment does not affect this. However, although men are not fertile, they may be sexually active (Liu 2003).

Can this happen again?

XXYY Syndrome occurs by chance so it is unlikely that it will occur in a subsequent pregnancy. However, some parents choose to have a test of the baby's chromosomes in their next pregnancy.

Causes

The great majority of parents of boys with XXYY Syndrome have a normal number of chromosomes themselves. The cause of the extra chromosomes is most likely to be a mistake that occurred at conception, when the baby was made, or during the formation of the father's sperm.

When sperm or egg cells are forming, the two members of each pair of chromosomes usually separate so that each sperm or egg contains 23 chromosomes. Sometimes one pair of chromosomes fails to separate. This is called non-disjunction and occurs surprisingly commonly at an estimated one conception in three. The extra chromosomes in boys with XXYY Syndrome are assumed to usually come from the father. In theory, it is possible for the extra Y chromosome to have come from the father and the extra X chromosome from the mother but this has never been shown to occur in boys with XXYY Syndrome. Non-disjunction is more common in older mothers, but not in older fathers and the cause is not understood. There is no evidence that XXYY Syndrome is caused by something the parents did before or during the pregnancy. It has not been associated with environmental or drug or alcohol exposure, illness or medication. It was not caused by anything that parents did or did not do.

Families say ...

“Aggression was a major concern during puberty, but he has been receiving adult dose of testosterone for six months administered weekly by injection and aggression has not increased - age 13.

“If he is with people he respects, particularly men in authority at school or in the workplace, he seems to be able to control his frustrations.

Support and Information



Rare Chromosome Disorder Support Group,

G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel/Fax: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

The XXYY Project

PO Box 2172

Littleton CO 80161-2172 US

www.xxyysyndrome.org | inquiry@xxyysyndrome.org

AXYS - Association for X and Y chromosome variations

www.genetic.org

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.

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 Nicole Tartaglia, MD, fellow in Developmental-Behavioural Pediatrics, UC-Davis Medical Center MIND Institute, October 2004 and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK 2005. Version 2 June 2007. (PM)

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