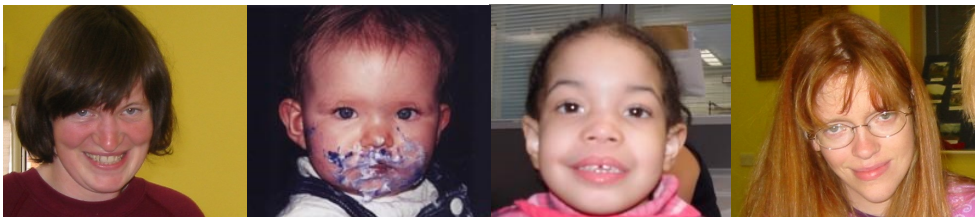
Unique

Understanding Chromosome & Gene Disorders

Tetrasomy X



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Sources

The information in this leaflet comes from the medical literature and from surveys conducted by *Unique* and by the Tetrasomy & Pentasomy X Support Group. As the information was collected informally, it may be slightly biased in representing responses from families who have joined a tetra X community and whose daughters may be more obviously affected.

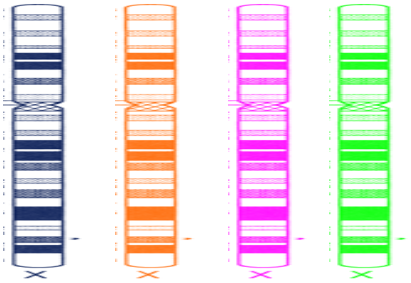
References

The text contains references to articles in the medical press. The first-named author and publication date are given to allow you to search for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain abstracts and articles from *Unique*.

Tetrasomy X

Tetrasomy X is also known as XXXX syndrome, Tetra X, quadruple X or 48,XXXX. It only affects girls.

The genes that instruct the body to develop and work properly are arranged along chromosomes. There are usually 46 chromosomes, twenty-two pairs numbered 1 to 22 plus two sex chromosomes. In boys the sex chromosomes are different: one is called X and one is called Y, so male chromosomes are usually described as 46,XY. Girls usually have two X chromosomes and can be described as 46,XX. Girls with tetra X have four copies of the X chromosome, giving the chromosome description (karyotype) 48,XXXX.



How rare is Tetrasomy X?

A worldwide community exists of around 100 women and girls with tetrasomy X, although there are certainly very many more who either have not been diagnosed or who have not joined the community. *Unique* has over 50 members with tetrasomy X. The Tetrasomy & Pentasomy X Support Group has more members.

It is a concern to these communities that no co-ordinated medical research has been conducted recently into the condition. Scarcely more than 40 women have been described in the published medical literature and many of the reports date from the 1960s and 1970s.

However, in 2004, following the first tetrasomy X study day in Oxford, UK, a Tetra Penta X Registry was established. For more information, please contact info@rarechromo.org

Typical features

The medical consensus is that tetrasomy X does not cause a specific clinical syndrome. Girls and women with four X chromosomes are very different from each other. Nonetheless, they may share certain features. Data collected by *Unique* and the Tetrasomy & Pentasomy X Support Group show that the features can be scarcely noticeable or have a profound effect.

- Mild delay in physical development.
- Speech delay.
- Slight to moderate learning difficulties.
- Possibly, above average adult height. This may follow slow growth as a baby and young child.
- Increased vulnerability to behavioural and social stress.
- Increased risk of dysfunction of the ovaries.
- Increased rate of respiratory infections in early childhood.

What causes Tetrasomy X?

Girls with tetrasomy X have inherited either three X chromosomes from their mother and a single X chromosome from their father or all four X chromosomes from their mother. During the formation of a mother's eggs, chromosome pairs usually divide so that each cell has a single X chromosome. Repeated mistakes during cell division can leave three or even four X chromosomes in the egg cell. Fertilised by a single X-carrying sperm, the egg will then develop into a baby with four X chromosomes or, more rarely, start life with five X chromosomes but lose one.

Very occasionally, other processes may be involved, such as a mistake in cell division after conception (when a baby is made) or the presence of an extra X chromosome in some cells in the mother (Robinson 1994).

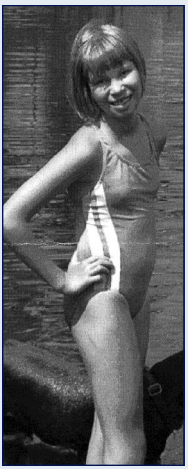
Was it my fault?

No. No environmental, dietary or lifestyle factors are known to cause sex chromosome conditions such as tetrasomy X. This means that there is nothing you did before you were pregnant or during pregnancy that caused tetrasomy X to occur but it also means that there is nothing you could have done to prevent it.

Diagnosis

Chromosomes are usually examined because of concern about a child's unusual physical features or development. In girls with tetrasomy X, the signs may be so subtle that the diagnosis is reached late.

The chromosomes are first separated from white blood cells grown from a small blood sample, then stained with a dye that gives each one a typical pattern of light and dark bands. The two extra X chromosomes are then clearly visible.



Will growth be normal?

Birthweight is low to low normal and some girls are small for their gestational age. Among 20 surveyed babies born at or near term, the average weight was 2810 grams (6.2lb) (range 1672 grams (3.69lb) to 3798 grams (8.37lb)). Most babies feed reasonably well and grow at a normal rate. All the same, a few experience feeding difficulties and failure to thrive and grow into small toddlers and children. Research reports show that some are born very small (below the fifth centile on the growth charts) and remain short.

By mid childhood, girls with tetrasomy X are typically above average height. Among six *Unique* members who gave their adult height, the average is 178cm (5'10") and the range is 160cm (5'3") to 187cm (6'2"). Research reports show average height as 169 cm (5'7"), compared with an average height for women of 167 cm (5' 6").

Recently the *SHOX* gene (Short stature HOmeobox gene of the X chromosome) on the tip of the short arm of the X chromosome was identified as a key determinant of height. Extra copies of the gene are likely to have an additive effect, so having two extra copies could partly explain the tall stature of women with tetrasomy X. Another explanation is shortage of the hormone oestrogen normally produced by the ovaries (Nielsen 1977; Plauchu 1988; Linden 1995; Rooman 2002; U).

Will a girl look different?

As you can see from the pictures in this leaflet, a girl with tetrasomy X will not stand out from the crowd. Facially, she will most probably have no special features to suggest that she has a rare chromosome condition. A few girls have minor differences but they are subtle and in everyday life unimportant. Doctors mention them in research reports because they may help when searching for a diagnosis.

Four out of 32 babies (13 per cent) surveyed by *Unique* or the Tetrasomy & Pentasomy X Support Group were born with one or more unusual facial features. These are all features that are common in other chromosome conditions and also occur in people with no chromosome disorder. Three girls had epicanthic folds (folds of skin across the inner corner of the eye), two had upward slanting eyes and one had excess skin at the back of the neck. Widely spaced eyes are also a common feature (Plauchu 1988; Linden 1995; U).

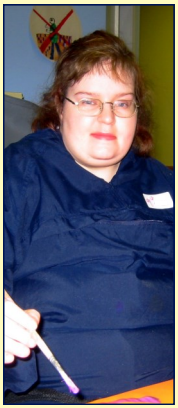
Effects on learning

Having two extra X chromosomes is usually expected to have some effect on a girl's ability to learn, although the extent is very variable. Up-to-date records suggest that many will have a mild or moderate learning difficulty, with an average IQ in the 60-80 range. This observation fits well with the rule-of-thumb that suggests an IQ drop of 10-15 points for each extra X chromosome. However, this may actually paint too negative a picture, as those with little or no learning difficulty may never come to the attention of doctors or be diagnosed. In the medical literature, there is one report of a girl with an IQ of 100 and both *Unique* and the Tetrasomy and Pentasomy X Support Group have members whose learning difficulties are no more than slight or specific. Older reports showing a more severe learning difficulty are biased and do not reflect the experience of either support group.

Tetra X girls typically start their education in mainstream school, but may switch eventually to a more supportive environment. Typically, reading and mathematics present particular challenges and their general performance is affected by their speech delay. Despite this, *Unique* knows of some who have completed secondary education and acquired the standard school leaving qualifications. Some show considerable talent in particular areas such as drawing and creative writing.

It is perhaps most accurate to say that some level of learning difficulty is, with speech delay, the most consistent feature of tetrasomy X. Girls therefore have an enhanced need for support, early intervention and appropriate teaching. Many years ago, Dr Mary Linden of the National Jewish Center for Immunology and Respiratory Medicine in Denver, Colorado, wrote a paragraph that should serve as a mission statement for all families and professionals supporting learning in girls with tetrasomy X.

'Where individuals are achieving at higher levels than those generally reported … parents have been involved in all aspects of their child's development and education. They have initiated early intervention by pursuing professional help for their child at the first sign of a delay. The parents have been actively involved in their child's education through interaction with school personnel and agencies. The children have been exposed to many varied activities and experiences and are praised for their strengths, while their limitations and delays are minimised' (Telfer 1969; Blackston 1972; Fryns 1983; Linden 1995).



Speech and communication

Speech delay is one of the most consistent features of tetrasomy X, mentioned by at least two-thirds of family members of the support groups and in most cases in the medical literature. In some girls, the delay in starting to speak is the first sign that leads to the diagnosis of a chromosome disorder. It is generally believed that speech development is in line with learning ability and is not specifically targeted by tetrasomy X .

The combined surveys of both support groups showed that the average age at which girls with tetrasomy X started to speak was three years (range 20 months to four years). Vocabulary in the pre-school years was typically limited and some girls learned to sign before they acquired speech. Although girls do overcome the delay, difficulties with complex speech and the subtleties of conversation may persist into the secondary school years.

Research reports suggest that many also have difficulties with pronunciation that may make them hard to understand but that is not necessarily the experience of the support groups.

All girls surveyed have acquired speech but one continues to use sign language as an adult to supplement her words. Some completely overcome their speech delay and grow into fluent and articulate speakers. However, others express themselves hesitantly and have difficulties understanding the subtleties of language. Most are aware of their speech delay and this can undermine their confidence socially and even within a family context where they can be reluctant to take part in group conversations(Pena 1974; Nielsen 1977; Linden 1995; U).

Feeding

Feeding is not usually regarded as a concern for girls with tetrasomy X. However, the evidence from the support groups is that around a quarter had difficulties feeding as babies that affected their ability to put on weight. The difficulties were varied and usually not severe. Five girls (1: 6) consumed very small quantities of milk or a limited range of foods, one had difficulties with swallowing and with reflux (where feeds return readily up the food pipe from the stomach), one progressed very late to solid food at 19 months and one had such extensive feeding difficulties that she needed to be fed through a gastrostomy tube direct into the stomach.

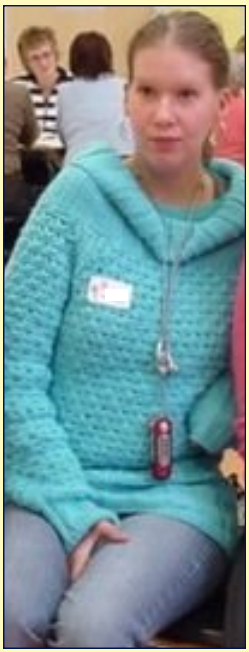
Constipation is common and in girls with tetrasomy X is likely to be caused by a combination of feeding problems, a low fibre diet, a low activity level and low fluid intake.

Sitting, walking, running, writing

The combined surveys showed that most girls were a little delayed in reaching their 'baby' milestones. They sat up alone on average at 7 months (range 5 to 12 months) and started walking alone at 21 months (range 15 months to 3 years). These figures agree well with reports in the medical literature which suggest that gross motor skills (whole body movements) are delayed more than fine motor skills (hand use). Hypotonia – low tone in the skeletal muscles, producing unusual floppiness – contributes to the delay in becoming mobile, as well as the lax ligaments that affect many of them. In the early years of mobility, some benefit from orthotic devices and leg supports and continue to wear supporting footwear. Eight of the girls surveyed - more than a quarter of the total - had sufficiently low muscle tone for a formal diagnosis of hypotonia.

Once girls achieve mobility, they go on by school age to run, jump, climb on playground equipment and ride tricycles. By the teen years, they may well swim, cycle and take part in a wide range of sports and activities. However, families consistently report that they take longer to learn physical skills than other members of the family and that they show a consistent lack of stamina, with less muscle strength and greater problems with co-ordination and balance.

In terms of fine motor skills, most are adept with a pen but poor grip and clenched or curved fingers can make everyday tasks like opening tins a challenge.



Medical concerns

Heart conditions

Almost one in three girls surveyed (10 out of 32) was born with a heart condition and in three others a heart murmur was detected. Of these, five (17 per cent) had a complex cardiac problem or one that required surgery. This suggests a higher rate of heart conditions than is generally reported in the medical literature.

Holes between the upper chambers (atria) or lower chambers (ventricles) of the heart occur in the general population but seem to be more common in girls with tetrasomy X. These are called atrial and ventricular septal defects. Atresia (narrowing) of the valves may also occur.

Of the girls in the survey with a more complex heart condition, one had Fallot's tetralogy, in which the pulmonary artery and valve that takes the blood from the heart to the lungs has an unusually narrow entrance (pulmonary stenosis) and there is also a ventricular septal defect. Two older girls have had a deep vein thrombosis, one while taking a combined oral contraceptive pill. One of these girls went on to have a stroke, which occurred because the blood clot was able to pass through a septal defect in the heart.

Orthopaedic problems

A high proportion of girls have either excessive or limited movement of both large and small joints. Among the more obvious orthopaedic problems, four girls in the survey were born with abnormal development of the hip joints or developed hip problems such as rheumatoid arthritis later in life. Eight had limited or excessive movement of at least one joint, most typically the elbows. A girl has been described in the medical literature with a 300 degree rotation of her elbows. A frequent finding was radio-ulnar synostosis, where the two bones in the forearm (the radius and ulna) are fused along part of their length, making certain twisting or turning movements difficult. Two girls were born with talipes equinovarus (club foot) affecting one foot and one girl had unusually angled big toes. Four girls (13 per cent) needed bracing or surgical fusion for a curved spine (scoliosis). Forty-three per cent of the girls surveyed had incurving 5th fingers (clinodactyly), which in two women caused difficulty in gripping. Seven girls (23 per cent) were described as having unusually small hands and/or feet, three had overlapping toes and two had the blue or purple discoloration of the hands and feet that is typical of Raynaud's phenomenon (Linden 1995; U).

Kidney problems

Kidney and bladder problems seem to be frequent with typically a single kidney, kidneys that are fused together or kidneys that have two

tubes connecting them to the bladder. The valve that prevents urine from the bladder going back to the kidney may not function well and that can create kidney infections. It is important to have an ultrasound kidney scan even if there are no symptoms because structural defects make infections more likely and frequent renal infections mean a high chance of later hypertension.

Frequent infections

Many families have reported a high rate of respiratory and ear infections in early childhood. The typically high-arched palate encourages frequent ear infections because the short connection between the mouth and the ears allows bacteria to travel easily from the throat to the ears. This can lead to glue ear (conduction deafness) and many girls need grommets or T-tubes, sometimes repeatedly. Hearing loss can have a big impact on learning and should be monitored regularly.

Dental problems

The abnormal palate formation can also give rise to dental abnormalities, with teeth that are missing, irregular or that erupt early or late. Some girls also have a small mouth or a cleft palate. Four girls in the joint survey (13 per cent) had adult teeth that erupted late, or enamel or dentine deficiencies. Reports in the medical literature and at *Unique* have also noted milk teeth that were late to fall out and severely worn front teeth (Farge 1985; U).

Puberty and periods

It is usually said that half of all girls with tetrasomy X will have normal periods, while the other half will either fail to start their periods and have underdeveloped sexual characteristics such as small breasts or have irregular cycles. The evidence from the support groups generally agrees with this, with seven girls out of 20 recording the start of their menstrual periods between 11 and 16. Of these, one girl had ovarian dysfunction (malfunctioning ovaries) and a complex anomaly of the uterus, one had very irregular periods and a third took a combined hormone supplement to stimulate the start of periods.

In girls with incomplete puberty, lack of oestrogen activity due to malfunctioning ovaries can raise the risk of fractures and cause osteoporosis. Giving oestrogen can promote breast development, stop excessive growth and stimulate bone formation, preventing osteoporosis. Another advantage of oestrogens is that they work in the brain, improving memory and raising mood peaks and lowering troughs. Whether or not to give oestrogen should be discussed with your daughter's endocrinologist (Park 1970; Nielsen 1977; Collen 1980; Linden 1995; Rooman 2002).

Will it happen again?

Tetrasomy X is very rare indeed and for the great majority of families the chances of it affecting another pregnancy are vanishingly small. Extremely rarely, however, it turns out that the mother has an additional X chromosome in some of her cells and this makes it more likely that a future pregnancy could be affected. As a parent, you will have an opportunity to discuss your individual situation with someone from your local genetics service and, if this is appropriate in your case, to have your partner's and your own chromosomes tested before embarking on another pregnancy.

Will a woman with tetrasomy X be able to have childen?

There are very few reports indeed of women with tetrasomy X having children. However, assuming that a girl has normal ovaries and periods, she may be fertile. Research reports show that four women have between them had seven children. One woman had two girls and a boy, all with the usual number of 46 chromosomes; one had a baby with normal chromosomes and another with trisomy 21 (Down's syndrome); one had a healthy daughter with 46 chromosomes; and one had a stillborn baby with an omphalocele (a hernia in the abdominal wall).

As it is very likely that the egg cells in a girl with tetrasomy X will contain more than one X chromosome, it is important that a genetic counselling service is involved with the family, so that the pregnancy possibilities are clear. To add to this, families with a daughter with tetrasomy X have suggested that girls who are fertile should be counselled thoroughly before considering a pregnancy because of the difficulties of caring for a baby and child (Bergemann 1962; Gardner 1973; Fryns 1983; Linden 1995; U).

Independence

Some adult women with tetrasomy X lead lives independent of their families. Experience suggests that a few girls achieve full independence while most need some level of support and supervision.

Does Tetrasomy X affect behaviour?

There is no consistent behaviour pattern for all girls with tetrasomy X. Nonetheless, certain traits appear to occur more commonly. Most are described as pleasant and affectionate, but some have a tendency to be shy. In surveys by the support groups, sixteen families (50 per cent) noted some emotional and behavioural problems. Most problems were caused by frustration at girls' inability to communicate but families also noticed impatience, bad temper, temper tantrums and rapid mood swings. Self confidence might be low and girls were typically sensitive to stressful environments. In particular, nine out of 11 families mentioned behaviour problems in girls over the age of 18.

Six out of 14 families of girls aged 15 or more had experienced psychiatric problems, including panic attacks, generalised anxiety disorder, depression and bipolar (manic-depressive) disorder. Psychiatric problems were controlled with medication.

This picture is mirrored in research reports in which girls are described as pleasant, friendly and co-operative, but also potentially aggressive and emotionally labile. Half of all adult women had monthly or bi-monthly episodes of unstable behaviour which was described as angry, disruptive and inappropriate.

Social concerns

There is accumulating evidence that some girls with tetrasomy X are vulnerable to social difficulties. However, this is not a consistent picture. Some girls are timid and lack self confidence, especially in groups and even within the family. As young girls, they may prefer to play alone. As teenagers, they may want friends but not know how to make and keep them and may behave in ways that others find inappropriate.

On the other hand, there are girls who are socially confident and outgoing.

The increased vulnerability to social problems means that families should have a high index of concern and not hesitate to enlist support. This is particularly important in stressful situations that can arise at school (Telfer 1969; Nielsen 1977; Berg 1988; Linden 1995; U).

Support and Information

Understanding Chromosome & Gene Disorders

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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.
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