

XXXY syndrome



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XXXY syndrome is a chromosome condition that only affects males. It is rare and there is little specific information available. Individuals with the condition have a wide spectrum of physical, developmental and behavioural characteristics, ranging from mild to severe. Interventional therapies such as physiotherapy and speech therapy, individual educational plans and ongoing support will maximise the potential of those with XXXY.

What is a chromosome?

All genetic information is carried on the chromosomes you find in the nucleus of the cells in your body. In addition to 22 pairs of chromosomes numbered 1 to 22, males usually have one X chromosome and one Y chromosome. Instead of a single X chromosome, males with XXXY have three X chromosomes. XXXY syndrome can also be called **48,XXXY** syndrome, because instead of 46 chromosomes, there are 48 (22 pairs, ie 44 chromosomes, plus the four sex chromosomes in XXXY).

Most males with 48,XXXY have three X chromosomes in all the cells of their body. A few have some cells with XXXY and some cells with different numbers of X and Y chromosomes. This condition is called **mosaicism**. For example, a male with cells with two Xs and cells with three Xs will have this chromosome make-up: 47,XXY/48,XXXY. A male with cells with three and with four Xs will have this chromosome make-up: 48,XXXY/49,XXXXY. Mosaicism makes it harder to predict the effects of XXXY. As a general rule, though, extra Xs intensify the effects, while fewer Xs lessen them.

Is 48,XXXY a variant of Klinefelter syndrome?

Individuals with 48,XXXY have their own unique physical and behavioural characteristics and should not be considered a variant of Klinefelter syndrome.

Males with Klinefelter syndrome have a single extra X chromosome, so their make-up is 47,XXY. During puberty their testosterone production is decreased and while having normal sexual function, they generally do not father children of their own. As a result of early language deficits, they have increased propensity for reading and spelling problems and social difficulties. Their overall IQ may be below their age-matched typical peers, and they are likely to have a lower verbal IQ due to language delay.

The additional X chromosome in 48,XXXY has more influence on physical, cognitive and behavioural features than in 47,XXY. For instance, males with 48,XXXY may have delays in motor skills, language and social development. So early and ongoing intervention and educational planning are critical in ensuring that boys continue to progress in their developmental skills. As we increase our knowledge of 48,XXXY, we will understand its distinctive features better and begin to formulate specific interventional strategies.

Sources & references

The information in this leaflet is drawn from key references in the medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain articles from *Unique*. The leaflet also draws on *Unique's* database. When this leaflet was written, *Unique* had twenty-four members with a 48,XXXY diagnosis, nine of whom have completed a detailed survey about their son's development.

How common is 48,XXXYY?

It is much less common than classical Klinefelter syndrome (47,XXY). An estimated 1 in 17,000 to 50,000 boys is born with 48,XXXYY.

What is the outlook?

In order to maximise the potential of males with 48,XXXYY, it is important to provide early speech and language therapy, physiotherapy, and occupational therapy. Educational resources should be designed to meet the individual's needs. Social skills training, a structured environment and strategies to build on strengths such as helpfulness will boost self esteem and develop competence (Visootsak 2007).

At birth

Babies with 48,XXXYY usually look much like any other baby at birth although some may have slightly unusual facial features, such as skin folds across the inner corners of the eye (epicanthic folds) or wide set eyes (hypertelorism). Some have unusual hand features such as a single palm crease or incurving fifth fingers. In some babies the genitals look normal but one or both testicles may not have descended (6/10 of the *Unique* cases). Others, estimated at 1/4 or 7/10 *Unique* cases, have a very small (hypoplastic) penis. Babies may be smaller than boys with normal chromosomes in weight, length and head circumference. Reported birth weights at term range from 2.8kg (6lb 3oz) to 4.76kg (10lb 8oz), with most at the lower end of the range (Linden 1995; *Unique*).

“ I had a natural delivery without medication and he looked perfect at birth, with a perfect Apgar score. But at 7lb 2oz, he was smaller than his brothers who were 8½ and 9lb

Genitals

Testicles Testicles are the ball-like structures in the scrotum that normally produce sperm and testosterone, the male sex hormone. The testes develop in the abdomen, moving down into the scrotum shortly before birth. In boys with 48,XXXYY it is common to find that one or both testes have not completed their journey into the scrotum. They may complete the journey shortly after birth or they may move in and out of the scrotum (retractile testes). In either case, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy. In boys with 48,XXXYY it is common also to find that one or more commonly both testes are unusually small.

Penis The penis in boys with 48,XXXYY is often small at birth. It is likely to remain small but may grow to within the normal range. Testosterone treatment for micropenis in infancy is controversial but two *Unique* families on both sides of the Atlantic have a positive experience.

“ His first testosterone shot for micropenis has had a dramatic effect. His penis has possibly doubled in size - 15 months old



Facial features

Many boys with 48,XXX \bar{Y} have no obvious features. Some have a slightly distinctive facial appearance: eyes may be unusually far apart (in one *Unique* boy they are unusually close); there may be tiny skinfolds across the inner corners of the eyes; the ears may be set below the expected line with the top level with the eyes; the lips may be full and the jaw may jut a little forward. Facial hair in adolescents and adults tends to be sparse.

“ In some photos, to me he resembled someone with very, very mild Down syndrome



Different boys

L to R:
14 months;
26 months;
7 years;
21 years

Feeding and growth

Babies with 48,XXX \bar{Y} do not appear to have any consistent feeding problems. The experience of *Unique* is that many babies feed normally and wean without difficulty to solid foods but a minority may have oral-motor discoordination with increased risk for reflux and other feeding problems. Reflux – the return of feeds and stomach contents from the stomach up the food passage – can occur and may be troublesome.

At birth, a typical baby with 48,XXX \bar{Y} may have long, thin arms and legs and the long limbs remain typical. Average adult heights are normal to tall, with relatively long legs and a short trunk. Most *Unique* adults are a little over 6 foot (1.83m).

Most boys are relatively slim in the early years, although they may show a slight belly. Muscle development can be low, but exercise improves tone, strength, speed and coordination. After puberty, a number of men tend to put on weight particularly around the waist and abdomen and can also tend towards a female fat distribution. The tendency to put on weight persists in adulthood and families deal with it by incorporating regular exercise and a healthy diet with a minimum of ‘junk’ food.

“ We try to limit rubbish food and get as much exercise as possible but he is not very physical

Puberty

In boys with 48,XXX \bar{Y} , puberty generally follows the pattern common in boys with 47,XX \bar{Y} : it starts at the appropriate time with normal levels of the male hormone testosterone. The penis starts to grow, body hair appears, the voice changes and deepens. However, typically, levels of testosterone start to decline and secondary sexual characteristics do not fully develop. The testicles do not enlarge fully and towards the end of puberty penis growth slows and body and facial hair is sparse.

You may find that the point at which your son’s testosterone levels start to decline is earlier or later than puberty and in some cases, puberty does not start until testosterone replacement is given. Your son should be evaluated by an endocrinologist and once testosterone levels have started to decline he will generally benefit from testosterone treatment (Visootsak 2006; Linden 1995; *Unique*).

Does my son need testosterone treatment?

In males with 47,XXY, the function of the testes in producing testosterone varies from near normal to severely deficient. For a boy with 48,XXXYY, your son's endocrinologist will tell you what his natural testosterone levels are and recommend the best time to start replacement therapy. Testosterone can be given by mouth, implant, gel, patch or injection and leads to increased muscle strength, bone mineral density, body hair and a more masculine body shape; it has a positive effect on mood and behaviour with less irritability and fatigue, more energy, better concentration and improved social skills (Joseph 2008; Nielsen 1988; *Unique*).

Controversially, certain doctors treat baby boys in infancy with 47,XXY, 48,XXXYY and 49,XXXXYY who have micropenis with three injections of testosterone at intervals of one month.

“ In the US, we were given a prescription for 120mg of testosterone in three shots over three months. Endocrinologists in the UK would not prescribe but agreed to 75mg over three months for treatment of micropenis. Our son has had his first shot and we have seen improvement in many areas - *15 months old*

“ Our son had three testosterone shots at 12, 13 and 14 months. We saw an increase in penis size and his muscle tone improved slightly but there was no effect on his energy levels. Shortly after the first shot, things began to 'click'. We saw huge improvements in eye contact, attention span and overall cognition and more of a desire to interact with adults - *21 months old*

“ Our son was given testosterone from 15 which led to a better overall body shape. His energy levels improved but remained lower than his brother's - *23 years old*

“ Our son has had three-monthly testosterone injections from age 24 when he stopped producing testosterone. This has had no effect on penis size and made no appreciable difference to his muscle bulk, behaviour or energy levels - *26 years old*

Growth of breast tissue

Growth of breast tissue (gynaecomastia) may occur, usually starting around puberty. It may resolve without treatment but if it persists can cause embarrassment and will be one of the points monitored by your son's endocrinologist. If breast tissue does grow and does not resolve, one option is reduction surgery.

Of six *Unique* members, two experienced growth of breast tissue, one at puberty and the other in his early 20s, well after puberty started in his early teens. One had successful reduction surgery at puberty, the other has not yet decided. Two *Unique* members had no breast growth at puberty; in two, testosterone treatment successfully limited breast and hip growth (*Unique*).

Can a man with 48,XXXYY have children of his own?

It is extremely unlikely that a man with XXXYY chromosomes will be fertile and there is no known instance of a man with 48,XXXYY fathering children. The overwhelming majority of men with 47,XXY do not produce sperm and cannot father children of their own and so far as is known, the failure to produce sperm is universal in men with 48,XXXYY. Testosterone treatment does not restore fertility.

Growing up with 48,XXXY

Development: sitting, moving, walking (gross motor skills)



At 26 months



Babies with 48,XXXY achieve their developmental milestones later than typically-developing babies. They have gross motor delay because they usually have low muscle tone and difficulties with coordination. Physiotherapy is important and in all cases known to *Unique* are fully mobile throughout childhood and as adults. Both rolling (*Unique* babies between six and 11 months) and sitting (*Unique* babies between five and 18 months) are delayed although there is some evidence that babies sit earlier and with greater confidence than they move. Moving by shuffling or crawling emerged in *Unique* babies between 11 and 18 months and walking between 17 months and two years two months. Bendy (hyperextensible) joints and flat feet are common and once on their feet, the typical gait is wide-based. In some boys the two bones in the forearm are fused near the elbow (radioulnar synostosis) which limits their ability to turn the

arm until the palms are facing upwards (Visootsak 2006, 7). To enhance mobility, increased sensory input with swinging, bouncing etc and early physical therapy is very helpful.

Activity in childhood and adulthood is affected by boys' typically low motivation and borderline energy levels, which mean that boys do not particularly enjoy sport and without encouragement can take little exercise. Activities that require keeping pace with others and team or contact sports are not usually helpful initially. Instead, activities in which the exercise is incidental (walking the dog; playing in a playground) or where the child can set his own pace (cycling; swimming) are most likely to be successful.

“ He achieved his milestones a bit later than his five brothers and sisters

“ He walked at 17 months, compared with 10 months for his two brothers

Development: hand use and coordination (fine motor skills) and self care

A recent study comparing boys with XXXY with a group of boys with XYY showed that the XXXY boys had shortcomings in their daily living skills (Visootsak 2007). Many boys, though not all, experience delay in controlling their hand use. They may show a weak hand grip, tire easily and find manipulating small objects a challenge. In *Unique's* experience, slower-developing children may continue to need help to feed, dress and care for themselves throughout early childhood. An additional factor is motivation, so that feeding skills may advance faster than dressing, washing and personal care, for which even grown men frequently need regular reminders. Handling cutlery, writing implements and tools occurs normally in some boys, while others show some delay or awkwardness and for them, occupational therapy is very helpful.

Toilet training is usually somewhat delayed, emerging approximately at 3½-4 years of age, but in some cases is not complete until 8-12 years.

“ His fine motor skills seem good. He uses utensils when eating but is very messy and prefers to eat with his hands - 2 years

“ He had great difficulty holding a pen and creating shapes; he used a special pen with easy grips and did lots of exercises joining dots to create letters. He is OK now but his hands get tired easily - 23 years

“ He has an essential tremor which makes hot drinks and food very difficult at times - 26 years

“ He needs daily reminders for personal care as he doesn't understand the consequences - 31 years

Learning

Effects on learning are expected to increase broadly with each extra X. As a rule of thumb, each extra X reduces overall IQ by around 15 points, with the most marked effect on communication (Linden 1995). However, since IQs of 70-130 have been demonstrated in boys and men with 47,XXY, it may be possible for individuals with 48,XXXXY to achieve an IQ within this range with ongoing intervention. Studies have shown that learning difficulties in 48,XXXXY are often mild to moderate, with an IQ range of 20-79 reported, and typically around 40-60.

Specific difficulties with a short attention span, poor memory and difficulty keeping things in the right order are common and a highly structured learning environment is usually helpful. A comprehensive psychoeducational assessment is needed to identify each boy's strengths and challenges and the educational plan or statement should include language-based communication activities (Visootsak 2006, 7; Linden 1995).

Several studies of boys with 47,XXY have shown a particular difficulty with reading and it is likely that this will be more severe in boys with 48,XXXXY, so that they are likely to need special education and individualised assistance in learning to read (Rovet 1995).

Unique's experience confirms these observations. The only member with a severe learning disability who is not able to read is one who has a mosaic 48,XXXXY/49,XXXXXY karyotype. Reading skills among other members range from a reading age of 4 years 10 months at a chronological age of 6½ to reading books for 6-7-year-olds at 14. Among the adults with 48,XXXXY, one can read at an 11-12-year-old level and prefers factual material while another can read but as it is hard work, does not enjoy it and chooses to read material with pictures or cartoons and magazines.

“ He has special and very complex problems with spelling and reading. He can spell words he can't read, and will read a word and say a related word eg reading river he says water or stream. Once he finished school, he stopped reading from books but he uses texts from his phone and has no problems with day-to-day reading. He chooses to read phone texts, areas relating to his job and sometimes tabloid newspapers - 23 years



Higher-level abilities among individuals include computer skills, creativity, woodwork, a good visual memory, mathematics, technical tasks and music (playing the keyboard).

“ He can programme the TV, DVD or phone without being able to read the directions. He is excellent with counting, time and maths-based issues - 23 years

A short attention span is common and families report difficulties concentrating either during explanations or when there are distractions.

All of *Unique*'s members except one had an educational plan or statement to entitle them to extra learning support, including speech therapy. Some started their education in mainstream schools, usually with a high input of learning support, but all attended special education, a school with a special needs department or one specialising in teaching those with learning difficulties and/or autism for their secondary education. Some progressed to college, usually for special needs but in one case for those with borderline learning difficulties.

“ In a static situation such as a classroom he gets very stressed and fidgety. A lot of learning support was provided but as he gets stressed easily, he often found the extra support was more of a problem than not.

Speech and communication

Boys with 48,XXXY commonly have a severe delay in communication skills, with expressive language (speaking rather than understanding) particularly affected. However, all adults known to *Unique* communicate using speech.

Boys with increased numbers of extra sex chromosomes are also at risk for auditory processing problems which can affect their learning, social and emotional adjustment (Visootsak 2006; Linden 1995). This is a chronic problem, so early and ongoing speech therapy is called for, specifically addressing oral motor planning deficits and developmental verbal apraxia (a disorder that interferes with the ability to pronounce sounds, syllables and words), with attention directed towards building and enhancing vocabulary and understanding sentences and stories of increasing complexity. Boys need to be taught how to express their feelings and emotions in order to relieve frustration (Visootsak 2007). There is further evidence that pronouncing words may be difficult and that it is helpful for parents to continue to read to their son for longer than for other children to help develop a pleasure in story telling and to help him counteract any difficulties he finds in keeping the thread of the story as he stumbles over reading.

Among *Unique* members, first words emerged between 14 months and 4 years 5 months. Pre-verbally, children use vocal noises, facial expressions and gestures to communicate. Some families use sign systems for pre-verbal communication and boys can acquire sign vocabularies of over 100 words before moving on to speech. Progress from single words to 2-3 word phrases is steady but delayed and some adolescents are still communicating in phrases, with full sentences emerging later. Some boys have specific difficulties with finding the right word and use approximations, mime, pictures or sounds to show what they mean. Pronunciation is not always clear.

Family experience suggests that speech therapy needs to be intensive, with a focus on pragmatics (social usage). One child made little progress with one hour a week of speech therapy at 3 years but after a year of therapy provided for three hours a day, four days a week at the age of five his speech was normal.

“ He communicates using vocal noises, word approximations and single words. He has a vocabulary of over 50 words but only uses 10 a day and doesn't seem to keep many of the words he learns - 2 years

“ Above average receptive language, above average cognition, below average expressive language. Speech therapy has been extremely helpful, the most effective response to treatment is with a PROMPT-trained speech therapist - 3 years

“ He panics very easily when trying to express himself - 14 years

He communicates using speech and has no difficulty creating sounds but his language is immature. His speech is normal, very witty at times but we usually have to start conversations: we ask questions, he replies - 23 years

“ He communicates with speech and holds fairly normal conversations, sometimes expressing things differently to us or rarely using a wrong word - 26 years

“ He communicates with speech, copying phrases he has heard and as a child used words like ‘tractor garden’ for field if he couldn’t find the right word - 31 years

“ He is still learning new words - 38 years

Behaviour

Males with XXXY are typically empathetic and enjoy helping others. Giving them roles around the house may play to one of their strengths – wishing to be helpful – while building up a weaker area – daily living skills. Their behaviour may seem immature, but it is usually consistent with their general intelligence. Individually, boys are described as passive, placid, pleasant and cooperative and rarely as aggressive. Their passive behaviour may leave them with poorly developed social skills and potentially without friends. They are both shy and friendly but can be sensitive and get hurt if they are rejected. They show occasional irritability and temper tantrums and have difficulties both with managing frustration and changing routines.

Social skills training programmes are very helpful as they will learn the meaning of social cues and appropriate responses. Supervised volunteering experiences may boost their self esteem and give boys the opportunity for positive social interactions. Exposure to normally developing youngsters is recommended to encourage social skills development and model appropriate behaviours. Boys also need to be taught how to express their feelings in order to relieve frustration and need adequate warnings to help them prepare for transitioning (Visootsak 2007; Visootsak 2006; Linden 1995). *Unique’s* experience is that babies are generally ‘the perfect baby’, undemanding and quiet, if passive. As they mature, bouts of frustration set in and babies and toddlers can have challenging temper tantrums.

Children can be shy and prefer to relate to others older or younger than themselves. Older children can be subject to bouts of fear or panic attacks - described by one family as ‘surges of angst and anger’ - and as puberty approaches, behaviour can become challenging in some boys, though not in all. Aggressive behaviour has been seen in a few boys, both in the toddler years and at puberty, and adolescents can use language that families find embarrassing. Mood swings are apparent in many boys, generally becoming more obvious around puberty and often persisting into adulthood, although they moderate with time.

- “ He is very passive and quiet but getting louder and when he is unhappy he can be quite stropy, throwing his head back or forward. He is very sociable - 15 months
- “ He kisses and pets his 4-month-old sister and tries to speak to her softly in a high-pitched voice. This warms our hearts very much - 2 years
- “ He is easily frustrated when he is unable to do something, occasionally banging his head on the floor or other surfaces, but is very well behaved otherwise - 3 years
- “ He gets upset very easily and is a very quiet, shy boy with other children, needing his mother to go everywhere with him. Since starting school his confidence has grown but he prefers to play alone - 6 years
- “ He is quiet and well-behaved at school but the complete opposite at home where he can be very aggressive at times and his behaviour seems to be more erratic and harder to control. Yet he can also be very lovable, so it is very hard to understand his mood swings - 14 years
- “ He is stubborn and gets upset easily by comments from work colleagues. He also often mixes with others who have behavioural problems which leads to difficulties. Overall he mixes better with older, younger or more understanding people - 23 years
- “ He gets angry when people wind him up: goes to his room, puts on his headsets and listens to music or sometimes shouts - 26 years
- “ He is generally friendly, happy, polite and helpful but has sudden anger surges, usually prompted by something internal but sometimes by perceived conflict or a personality clash. He will shout and stamp and then reflect, calm down and say he is sorry. These periods of angst and anger are now getting less and his medication has been reduced - 48,XXXY/49,XXXXY, 38 years

Health matters

■ Bones



Men with low testosterone levels are at risk of low bone density and osteoporosis but early treatment with testosterone can prevent this. Your son’s endocrinologist will explain the best time for any treatment to start. A bone density scan will reveal decreasing bone mass and is usually part of the routine screening for men with 48,XXXY. In *Unique’s* experience, none of the four men who have been regularly scanned has shown evidence of decreased bone density.

■ Other conditions

A number of health concerns have been reported in males with 47,XXY, including autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis; diabetes and insulin resistance; hypothyroidism; the development of varicose veins and leg ulcers; lung disease such as chronic bronchitis. The risk of breast cancer is also raised, although it remains considerably lower than the risk for women. Although the risk of developing these disorders is raised, there is no evidence from *Unique* that any of their 18 members with 48,XXXY have developed any of these disorders. Disorders that are relatively common among *Unique’s* membership are allergies (6/18); asthma (6/18); infections of the upper or lower respiratory tract (6/18);

and seizures (4/18). One boy was born with both elbows dislocated and gross anatomical deformities of both forearms. It is important for males with 48,XXXXY to have regular physical examinations and follow-up with their primary care physician/ GP.

■ Teeth

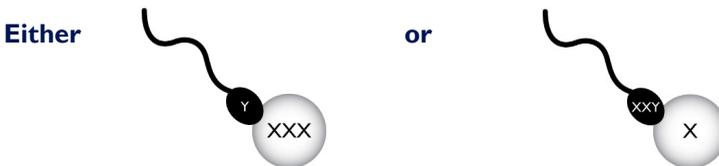
A typical feature is enlargement of the inner pulp chamber, known as taurodontism. This occurs naturally in 2.5-11% of the population but is more frequent in 47,XXY and is likely to be even more frequent in 48,XXXXY. Taurodont molars are typically treated with stainless steel crowns to avoid pulp exposure but this may not completely prevent further decay and root canal treatment may be needed (Joseph 2008).

Other dental features include missing permanent teeth, enamel defects and shovel-shaped incisors. As oral hygiene may not be as thorough as in youngsters without a chromosome disorder, dental decay is common and there is some evidence that extractions are twice as common in boys and men with 47,XXY as in their brothers. The experience of *Unique* members includes late eruption of milk teeth (from 12-15 months); missing canines; malpositioned and overcrowded teeth; severe decay despite a good diet; missing permanent teeth.

How did the XXXY syndrome arise?

The parents of a son with 48,XXXXY almost always have normal chromosomes in their body's cells, so they are not routinely tested. Why the two extra X chromosomes were incorporated is not well understood but it is known that they can come from either the mother or the father but not so far as is known from both parents.

A normal female egg contains one X chromosome and normal male sperm contain either one X or one Y chromosome; together they create a fertilised egg with either 46,XY or 46,XX chromosomes. 48,XXXXY syndrome usually arises when a Y-bearing sperm fertilises a woman's egg carrying XXX chromosomes or when sperm with an XXY chromosome make-up fertilise an egg with a single X chromosome.



In the great majority of cases we don't know why this happened. In a few cases an older mother's egg may have aged before ripening. What is known is that the syndrome arose before conception (when a baby is made) and there is nothing that the parents did before or during pregnancy to make it happen. No environmental, dietary or lifestyle factors are known to cause it. It is no-one's fault. When boys or men with 48,XXXXY have a mosaic form of the condition, it is likely that a further error occurred in the very earliest days after conception when the embryo is developing.

Can it happen again?

It is important to discuss this issue with a genetic counsellor or geneticist because the chance of having another child with a chromosomal condition depends on several factors such as family history and parental age.

“ His quick wit is always amazing and so is his ability with technical issues.
Beneath his problems he is a lovely, loving boy who is very kind.”

Support and Information



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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!

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 Dr Jeannie Visootsak, Assistant Professor, Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia, US, and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK 2008. (PM)

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