Understanding Chromosome & Gene Disorders

49,XXXXY

rarechromo.org

49,XXXXY syndrome

Men and boys typically have 46 chromosomes which include two copies of each chromosome, numbered 1 to 22, and two sex chromosomes, an X and a Y. This is known as 46,XY (44 numbered chromosomes and two sex chromosomes). Boys with 49,XXXXY syndrome have an additional three X chromosomes, giving them a total of 49 chromosomes. 49,XXXXY syndrome is less common than other syndromes where boys have more X chromosomes than expected, with an estimated one boy in every 85,000 to 100,000 being affected (Linden 1995; Peet 1998). Given the current world population estimates (2015), the total number of people with 49,XXXXY syndrome would be about 4,000. However, just over 100 boys and men with XXXXY have been described in the medical literature. When this guide was updated in 2015, *Unique* had 62 members with XXXXY syndrome ranging in age from 10 months to 46 years. In 2020, *Unique* had 83 members.

Sources and references

The information in this guide comes from published medical literature and from *Unique*'s family members. The medical literature is quoted with the name of the first author and the date the research was published. Abstracts and some original articles can be found on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). Not all publications are freely available but most of these can be obtained from *Unique*.

Most common features

Most boys and men with 49,XXXXY syndrome will have:

- A variable level of learning difficulties or learning disabilities
- Specific speech difficulties. Understanding is usually better than expression and visual skills are usually more advanced than verbal skills
- Low muscle tone (hypotonia), often with reduced muscle strength and motor skill difficulties
- Underdeveloped sex organs and/or undescended testis at birth
- Atypical development during puberty, with small testicles and low production of sex hormones (testosterone)
- Musculoskeletal features including bone growth changes and lax ligaments
- Infertility

Other features

There are a number of recent publications from groups studying the muscles/bones (Sprouse 2013), brain (Blumenthal 2013), overall features, behaviour, care (Tartaglia 2011) and clinical variability (Gropman 2013) of children and adults with 49,XXXXY. A few more studies have been reported more recently (Mazilli 2016, Burgemeister 2019, Lasutschinkow 2020, and Tosi 2020).

Internet sites and 'e-groups' also allow parents to informally highlight features of their children's development that have not been recorded in the medical literature. Many of these features are also apparent in *Unique*'s offline and private database and are detailed below. Some features may not be caused by 49,XXXXY syndrome but may have occurred by chance or due to additional undiagnosed genetic variations.

- Low birth weight, with catch-up growth during childhood
- High rate of respiratory infections in babies and during early childhood
- Circulation difficulties leading to persistently cold extremities
- Facial features such as low nasal bridge with epicanthic folds (a skin fold of the upper eyelid covering the inner corner of the eye), eyes wider apart (hypertelorism) and slanted upwards towards the hair line (upslanting palpebral fissures). Small chin (micrognathism) that may become larger with age (prognathism). Unusual teeth, including late emergence of first teeth, poor enamel development and missing adult teeth
- Incurved fingers (clinodactyly, most commonly of the fifth finger), small hands, club foot (talipes equinovarus), flat foot (pes planus), overriding toes
- Specific anomalies of bone structure, in particular fusion of the two long bones of the lower arm (radioulnar synostosis)
- Heart condition, most commonly the failure of a blood vessel that links two major arteries of the heart to close after birth (PDA:patent ductus arteriosus)
- Kidney anomalies
- Anomalies in brain structure
- A typical body shape that includes narrow shoulders and chest, long, thin and tapering legs and knees that touch (genus valgus)

Diagnosis

Diagnosis of 49,XXXXY syndrome is usually straightforward once a doctor has agreed to a genetic test. Sex chromosome number variations can be identified in pregnancy by counting chromosomes (karyotyping) in cell samples taken from placental tissue by CVS (chorionic villus sampling), or from fluid that surrounds the fetus (amniocentesis). Non-invasive prenatal testing (NIPT) using cells from maternal blood may be offered depending on the country and region in which you live and if you are seen privately or through a national health service. This test can also be done using a small blood or saliva sample taken from a child at any point following birth. A more recent technique called array CGH (array comparative genomic hybridisation) may be carried out on a sample of DNA (genetic material) taken from the same cell samples. Since this technique analyses DNA sequences rather than chromosome images it gives a much more detailed description of genetic changes.

A review of families known to *Unique* revealed that many boys are diagnosed shortly after birth as a result of chromosome tests run due to their small genitals. Other signs may also suggest the possibility of a chromosome disorder

without pointing specifically to a sex chromosome variation, such as an unusual head shape, unusually formed eyes or ears, broad forehead or a single crease across the palm of the hand. Quite commonly, boys have also experienced intrauterine growth retardation (IUGR, slow growth during pregnancy) and are small for dates at birth.

However, not all boys raise concern at birth and a substantial proportion are diagnosed during their first year after their development shows obvious delay. One *Unique* boy was diagnosed after his repeated respiratory infections brought him to the attention of doctors at 18 months and another boy was diagnosed first with a heart condition. It is likely that increased antenatal testing will identify more affected babies before birth. However, a test may only be carried out if an abnormality is identified during a prenatal scan or if there are other risk factors for genetic abnormalities such as advanced maternal age during pregnancy.

> *"It was hard no doubt, but finding out early meant that we could be proactive in his treatment, instead of wondering 'why' all these issues kept happening. Basically, it helped that we expected issues, instead of being blindsided by them."*

> *"After diagnoses – Love and enjoy your baby as much as you can because you never get the time back that you wasted worrying about the future."*

Pregnancy

Many *Unique* mothers, and reports in medical literature, described pregnancies with 49,XXXXY syndrome babies as uncomplicated and babies were born near their expected due date. Occasionally unusual observations were made including heart arrhythmia (irregular heart beat) in the developing fetus (Duenas 2007; Hadipour 2013). A large number of babies showed growth delay in the womb, most typically in the third trimester, and were found near term to be small for dates. Some mothers had a shortage of amniotic fluid (oligohydramnios) and a few *Unique* mothers remarked both on their low overall weight gain during pregnancy and on a low level of fetal movement. Where placental function was investigated, the growth delay occurred despite adequate blood flow to the fetus.

> *"There was little movement throughout the pregnancy."*

> *"A normal pregnancy. During monitoring, the baby was very quiet and had to be stimulated for a reaction."*

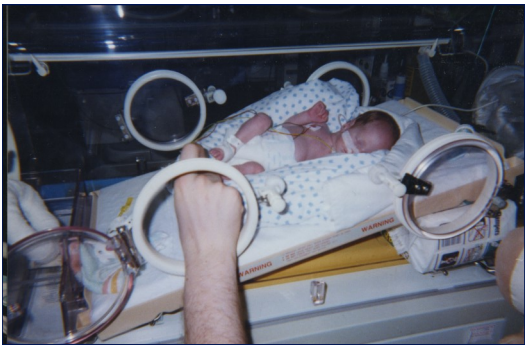
> *"No problems. We were told that the baby was small but as his mother is not large, they took no further action."*

Newborn

Every family in the *Unique* review reported something that concerned them about their baby in the newborn period. A few families took months to convince their doctors that their concerns were not groundless. Birth weights at term ranged from 1.361kg to 3.543kg (3lbs to 7lbs 8oz) and were correspondingly

lower for premature babies born between three and six weeks early. IN a recent study (Tosi 2020) nine 49,XXXXY babies out of 72 were born prematurely at less than 37 weeks.

Apgar scores, which give a general indication of the baby's condition at birth, ranged from 3 to 9 at one minute and from 8 to 10 at five minutes. Around one boy in three described to *Unique* needed resuscitation after birth and spent some days or weeks in special care. Most boys had difficulty latching on and sucked weakly or hardly at all in the early days. Almost all were unusually quiet for a new baby, scarcely cried or just made a soft, cat-like mewing sound or low grunting noise (Linden 1995; Dissanayake 2010).



A 49,XXXXY baby born early at 34 weeks (4 weeks old in this photo)

Feeding

Initial feeding difficulties are common. Most babies have a very weak sucking action and fail to latch on to the breast. Typically, they are sleepy, do not wake up or cry for feeds and if woken for a feed fall asleep again. A switch to bottles of expressed breast milk and/or standard/enriched formula works for some babies but a minority of boys continue to feed too slowly to meet their own nutritional needs and need nasogastric tube feeding for a time. Eight *Unique* boys experienced reflux (the contents of the stomach returns up the food pipe) although this is not usually severe. At least two *Unique* boys were fed for some time via gastrostomy tube (G-tube) directly into the stomach. A move to solid foods may expose a reluctance or inability to chew, partly caused by hypotonia and incorrectly aligned teeth, so that boys prefer puréed foods and may still eat baby foods at the age of three or four years. The typical picture of a reluctant eater with a small appetite, a small and undernourished baby and anxious parents calls for consistent expert feeding support in order to prevent longer term feeding problems. In *Unique*'s experience however, boys overcome their feeding problems by around school age and consume a variety of foods, albeit in quantities that may seem small to their parents. *Unique* has not identified any evidence of feeding difficulties among adults.

> *"At 4.5 months, he was weak and undernourished, so in consultation with the doctors we started using a nose tube. This was a huge help for him and his condition immediately improved. At 10 months, we tried feeding him*

without any aids , but he had a relapse. He didn't want to eat because we had probably pushed him too hard and his outlook on eating became very negative. He then practically starved himself by being 'scared' of food. We then decided, with the paediatrician, to have a gastrostomy placed (a tube is placed so that food arrives directly in the stomach). This turned out to be the ideal solution, as it was invisible and it didn't hurt. He fed through this tube until his fourth year of life. During this period, with his school, we taught him to eat normally. This was a huge struggle, but we did it. Now he is eating well and with pleasure and likes to taste new things." *Age 4 years*

6 months old

Growth

A typical baby with 49,XXXXY syndrome starts out relatively small and thin and the growth pattern is variable. The average birth weight is below the 10th centile and average length is between the 25th and 50th centile. Slow growth with delayed bone age is considered typical but in *Unique*'s experience, once feeding problems have been sorted out, boys usually grow normally as babies and children and eventually show catch-up growth in childhood or puberty, reaching an average adult height in the top quarter of the population. However, growth hormone deficiency has been found (Borghgraef 1988; Haeusler 1992; Sijmons 1995; Peet 1998). *Unique*'s two oldest members are both 185 cm (6'1") tall but the mean stature of 49,XXXXY males from the medical literature has more recently been described as below average (Tartaglia 2011) or average (Blumenthal 2013).

Development

Boys with 49,XXXXY syndrome will usually take longer than other children to reach developmental milestones such as rolling, sitting and walking but the great majority will eventually achieve them. Boys in the *Unique* series rolled over on their own or sat unaided between the ages of 6 months and 1.5 years, crawled between the ages 1 - 3 years and walked at 1.5 - 5 years.

"Where he is at now is GREAT. We used to get so discouraged by his delays but now, when he does accomplish a milestone, we are thrilled and he is so proud of himself. We love his high self esteem and his tenacity to keep trying. He is a really funny kid – he likes to play jokes, like hiding from us to 'scare' us and pretending to put his pants on his arms or his shirt on his legs and say 'What happened?'." Age 4 years

Outlook

After early childhood, most boys with 49,XXXXY are generally healthy. Any birth defects do not usually affect vital organs or life expectancy. In childhood many boys have severe respiratory infections or asthma and these may continue into adult life. A minority of boys also have severe and complex heart conditions needing surgery. The longer term outlook for adults is hard to predict because so few boys have been followed for long enough. *Unique*'s oldest member (who has a mosaic chromosome make-up with some 49,XXXXY cells and some 48,XXXY cells) is a healthy 46-year-old (2015). A number of adults are also described in medical literature, most recently, a man diagnosed at the age of 54 (Collet 2014).

Appearance

Most boys with 49,XXXXY syndrome have a distinctive facial appearance, both as babies and as they grow older. Typically, boys look wide-eyed and round-faced, with a chin that is small in babies but may grow to become a chunky jaw in adolescence. Their head may be small but is in proportion to their stature. It may take on an unusual shape, most often square, and they may also have a short neck. The skull in babies who lie still for long periods may mould to flatten at the back of the head. Eyes may be wide apart, they may have a low nasal bridge with epicanthic folds, eyes that slant upwards and low set ears. Six *Unique* boys had skin tags on their face that were either removed or fell off naturally; one boy described in the medical literature had skin tags on his bottom (Peet 1998) and one on his ears (Hadipour 2013). In childhood, boys often develop a stature that includes a narrow chest and shoulders, long, thin, tapering arms and legs with knees that meet. Boys may also have small/flat/club feet. Many *Unique* families have also noted hand and finger anomalies; seven *Unique* members have clinodactyly (incurved fingers) and this is common in boys described in the medical literature; five had small hands, one had an unusual thumb placement and three had a single palm crease.

Genitals and puberty

Sex differentiation starts in the sixth week of the life of a developing embryo, a process triggered by a gene (SRY) on the Y chromosome. Since 49,XXXXY boys have a functional Y chromosome this process does start but when extra X chromosomes are present, the process may not continue as it should. The cells in the developing testes may not produce enough of the male hormone testosterone for the penis and scrotum to grow to their full size at birth or for the testes to move down completely into the scrotum. Sometimes the testosterone-producing cells are destroyed. This diminished functional activity of the testes is commonly termed hypergonadotropic hypogonadism and is identified by high levels of follicle stimulating hormone (FSH) and luteinising hormone (LH) together with low levels of testosterone. However, for reasons that are not well understood, the hormonal function of the testes can vary from

nearly normal to severely deficient. The spectrum of effects is broad, ranging from a barely noticeable difference in penis size at birth and undescended testes to ambiguous genitalia. Other findings may include hypospadias, where the hole usually situated at the end of the penis is misplaced on the underside, transposition of the penis and scrotum and absent testes. For some boys with hypospadias surgery helps to achieve a more normal urinating position. Twenty two *Unique* families mentioned a genital anomaly but only one identified hypospadias.

Most boys with 49,XXXXY start puberty naturally, but their testicles do not produce enough testosterone hormone to complete puberty. They should be evaluated by an endocrinologist to discuss treatment with testosterone replacement therapy. During puberty, other signs may emerge: boys may grow some breast tissue, the bones in their arms and legs may grow disproportionately long, and their muscles may be less developed compared with those of other boys. In addition to enlarging penis size, testosterone will reduce any breast development, improve muscle bulk and protect against osteoporosis (loss of bony tissue) as well as help control eventual adult height. Some families believe that it helps with behaviour management but others observe an increase in aggression. Other effects noted by families include an increase in activity and sociability. An endocrinologist will be able to discuss the effects of testosterone treatment. It is thought that, even with testosterone therapy, boys with 49,XXXXY are infertile.

Hormonal replacement therapy is also thought to increase expressive language in 49,XXXXY boys as well as increase sociability and so may also have an impact on symptoms of anxiety and frustration (Galasso 2003; Linden 1995, Samango-Sprouse 2019). In a recent study of 72 boys with 49,XXXXY (aged between 3 months and 19 years), 54 were receiving testosterone replacement therapy (Tosi 2020).

Ability to learn

A boy's ability to acquire academic skills will be affected, but the extent is extremely variable. Just how much support a child needs will become apparent with time but in general it is important to have reasonable expectations which early intervention workers and teachers will help to indicate. As a general rule, boys with 49,XXXXY syndrome perform better at visual and construction tasks than they do at tasks that require verbal fluency. The difficulty that many boys experience with hypotonia and fine motor control (see below) may add to their delay and the specific arm limitation caused by radioulnar synostosis (fusion of the two bones in the lower arm) may affect their writing abilities. The experience of *Unique* parents is that by 2 or 3 years, boys can hold a brush or pencil and scribble and by five or six years they may be able to write letters and eventually their own name, although they may be more at ease copying or joining up dots than generating forms independently. These skills will emerge more slowly in some boys and it is important not to put them under too much pressure

to achieve as this can cause frustration and difficult behaviour. *Unique* parents noted that their sons with 49,XXXXY syndrome learned to read at 4 - 9 years and write at 5 - 9 years. Some boys may always have difficulties and not achieve independent reading skills. Many boys are described as having a good memory, especially for visual mapping and images. Their relative visual strength is good for computer work and games.


4 years old

In terms of personality, as a group they are determined and try hard. Most boys are sociable and they like to perform as well as their classmates and to please their teacher. Among boys of secondary school age and older, some are able to read and write a little but they may need prompting and support. They may acquire enough skill at a computer to play games and use word and image based programmes.

In general, the level of learning difficulty can vary from mild to severe. Early studies assumed boys to be 'universally cognitively impaired' meaning that their overall brain function was thought to be reduced with reports describing IQ's ranging from below average to severely intellectually disabled. However, these assessments relied heavily on verbal output and boys with XXXXY syndrome struggle with verbal skills and language formation. More recent studies have identified non-verbal IQ and visual perception to be within the average range in some boys with 49,XXXXY highlighting previously unappreciated areas of strength in cognitive skills (Gropman 2010; Gropman 2013). Boys with 49,XXXXY syndrome may also be diagnosed with other disorders that can affect their ability to learn. Two XXXXY *Unique* members have been diagnosed with autistic spectrum disorder, two with ADHD and one with dyspraxia.

Speech and communication

Speech and language development is affected in almost all boys. Most boys show a distinct delay in acquiring words that is disproportionate to their general ability to learn and some also have difficulties with articulation or difficulties with motor planning of speech (called apraxia or dyspraxia). Thirty *Unique* members identified their child as having a moderate to severe speech delay or problem. Children began to speak between the ages of 1 - 4.5 years, seventeen *Unique* families mentioned their child benefited from the aid of a speech therapist and fourteen learned a form of sign language. Many boys learn to sign competently as toddlers and young children and progress to a mixture of signing and speech. In almost all cases known to *Unique*, understanding is far better than expression. Occasionally boys do not develop speech but this appears to be

exceptional (Borghgraef 1988; Lomelino 1991; Sijmons 1995; Linden 1995; Peet 1998). There are many reasons why speech and communication may be affected and *Unique* has produced a guide to communication which can be freely downloaded from their website.

“ *He understands everything, but can't repeat a word back to you.* ” - Age 3.

“ *He speaks unclearly and gets annoyed when you don't understand instantly.* ” - Age 4.

“ *When he is unsure what's been said, he pretends not to hear or says something irrelevant. He used to shake his head to indicate a negative, saying 'It's hot' and shaking his head to mean it wasn't.* ” - Age 4.

“ *His speech therapy has been hopeless as he took too long to get to know and trust new people.* ” - Age 8.

“ *Words he learned recently are clearer than those he learned long ago.* ” - Age 10.

“ *He expresses himself perfectly.* ” - Age 12.

“ *His speech is still improving.* ” - Age 35.

Gross motor skills and mobility

Boys with 49,XXXXY experience gross motor delay and co-ordination difficulties. In addition, some also have low muscle tone (hypotonia) and hyperextensible (bendy) or contracted joints, unusually small feet and motor planning difficulties. Standing and walking with the support of an adult or a frame is often achieved by 2-3 years and while some boys remain cautious on uneven surfaces, others become confident walkers and cyclists. Many boys go on to become physically active although others show a lack of stamina. One 49,XXXXY boy has been a special Olympic swimming medallist. All boys benefit from physiotherapy from the earliest months and many need special boots, insoles, splints or braces to support joints in the lower limbs. In some boys the hypotonia resolves during childhood but they may continue to need the support of standing and walking frames. Eighteen *Unique* members were identified as having hypotonia, eight had club foot while six required surgery on their feet. Seven *Unique* members were described as having small feet, thirteen mentioned misshapen feet and/or toes and eight had poor blood circulation to their hands and feet.

“ *Due to the flexibility of his elbows, his arms often give way while crawling. His balance is fairly poor, so he will often steady himself with one hand when sitting.* ” - Age 3.

“ He ran with both feet off the ground at 3, jumped soon afterwards and recently started riding a bike with training wheels. He LOVES to dance and run and chase his friends. ” - Age (almost) 4.

“ He loves all activities except for swimming. He rides a tricycle but with his limited wrist rotation finds it hard to catch a ball. When he falls and puts his arms out, his arms often fail him and his head throws forward and meets the ground. He wears a leather padded helmet for play. ” - age 6.

“ We encourage him to try many activities. He trains with a local football team, tap dances and has ridden his bicycle alone since he was 7. He has swum 50 metres and copes with his elbow limitations. He has completed a local triathlon: swimming 40m; cycling 800m; running 600m. ” - age 10.

“ We do a program called “perceptual motor development”. PMD is 2 hours, once a week, where the first hour is “gym” time and they work on both fine and gross motor skills, the second hour is in the pool and they work on water skills. PMD is the program that I credit the most for helping him meet his potential. It is focused on just him and his needs. The water portion of PMD has helped his muscle tone improve so much he is not considered low tone anymore. ” - Age 4.

Fine motor skills

In *Unique*'s experience, most boys will need some occupational and physiotherapy in the early years to improve their fine motor skills. While hand-eye coordination may not be significantly affected, some boys have motor planning difficulties and boys with lax joints in the arms and hands will need additional practice to master actions requiring strength. Boys with radioulnar synostosis (fusion of the two long bones of the lower arm) will also have limited arm and hand movement, affecting the twisting, turning and scooping actions that they need to feed as well as to dress and undress themselves.

Medical concerns:

Respiratory infections

In *Unique*'s experience, respiratory tract infections are a very common finding, affecting 25 of the 56 boys in the series. They typically start in the second half of a baby's first year and lead to frequent hospital stays throughout early childhood. Croup, bronchiolitis, bronchitis and recurrent pneumonias are all common and while some boys are diagnosed with reactive airways disease or asthma there is no evidence that an atopic or allergy tendency is more common than in other children. One boy who experienced a dozen episodes of pneumonia before the age of 4 was found to be deficient in the antibody immunoglobulin A (IgA). Babies with hypotonia and those with gastro-oesophageal reflux may be vulnerable to pneumonia but the extent, duration through childhood and severity of the respiratory illnesses are remarkable among boys with 49,XXXXY syndrome. The pattern of eventual recovery is uneven: while some boys outgrow their tendency to pneumonia as they become more mobile and certainly by mid-childhood and in others the infections become less severe, some boys continue to experience severe respiratory infections or asthma as adolescents and adults (Linden 1995).

Heart

Most boys with 49,XXXXY have a healthy heart and circulatory system but because it is known that between 15 and 20 per cent of boys are born with a structural heart defect, a thorough cardiac examination is recommended. The most common structural faults are a persistent fetal arrangement that leaves open the blood vessel (ductus arteriosus) that leads from the aorta to the artery that leads to the lungs (PDA: persistent ductus arteriosus); persisting or large holes between the two sides of the upper or lower chambers of the heart (atrial septal defect – ASD or ventricular septal defect – VSD); pulmonary stenosis, an unusually narrow valve in the artery that takes blood to the lungs. In some cases, no treatment is needed, while other boys will need surgery. A smaller number of boys have a more complex heart condition such as tetralogy of Fallot, which consists chiefly of pulmonary stenosis and a hole between the two lower chambers of the heart (Karsh 1975; Peet 1998; Pai 2003). Seventeen *Unique* members are known to have experienced some form of heart anomaly, five of whom underwent surgery.

Kidneys

Most boys have two kidneys of a normal size that function well. However, because it has been observed that a small percentage of boys have some disorder of kidney structure, a renal scan is recommended. When there are abnormalities, most commonly, one kidney is markedly smaller than the other and it may not function correctly. On occasion both kidneys are small. Eight *Unique* members mentioned that their child had a kidney anomaly. Renal

microlithiasis (formation of minute hard masses in the kidney; Hadipour 2013) and proteinuria (increased quantities of protein in urine; Okuyama 2004) have been reported in case studies.

Circulation

There is evidence that in some boys the circulation to the extremities, particularly the legs and feet, is affected. A number of *Unique* families noted a marked tendency to cold and discoloured hands and feet, particularly during cold weather (Hecht 1982). Blood vessels may also be small, making it hard to take blood samples, particularly from babies.

> *"His hands and feet go cold and blue. His body temperature drops very low and he seems unable to control it. When this occurs, we keep him warm and observe his temperature carefully. If it stays low for more than 20 minutes, we wrap him in a tinfoil blanket and take him straight to hospital."*

Seizures

Although seizures have been described in association with 49,XXXXY syndrome it is not the experience of *Unique* that they are common or typical, and they are not commonly reported in recent medical literature. However, four out of 62 *Unique* children have been reported to have had seizures which are controlled with medication (Pallister 1981; Hecht 1982; Linden 1995). If seizures are present, treatment by a neurologist is important.

Brain

Following diagnosis, boys/men with 49,XXXXY syndrome may be given a brain scan. A variety of unusual findings have been reported in a small percentage of boys including: an underdeveloped band of nerve fibres between the two hemispheres of the brain (hypoplasia of the corpus callosum) and enlargement of the fluid-filled ventricles within the brain as well as Chiari malformation, a condition in which the cerebellum part of the brain protrudes into the spinal canal. Cortical atrophy has also been observed (degeneration of the outer layer of the brain). One *Unique* member experienced an acute episode of progressive brain stem dysfunction with effects on speech, balance and swallowing at the age of 12 (Pallister 1982; Haeusler 1992). Recent reports in medical literature have also identified white matter abnormalities that may be related to cognitive function in 49,XXXXY boys (Hoffman 2008, Blumenthal 2013), although the significance of these small white matter abnormalities is not clear and they do not typically increase in size or number with age. An overall reduction in brain volume was also identified as well as a high rate of minor skull deformities. There are three case studies in the medical literature of boys with 49,XXXXY who have microcephaly (a neurodevelopmental disorder defined by a small head circumference), two *Unique* boys were also reported to have been born with microcephaly.

Palate

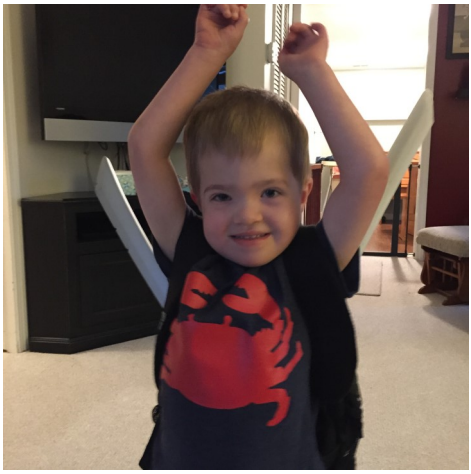
Part of a child's newborn examination will be a check for a cleft in the palate. Boys with 49,XXXXY do have an increased occurrence of clefts of the hard or soft palate and some boys have an unusually high, but intact, roof to the mouth. Among boys with a high palate, expert feeding advice and sometimes a specially adapted teat may help feeding. Three *Unique* members were reported to have been born with a cleft palate. It is also important for boys with XXXXY to be evaluated for a condition called velopharyngeal insufficiency (VPI), which can affect palate function and speech without defects in the hard palate. An otolaryngologist (or Ear, Nose, and Throat) or palate specialist will be able to perform this evaluation.

Bone structure

Boys with 49,XXXXY may have specific and unusual skeletal features. In many boys, including seven *Unique* members, the two bones of the lower arm in one or both arms are fused at some point (radioulnar synostosis), making turning and twisting movements difficult and limiting movement of the forearm. It is thought that the two bones fail to form separately (Tsai 2017). A recent research publication reporting musculoskeletal features in a group of children (age 3 months to 19 years) with 49,XXXXY (Tosi 2020) identified 46 out of 68 children as having clinical signs of radioulnar synostosis (that's 67%). 'Nursemaid's elbow' (radial head dislocation) and clinodactyly (curvature of fingers) have also been reported (Burgemeister 2019). It has also emerged that among adults with 49,XXXXY syndrome, the articular cartilage (the tissue covering the ends of the bones) starts to wear early, especially at the elbows (Pallister 1982; Linden 1995; Sijmons 1995; Peet 1998).

Spine

Scoliosis – a sideways spinal curve – is more common in children with hypotonia and is evident in some boys with 49,XXXXY, particularly those over 13 years old. Scoliosis may improve with age as hypotonia resolves. Six *Unique* members have scoliosis. There have been three case reports in the medical literature of babies with 49,XXXXY and scoliosis (Muis 1982; Wikiera 2009; Hadipour 2013). Tosi 2020 reported 13 out of 70 children with 49,XXXXY as having scoliosis and 8 children out of 66 as having kyphosis (curvature of the spine).



Joints

It has been estimated that one baby or young boy in three with 49,XXXXY syndrome has extremely flexible joints and will need support from custom-made boots, splints or braces for standing and walking. Shoulders, elbows, wrists and thumbs tend to be hyperlax and this affects the ability to take weight on the arms when crawling. Congenital hip dysplasia (leading to easily dislocated hip joints) is frequently found and many boys have a characteristic stance in which their knees touch and their feet, which are typically flat, splay out.

An extremely rare condition, congenital knee dislocation, has also been found in boys with 49,XXXXY syndrome. Club foot (talipes equinovarus), in which the front part of the foot commonly turns inwards and downwards, can also occur and if it does not respond to splinting, will require surgery. Toes may be crooked and override each other. Joints may need splinting at least for part of the day to improve function and all boys will benefit from physiotherapy. There is some evidence that joint laxity may contribute to an early decline in mobility among adult men with 49,XXXXY.

Tosi 2020 reported that 32 children with 49,XXXXY out of 48 assessed, had ligamentous laxity which is better known as generalised joint hypermobility. Further observations included that 21 out of 50 children had hamstring tightness, 14 children out of 40 had an abnormal shoulder range of motion and 22 out of 68 had torticollis (tightened neck muscles).

Teeth

Dental concerns are common, affecting 13 boys in the *Unique* series, and regular preventative treatment is often needed. Baby teeth tend to emerge late, frequently not appearing until after the first birthday. When they do appear, either baby or adult teeth may be unusually large, small, discoloured or incorrectly aligned. While some of these features are seen in boys with a palate anomaly, they are also seen in boys with normal palates. Because of a tendency to decay, with deficient enamel and in some boys abnormal dentine as well, your dentist may recommend additional fluoride, as well as sealing or capping the molars. A jaw X-ray can be carried out to establish whether adult teeth are missing (Hecht 1982). Orthodontia is also often needed.

Hearing

Boys may be prone to develop glue ear (where the middle ear becomes filled with fluid instead of air which may cause dulled hearing) and suffer ear infections. Boys should have regular hearing tests and if necessary short term grommets or longer term T-tubes will be fitted to equalise air pressure inside and outside the

middle ear and to improve the function of the ear drum. Permanent hearing loss is not a documented feature of 49,XXXXY syndrome, although one *Unique* member has a severe hearing impairment and three had hearing problems not associated with glue ear.

Vision

There is a report in the literature of a 26-year-old adult with severe myopia (short sight) and one of the standard chromosome textbooks states that progressive, severe short sightedness may occur in 49,XXXXY boys, even causing blindness. However, visual impairment is not commonly mentioned in case reports or reviews of the syndrome. *Unique*'s experience with its adult members is that vision is normal and long sight and abnormal alignment of the eyes (strabismus) are both common among children (Sarto 1987; Peet 1998). Five *Unique* members are known to be long sighted and two are short sighted, six members wear glasses. One member had eyes that diverge slightly and one had unusual shadows across his pupils. A recent case report describes a boy with high myopia (severe short sightedness), the extent of his visual impairment was diagnosed under anaesthesia and after he was prescribed suitable glasses his parents noted a significant behavioural change (Qureshi 2007).

Behavioural concerns:

Behaviour

In *Unique*'s experience, many boys show similar patterns of behaviour. As babies they are typically placid and undemanding and may have a characteristically faint, weak cry. As they become mobile and interact with their environment, their personality starts to show and boys with 49,XXXXY syndrome are commonly described as easy-going, social with a sweet sense of humour and a wish to please. Boys are most at ease in a familiar environment and adapt a little slowly to new social challenges, so may initially appear timid and shy with strangers, and may hide their faces. However, their gentleness and pleasant personality makes them popular in pre-school educational settings where they may find themselves treated as the group favourite because of their diminutive size (Borghgraef 1988). Against this pleasant background, episodes of irritability start to show around toddler age as frustration usually at their inability to communicate becomes apparent. Many boys have temper tantrums and exhibit a low frustration tolerance and resistance to changes in routine. They may hit, throw, lash out at other people, throw themselves to the ground, and have some self-harming behaviours. Families need professional support and many have tried both behaviour management techniques and a range of medications. Parents of older boys suggest that the most effective treatment is a consistently applied behaviour management plan with in-built rewards for good behaviour. However, medication may be helpful for behavioural difficulties from childhood through adulthood.

Some parents of boys around puberty have noted an improvement once testosterone replacement therapy is given. In one boy tantrums proved unresponsive to treatment. In two boys, autistic features were diagnosed at follow-up, calling for a structured daily routine and specific support (Borghgraef, personal communication). Some *Unique* families have also noticed features of obsessive or compulsive behaviour and six *Unique* families noted that their child had a tendency to self harm or hurt others.

> *"He has sudden surges of anger, followed by apologies. Something inside sparks the anger but it can also be sparked by perceived conflict or a personality clash. He shouts, stamps and walks out but then reflects, calms down and says he is sorry."* - Age 35.

> *"Between seven and nine, he began to get frustrated with himself if he was unable to complete a task easily. We showed him how to breathe slowly and count to 10, and also to blow down 10 finger candles, one in turn."* - Age 10.

> *"He gets very nervous at times although he is much better than when younger. We take our lead from him rather than impose our ideas, which has made him much more secure."* - Age 8.

> *"He was very compliant as an infant, but from the age of 2 has become independent and headstrong. He knows what he wants and has the drive to succeed."* - age 4.

> *"When he is really upset, he'll bite himself. We've recently learned to whisper 'Take a break, buddy' and breathe deeply in his ear until he takes a breath too and this seems to be working well. What helps most is choices. Giving him a choice for almost everything has really lowered his frustration level. For example, if he wants to go for a walk, I ask 'Should we walk to the park or to the shops?' 'Should we wear your sandals or your tennis shoes?' Giving him as many choices as possible makes him feel more in control (I think) and very proud that he has created our fun."* - Age 4.

> *"He gnashes his teeth when he is tired. He needs a lot of attention but at the same time he can sit and play with someone very calmly and quietly. As a baby, he was very quiet. The older he became, the more difficult he got. He became headstrong and will do anything to get his way. We have experienced that you have to be persistent and consistent, repeat a lot and work with a detour. If you make it too direct, he gets scared."* - Age 4.

> *"He didn't move around until he was two years old and didn't walk until he was 3½. He wasn't able to do anything wrong so he didn't learn what was and wasn't acceptable behaviour. I think this still has a lot to do with the way he behaves."* - Age 4.

A recent study (Lasutschinkow 2020) of 69 boys with 49,XXXXY revealed some interesting insights into behaviour. A lower level of communication abilities and social cognition (how people process, apply and store information about other

people and social situations) was identified beginning in preschool. However, children were also identified as having social awareness and motivation for social activities. Anxiety was also identified during preschool years and increased in severity as boys became older. Internalising problems seems significant.

Although some boys do not have behavioural concerns, others do struggle with emotional control. Social difficulties may be related to language based difficulties rather than other neurodevelopmental disorders like autism.

Lasutschinkow and colleagues suggest that behavioural difficulties are observed in 49,XXXXY boys more so than in neuro-typical boys at school age. School age 49,XXXXY boys may be more prone to internalizing problems (they may have actions that direct problematic energy toward themselves) or externalizing problems (actions that direct problematic energy toward other people) and they may experience thought problems. The behavioural difficulties indicate that many of the externalizing symptoms may be a result of anxiety rather than rule-breaking or aggressive behaviour. Social motivation and social awareness were described as less severely affected than social cognition and communication, which indicates that while boys with 49,XXXXY may appear less social, they have some motivation to be social. The authors suggest that social anxiety may not be directly contributing to social communication difficulties and that language difficulties may contribute to anxiety.

In this study, with the exception of thought problems and anxiety, behavioral symptoms were found to lessen from school age to adolescence. In addition, some 49,XXXXY boys were found to have difficulties with working memory. The authors suggest that boys with 49,XXXXY may benefit from being evaluated for ADHD with possible consideration of appropriate medication (although it's important to evaluate potential influence on anxiety).

Treating anxiety at an early age may be important to help minimise behavioural difficulties as boys age. Speech and language therapy may help lessen anxiety, and help behavioural and socialising difficulties. The authors state that boys with '49,XXXXY should be placed in school programs that allow for interaction with neurotypical peers in order to promote desired behaviors and increase peer-to-peer communication'.

Toilet Training

Boys may be late to become clean and dry but in *Unique*'s experience they achieve day and night time control by mid-childhood, between the ages of 1.5 and 6.5 years. However, this control may be insecure and one *Unique* boy showed regression in mid-adolescence.

Social skills

Despite their sociability, 49,XXXXY boys do not typically take the social initiative and often behave with timidity in new situations. They are sensitive to environment and usually need considerable social support from their family.

Some boys are prone to anxiety and in the early stages of a new situation or relationship need considerable social support. The parents of older boys counsel that it is important to listen to their opinion: they will tell you when they have had enough of a social situation. Anti-anxiety medications and drugs to increase attention span have worked well in some boys (Borghgraef 1988; Sijmons 1995). Lasutschinkow and colleagues state that, although social cognition and social communication appears to worsen from preschool through to adolescence, social motivation appears to increase which means 49,XXXXY boys may benefit from interventions that help address social difficulties.

"He needs time alone. If the friend he wants a break from comes back too soon, we turn them away, saying he is napping." - Age 14.

"We see no signs of social stress yet, but he gets upset in films where the family group is disrupted, such as Bambi or the Lion King." - Age 10.

"He finds it difficult to accept new people but this has improved. If he decides not to like you it never changes." - Age 8.

"He is sociable with children younger than himself but in a large group prefers to sit back and watch." - Age 6.

"You have to guide these children a lot more than a 'normal' child." - Age 4.

Adults with 49,XXXXY

There are now a number of adult men with 49,XXXXY syndrome. Most continue to live at home or in a group home with other adults with special needs under some level of supervision or in a semi-supervised setting. They may work part time on a voluntary basis or for payment doing jobs that are not intellectually challenging. The level of independence they enjoy is quite individual with some young men able to use public transport and shop alone while others need supervision (Linden 1995). As adults, men with 49,XXXXY syndrome appear to enjoy a good quality of life. They have varied interests, and have friends and acquaintances. Some would like to have a long term partner but it remains to be seen how feasible that is.

Interests

In many ways, men and boys with 49,XXXXY syndrome are interested in what interests other men and boys: as a group they are active, and video and computer games figure on the list of hobbies. Organised sport does not figure prominently, although one *Unique* member plays baseball and another was a swimming medallist. Many families mention their son's enjoyment of social contact and other people's company; others remark on their son's fondness for animals.

Sexual activity and fertility

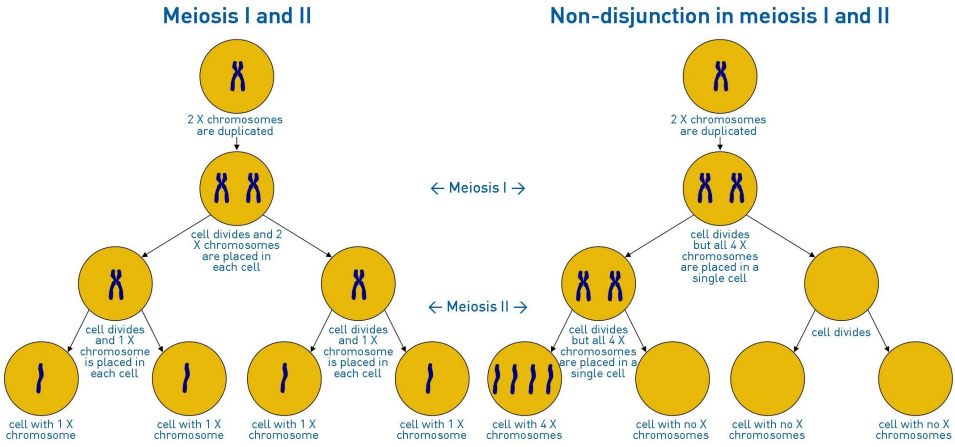
Sexual activity is possible and has been described in the medical literature after testosterone administration. Some boys show little interest in sexual matters (Borghgraef, personal communication; Linden 1995). The additional X chromosomes impair sperm production and the semen of men with 49,XXXXY generally contains no sperm. Fertility has not been reported and treatment with testosterone does not affect this.

About the extra chromosomes:

Where do the extra X chromosomes come from?

It is thought that the extra X chromosomes come from the mother's egg cell that has retained all of the X chromosomes that would normally be placed into 4 separate egg cells during cell division. Four egg cells each containing a single X chromosome are usually formed from a single cell by two cell divisions known as meiosis I and meiosis II as shown on the left hand side of the following image.

When an egg cell (which is typically 46,XX) divides during meiosis I, it makes a copy of its chromosomes (XX becomes XXXX) and, as it divides, it shares them equally between the two resulting cells. These two cells then undergo meiosis II, and when they divide again, the chromosomes are not copied but are shared equally between the two resulting cells. This process usually produces 4 egg cells with a single copy of each chromosome. The second copy of each chromosome pair usually found in most of our cells, will come from the sperm when the egg is fertilised. When an egg cell carrying four X chromosomes is formed, all X chromosomes are kept in a single cell during both cell divisions. This is termed non-disjunction of meiosis I and II as shown on the right hand side of the image below. When such a cell is fertilised by a sperm carrying a Y chromosome, the cell will have 2 copies of each chromosome 1-22 (one from each parent) plus a Y chromosome and four X chromosomes.



Non-disjunction for other chromosomes is usually associated with older mothers but there is no evidence of this for 49,XXXXY. It is not known why the X chromosomes fail to separate properly but there is no evidence that it is related to environmental, dietary or lifestyle factors. It is not due to anything that parents did or did not do during or before pregnancy (Lorda-Sanchez 1992; Linden 1995; Peet 1998; Cammarata 1999).

Some 49,XXXXY boys/men have a mosaic chromosome make-up, this means that some cells of their body contain four X chromosomes and some cells have a different number of X chromosomes. This is thought to arise when an embryo with XXXXY grows and one or more of the extra X chromosomes is lost from one or more cells. This means that during growth, the XXXXY-containing cells divide to produce more XXXXY cells and the cells with fewer X chromosomes reproduce to make more cells with fewer X chromosomes. The type and number of cells containing each variation depends on which cells, and at what stage of development, the extra chromosome (or chromosomes) are lost.

How do the extra X chromosomes cause the syndrome?

Only one X chromosome in any cell is fully active. Extra X chromosomes are almost completely switched off, and this is also the case in girls/women who usually have two X chromosomes. However, two small regions at the ends of the X chromosomes as well as 15 per cent of the genes are not switched off. The additional X chromosomes in boys with 49,XXXXY syndrome may have caused some of the effects before they were switched off and the genes still expressed on the additional X chromosomes may also play a role (Sarto 1987; Peet 1998). It is also thought that the changed positions of the chromosomes within the nucleus of cells (due to the extra X chromosomes) may have an effect (Petrova 2007).

The presence of the extra chromosomes and potential additional gene expression disrupts the development and function of a number of systems in the body such as the neurological, skeletal, genital and cardiac systems. The early lack of testosterone may also be linked to later neuro-cognitive (brain) development.

Can it happen again?

49,XXXXY is not hereditary and the chances of having another child with a chromosome disorder are believed to be no higher than for anyone else in the general population. There have been no studies specifically examining other pregnancies and children in families with a boy with 49,XXXXY syndrome but the evidence from families with other chromosome anomalies that occur by chance suggests that if there is any calculable chance of it happening again, it is very low. For reassurance, parents may wish to have a test of their baby's chromosomes in their next pregnancy and should have an appointment with a genetic counsellor or geneticist to discuss future pregnancies.

Other families

> *"The most important thing to know is it will be ok. Your boy will be the light of your life. This is a spectrum disorder so some issues one boy has another will not have, and vice versa. Expect the best from your boy and you will not be disappointed."* - Age 4.

Some families find it helpful to join support groups so they can get information and advice or just chat with other families who have a child with 49,XXXXY or similar learning, social or medical issues. You will find information regarding these groups on the back page of this booklet. *Unique* also runs a Facebook 'café'; for more information, email Marion Mitchell at marion@rarechromo.org.

Here are a few comments our members have made about what makes their child with 49,XXXXY so special:

> *"Deep friendship, affection and companionship."* – Age 35.

> *"A very happy and loving child who never moans and is very rarely miserable, loves to be with people and has a very large number of adult friends."* – Age 12.

> *"His wicked sense of humour and very infectious dirty laugh. Very sparing with his affections so one hug from him is worth tens of someone else's."* – Age 8.

> *"He always finds a way to do things even if it is different to the typical way."* – Age 4.

> *"A happy, healthy little boy who enjoys life. I treat him as a normal little boy and he always finds a way to make me smile."* – Age 3.

> *"His enormous determination."* – Age 2.

> *"He is a sweet, funny, shy boy. At home he is very silly, likes to play jokes and be the center of attention. In public he stays close to me, not yet confident in his ability to navigate the world, but I am seeing more and more his independence grow. At 4years old, his favorite things in the world include his daddy, curious George, crackers and peanut butter, and jumping off the couch. He makes me smile and makes me frustrated and makes my heart melt with love, sometimes all in a 2 minute period."* - Age 4.

> *"He has continued to mature and enjoy life to the full as he has got older. He lives in a flat in a home with 5 others, attends a day care centre daily which he really enjoys. He sails ,plays bowls and is a very sociable young man."* - Age 46.

Comments from our members for parents who have just received a diagnosis:

> *“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).”*

NOTES:

Inform Network Support

Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
Tel: +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/donate Please help us to help you!

Support groups and further information:

4-XY 49 syndrome private facebook group
'The 49ers group': 49variant@yahoo.groups.com
49,xxxxy Family and Friends facebook community
www.genetic.org—Association for X and Y chromosome variations

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