Tetrasomy 9p
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Tetrasomy 9p is a rare condition that was first described in 1973 (Ghymers 1973). People with this syndrome usually have a small extra chromosome made up of two copies of part of chromosome 9. This extra chromosomal material makes it very likely that people with tetrasomy 9p will need support with their learning and development as well as help for some birth defects and health problems.

**Genes and chromosomes**

Our bodies are made up of billions of cells. Most of these cells contain a complete set of thousands of genes that act like instructions, controlling our growth, development and how our bodies work. Inside all human cells, except the red blood cells and platelets, there is a nucleus where the genes are carried on microscopically small, thread-like structures called chromosomes.

Chromosomes come in pairs of different sizes and are numbered from largest to smallest, roughly according to their size, from number 1 to number 22. In addition to these so-called autosomal chromosomes are the sex chromosomes, X and Y. A normal, healthy cell therefore has 46 chromosomes: 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in pairs. A girl will have two X chromosomes (XX) while a boy will have one X and one Y chromosome (XY). Each chromosome in a pair has a short (p) arm (from the French petit, small) and a long (q) arm. The number and appearance of the chromosomes present in the nucleus of the cells is known as the karyotype.

People with tetrasomy 9p usually have two normal chromosome 9 (one inherited from each parent) as well as an additional small 47th chromosome made up of material from two extra copies of material from the short (p) arm. This means in total they have four copies of the 9p arm, hence the name ‘tetrasomy 9p’ from the Greek word ‘tetra’, meaning four.

**Sources & references**

The information in this guide is drawn partly from medical publications, where approximately 65 cases are reported. The first-named author and publication date are given so you can look for articles on the internet in PubMed. The guide also draws on Unique’s database. When this updated guide was written, Unique had 35 members with tetrasomy 9p, aged from a few months to 38 years old.
An extra chromosome made up of two copies of the same part is called an isochromosome. Sometimes the isochromosome also contains part of the long (q) arm. One person with partial tetrasomy 9q with similar clinical features to those observed with tetrasomy 9p has been reported (McPherson 2005).
To date, approximately 65 cases of tetrasomy 9p have been described, including 20 prenatal cases (El Khattabi 2015; Wang 2015). No bias in the ratio of boys to girls affected has been observed (Chen 2014).

**Tetrasomy 9p mosaicism**
When all the cells of the body contain the extra isochromosome 9, this is known as non-mosaicism. Non-mosaic tetrasomy 9p usually results in miscarriage and babies with non-mosaic tetrasomy 9p are not usually able to survive beyond the newborn period. In most newborn babies the isochromosome 9 is only found in some cells and the remaining cells have a normal karyotype of 46 chromosomes. This is known as mosaicism and affects almost 40% of cases (El Khattabi 2015; Ogino 2007). The cells tested for the karyotype [see below](#) are most often taken from a blood sample. In tetrasomy 9p, blood cells often show non-mosaicism (that is, only tetrasomy 9p cells), even where there is mosaicism or cell lines with only normal cells in other parts or tissues of the body. So a baby who has only had a blood test may be thought to have non-mosaic tetrasomy 9p, when in fact there is mosaicism in other tissues. For this reason, most genetics centres recommend testing samples from more than one tissue, usually either from the skin or from inside the cheek (Lloveras 2004).
Babies found to have mosaic tetrasomy 9p are likely to do better than those with non-mosaic tetrasomy 9p, especially in terms of survival (El Khattabi 2015; de Azevedo Moreira 2003; Dhandha 2002; Dutly 1998).

**The karyotype**
Your genetic specialist can tell you more about how much material there is in the extra isochromosome. The chromosome usually breaks in the short (p) arm close to the centromere (the point where the short arm meets the long (q) arm). Sometimes it breaks in the long arm, also usually close to the centromere.

**47,XY,+i(9p)** This shows that there are 47 chromosomes, it’s a boy [XY], and the extra (+) chromosome is an isochromosome (i) made up of material from the short (p) arm of chromosome 9.
47,XX,iso(9)(q12)\text{de novo}\) This shows that it’s a girl (XX) and that the extra chromosome is made up of the short arm and material as far as band q12 in the long arm. De novo means that the parents’ chromosomes have been examined and are normal. Iso was used by laboratories in the past but today would be (i) or, strictly speaking in this case, idic [see below].

47,XY,+idic(9)(q13) This shows that the extra chromosome is made up of material from the entire short arm and the long arm as far as q13, including the centromeres where the short arms meet the long arms. An extra isochromosome that includes two centromeres is called an isodicentric chromosome, shortened to idic (pronounced ‘eye-dic’).

47,XX,+mar.ish i(9)(p10)(wcp9+) dn This means that it’s a girl (XX) with a small extra chromosome that couldn’t at first be identified. A small unidentified chromosome like this is called a marker (mar). Using a technique called FISH (ish) that allows chromosomes to be examined in greater detail, the marker was found to consist of material from chromosome 9. The chromosome has broken off at band p10, another way of describing the centromere. The specific technique used was whole chromosome painting (wcp), in which the test recognises different parts of the extra chromosome as coming from chromosome 9. You can write de novo as dn, meaning that the parents’ chromosomes have been examined and are normal.

47,XY,+i(9)(p10)[4]/46,XY[16] This is a boy in whom 20 cells were tested. Four [4] showed tetrasomy 9p while sixteen [16] showed a normal karyotype for a boy or man.

**Most likely features among those with mosaic tetrasomy 9p**
The most likely features among those with mosaic tetrasomy 9p - found in at least half of all children and adults reported or described so far - are listed below (El Khattabi 2015; Papoulidis 2012; Ogino 2007; de Azevedo 2003; Dhanda 2002; Unique).

- Developmental delay: In 9/11 Unique cases and 73% of cases reported in the literature (El Khattabi 2015), a delay in expected development was the first sign of anything wrong. Signs were first noticed between the newborn period and early secondary school age.
- Central nervous system (brain and spinal cord) anomaly.
- Abnormal features of arms or legs. These can include dislocated joints and clubfeet.
- Growth delay before or after birth.
- Heart defects.
- Abnormalities of the kidneys, urinary or genital systems (43%) (El Khattabi 2015). In boys, minor anomalies of the genitals or undescended testicles are common. Abnormalities in the genitals of girls are less common.
- At birth, wide gaps between the bony plates of the skull. The front soft spot (fontanelle) may be large.
- Short neck, sometimes with excess skin.
- Typical facial features including wide set eyes, small jaw (chin), oddly formed or positioned ears and a bulbous or beaked nose.
- Cleft lip, palate or a high-arched palate.

**Other typical features**
- Unusually formed nails; a single crease across the palm; incurring fingers, especially the fifth finger; short hands and feet with small toe and finger joints.
- Widely spaced eyes; small skin folds across the inner corner of the eyes; eyes that slant somewhat downwards; a small lower jaw, set back from the upper jaw; downwards slanting mouth
- Low muscle tone, making the body feel floppy (hypotonia).
- Unusual head size – small (microcephaly) or large (macrocephaly).
- Enlarged fluid-filled ventricles within the brain (hydrocephaly).
- Strabismus (squint) or short sight (myopia).
- Dimple near the base of the spine.
- Sunken eyes due to the eyeball being recessed within the orbit.
- Missing or underdeveloped bones.

**How is tetrasomy 9p diagnosed?**
Tetrasomy 9p cells are usually found in highest concentrations in blood, so diagnosis in a baby, child or adult means taking and analysing a blood sample. (Lloveras 2004). A blood sample that shows the presence of an isochromosome in every cell may suggest that a person has tetrasomy 9p in its non-mosaic form, but testing cells present in the saliva and other tissue types may reveal that abnormal cells are present at much lower levels or are completely absent. This could explain why a person may have only mild features despite an initial diagnosis of non-mosaic tetrasomy 9p based on testing only cells found in the blood (Shehab 2011). There is, of course, a limit to the types of tissue that it is possible to test through these less invasive means.
**Prenatal diagnosis**

Diagnosis during pregnancy is challenging as routine fetal ultrasounds may appear normal and tetrasomy 9p cells may not be found in fetal cells in the amniotic fluid (Papoulidis 2012). It is therefore quite possible for a pregnancy to be affected by tetrasomy 9p but for the amniotic fluid or chorionic villus sample to show only cells with normal chromosome numbers (Chen 2007; Eggermann 1998; Grass 1993). The more sensitive molecular cytogenetic testing technique interphase fluorescence in situ hybridisation (FISH) can be used to confirm the diagnosis of tetrasomy 9p and help determine the true degree of mosaicism (El Khattabi 2015; Chen 2014; Shehab 2011).

*Unique has a supplementary information sheet on prenatal diagnosis*

**Why are some people with tetrasomy 9p more severely affected?**

There are quite a few reasons. One is likely to be the size of the isochromosome, although researchers do not always agree on how important this is. Some believe that a larger isochromosome or the presence of additional material from 9q will result in an individual being more severely affected (El Khattabi 2015; Wang 2015; Chen 2007; Wisniewski 1978). Others are not so sure (Stumm 1999). It is also true that individual differences between children even with the same karyotype can be fairly marked. We do know that of 14 cases of prenatally detected tetrasomy 9p (three mosaic and 11 non mosaic), all the reported cases with non mosaic tetrasomy 9p were associated with severe abnormalities (Chen 2014). Equally, there have been five reports of patients with tetrasomy 9p with no apparent clinical symptoms (Papoulidis 2012; Baronchelli 2011; McAuliffe 2005). It might seem obvious to suggest that when a higher proportion of tetrasomy 9p cells is found, the effects are likely to be more severe. But this is not necessarily true (Papoulidis 2012). One reason for this discrepancy may be varying proportions of tetrasomy 9p cells in tissues of importance for development – tissues which often cannot be investigated.

**Why is tetrasomy 9p so variable?**

There are four key reasons: whether the person has mosaic or non mosaic tetrasomy 9p; whether this mosaicism is limited to certain tissues; the size of the isochromosome; which regions of chromosome 9 have been duplicated (Wang 2015; Nakamura-Pereira 2009).
Mosaic or not mosaic: When only tetrasomy 9p cells and no normal cells are found in both blood and skin cells or amniotic fluid, the effects are likely to be more obvious and more severe. Babies with mosaic tetrasomy 9p survive the newborn period better [El Khattabi 2015].

Tissue-limited mosaicism: The proportions of tetrasomy 9p cells are different in different body tissues. A review in 2015 found that approximately one third of reported cases of tetrasomy 9p showed tissue-limited mosaicism [El Khattabi 2015]. In blood there are more tetrasomy 9p cells and sometimes no normal cells are found. In other tissues, especially skin and mucous membranes, the proportion of tetrasomy 9p cells is usually lower and no tetrasomy 9p cells may be observed. Organs such as the brain and lungs, may have different proportions again and this variability is very likely to affect the outcome [Lloveras 2004; Dhanda 2002]. It should be noted that in some cases the degree of mosaicism did not seem to correlate with the severity of the symptoms observed [Papoulidis 2012].

Size of isochromosome: That is, the amount of extra chromosome material. Common sense suggests that those with larger extra chromosomes will be more severely affected; however, there have been reports of people with isochromosome 9p who are only very mildly affected or indeed seem not to be affected at all. It should be noted that a recent review of almost 60 cases suggests that developmental delays are more frequent when a portion of the long arm of chromosome 9 (9q) forms part of the isochromosome [El Khattabi 2015]. This variability means that when tetrasomy 9p is identified prenatally, providing appropriate genetic counselling can be difficult.

Specific duplicated regions: Not unsurprisingly, the specific region that is duplicated and the genes that are disrupted can have a marked influence on the severity of symptoms.

A boy with three copies of the section of chromosome 9 between band p13 and p22 shared some similarities with children with an isochromosome 9p, but had no major anomalies apart from enlarged ventricles within the brain. This could suggest that the part of 9p that he did not have extra copies of (9p23 to the tip of 9p) is the part that causes important birth defects [Verheij 1999].

A 10 year old boy with tetrasomy 9 mosaicism had features that mimicked Klinefelter syndrome. Klinefelter syndrome occurs in males with an extra X chromosome (47, XXY) and is associated with tall stature and anomalies of the genitals, including an inconspicuous penis (when the penis appears to be absent or too small) and testicular dysfunction. Otherwise, this boy exhibited normal motor skills, was in good health and progressing well at school. In this case, it is likely that the percentage of tetrasomy 9p cells in the testis was higher than in the blood or saliva. This was in fact the second reported case of tetrasomy 9p mosaicism mimicking Klinefelter syndrome and other cases of trisomy 9p and mosaic tetrasomy 9p cases with gonadal hypofunction, when the testes or ovaries show a diminished level of function, have also been reported. This suggests that over expression of some genes on chromosome 9p may lead to gonadal/testicular hypofunction [Ogino 2007; Peters 1982].
Are there people with tetrasomy 9p who are healthy, have no major birth defects and have developed normally?

Yes, there are. Out of around 65 reports in the medical literature, there are at least five people with apparently normal development and a possible sixth. One adult is an accountant and was discovered to have tetrasomy 9p when infertility was investigated. Two apparently healthy 20- and 28-year-old women with tetrasomy 9p mosaicism were also reported, and highlighted that there is not always a correlation between the level of mosaicism and the degree to which a person is affected. Another adult was investigated for skin lesions. Another case is of a child who has developed normally to the age of five, although he showed growth delay before birth; a six-month-old baby also had no apparent abnormalities at the age of 6 months (Papoulidis 2012; Shehab 2011; Baronchelli 2011; McAuliffe 2005; Lloveras 2004; Nakamura 1990). Among Unique’s members, two children were only diagnosed after being investigated for developmental delay in the late primary school or early secondary school years.

What is the outlook?

The outlook for babies diagnosed with tetrasomy 9p is extremely variable. In some babies there is little or no effect on development or health, while in others the effects are obvious and sadly survival may not be possible. Among Unique’s members, two babies were stillborn, and another died at 13 months. Those babies diagnosed with non-mosaic tetrasomy 9p appear to be at greatest risk and typically do not survive the newborn period. Babies with a mosaic form of tetrasomy 9p have a better outcome. People with an isochromosome containing part of the 9q region or when at least two tissues are affected appear to be more likely to have heart defects and learning difficulties and may be less likely to survive the newborn period (El Khattabi 2015).

As tetrasomy 9p is most likely to appear to be non-mosaic in blood, it is important that all babies with the diagnosis made from a blood test have tissue from another part of the body (such as skin or mucous membranes) examined as well, as this is more likely to show mosaicism (Shehab 2011; Tang 2004; Moreira 2003; Dhanda 2002).

There is little published information on the long term outlook for babies born with tetrasomy 9p. Among Unique members born without complex heart problems, 10 (out of 16) aged 1 to 25 were healthy and active and taking no regular medications apart from vitamins. One child has Raynaud’s disease, with spasm of the blood vessels in the extremities, and polyarthritis causing pain in many joints; one has developed chronic relapsing fatigue; and one has a recurring cyst, while another has had a very large benign cyst removed (see page 21) (Unique).
What is the outlook? One adult’s story

J is now 25 years old and continues to make progress, though we as parents do not necessarily see all the steps. Supported by Real Employment, a local scheme for adults with learning disabilities, he now has a part-time job at the Co-op supermarket in a village nearby. He started on two shifts a week unpaid and has worked his way up to 9 hours a week, fully paid. He has joined the company pension scheme and really enjoys his job and feels that he is a valued member of the team. His colleagues are friendly and he is included in social events such as meals out at Christmas. His duties are to unload the deliveries and work in the stock room. He also works in the shop, shelf-filling and checking for items which are past their sell-by date and in this regard he is very thorough! He even comes home and checks through my cupboards. He was delighted to receive a £5 voucher from the manager recently, in recognition of his customer service skills: he had assisted a lady who was struggling with her toddler and her shopping by helping her to the till and then taking her shopping to the car. He needs time to accustom himself to a new challenge, but with support soon grows in confidence. He is 100% reliable and always punctual. He was so proud when he received his uniform and in particular his company name badge. The development of his self esteem, the acquisition of new skills and the opportunity to meet new people in a safe environment have been real positives from this workplace opportunity. It is so important to meet people beyond the family unit. Real Employment has recently approached him and the Co-op to make a short film to raise aspirations in young people in respect of gaining employment. We were delighted that he had the confidence to agree.

In terms of hobbies, he is an avid Sheffield Wednesday fan, and can tell you all the latest football news. We have also taught him to ski: much patience was required! He does not have the best technique in the world, but he is a strong young man with a very strong snow plough, who happily skis the full mountain on red runs!!

On the negative side, we are experiencing some difficulties with him leading a healthy lifestyle. The word moderation is not on his radar in terms of food and drink. He will eat a pound of cheese rather than make a sandwich, snack on 4 pork pies and he drinks more alcohol than is good for him. We were trying to promote some financial independence, but have had to go back to fully managing his money and giving him small amounts of cash.
How did this happen?
In the great majority of children, the extra material from 9p appears as a separate, small chromosome. When the blood of parents with an affected child is examined, it has so far always revealed normal chromosomes (McAuliffe 2005). In this situation, studies have indicated that the most common reason for the extra chromosome is the failure of the chromosomes 9 in one parent to separate in the process of preparing the eggs or sperm, leading to an extra whole chromosome 9. This extra chromosome is believed to then undergo an unusual type of division, leaving it with two top halves (short arms) while the two bottom halves (the long arms) are lost (Dutly 1998). Separation failure, termed non-disjunction, is more common in older mothers (as in Down’s syndrome) and both the maternal and paternal average age of those having a child with tetrasomy 9p is slightly higher than average; however, a clear correlation between advanced maternal age and the occurrence of tetrasomy 9p has not been reported (El Khattabi 2015; Di Vera 2008; de Azevedo Moreira 2003; Dutly 1998; Grass 1993).

Can it happen again?
So long as the parents have normal chromosomes, the extremely unusual sequence of events that led to a fetus with tetrasomy 9p is very unlikely to happen again. Many couples will want the reassurance of having their next baby’s chromosomes tested during pregnancy by chorionic villus sampling or amniocentesis. Although these techniques do not necessarily show tetrasomy 9p (see How is tetrasomy 9p diagnosed?), a normal result is reassuring. Only one instance of two children affected by tetrasomy 9p being born to the same parents has been reported and is likely to be due to gonadal mosaicism, that is the presence of tetrasomy 9p in the testes of the father or ovaries of the mother. If a sperm or an egg produced from those cells that have tetrasomy 9p is used to form a fetus, then the child will be affected (El Khattabi 2015).

Can it be passed on?
The great majority of children with tetrasomy 9p have parents with normal chromosomes. But there are some people - and no-one really knows how many of them there are - who themselves have tetrasomy 9p but are very mildly affected by it. They can pass it on. They can also have normal children. One man with tetrasomy 9p had two children with normal chromosomes, but his wife also had five pregnancies resulting in miscarriage (McAuliffe 2005).
A child with tetrasomy 9p

Facial appearance
Certain facial features are found more often in children with tetrasomy 9p than in other children. These features do not matter to your child, but they may mean that you see unexpected similarities between your child and others with tetrasomy or even trisomy 9p. The common features are: unusually formed or positioned ears; a small lower jaw (micrognathia) that may also be receding (retrognathia); widely spaced eyes that can be deep set or even sunken and slant upwards or downwards; a broad, bulbous or beaked nose; a large mouth with downturned corners or a short groove between the upper lip and the nose; a short neck or too much nuchal skin; and skin folds at the inner corner of the eyes. Your child’s head may have an unusual shape and may be small or enlarged. Newborn babies may have wide gaps between the bony plates of the skull and a very large soft spot (fontanelle) on top of the head that can take years to close. Affected babies also show a decreased rate of growth (El Khattabi 2015; Ogino 2007; Tan 2007; Henriques-Coelho 2005; Dhanda 2002; Park 1995; Schaefer 1991; Moedjono 1980; Unique).

Feeding
Feeding problems are common in babies and children with a chromosome disorder but in this group breastfeeding was possible for many and in one case continued to two years. There was one report of a baby who struggled with both breast and bottle feeding and tired quickly due to hypotonia, and another of a baby whose feeding problems resolved after his tongue tie was snipped. Some babies were diagnosed with allergy to a milk formula, and in one case to soy, and fed on replacement milk. It is not known whether a mild degree of reflux (bringing feeds back) was interpreted as a milk allergy (Unique). Upon the advice of a dietician, a number of parents reported the successful use of fortified baby milk substitute to promote weight gain (Unique). Swallowing difficulties and episodes of choking have been
seen. Only one feeding report was received for a baby with significant heart problems; not unexpectedly, this child was fed by gastrostomy tube direct to the stomach. Several other children have needed a gastrostomy tube; in at least one case it was successfully removed at the age of 5 years (Unique).

Quite a few babies with tetrasomy 9p have a cleft palate (a split in the roof of the mouth), sometimes with a split in the upper lip as well, but feeding was even problem-free in one baby with a cleft lip and palate (Orye 1975). Typically, babies with a cleft lip or palate have greater feeding difficulties until their condition is stabilised or surgically corrected.

One adult we know of eats well, but seems to have problems with chewing and cannot suck through a straw [Unique]. See also page 9, One Adult’s story

**Growth**

Birth weights at term: Non-mosaic 2lb 11oz / 1.21kg to 5lb 15oz / 2.7kg
Mosaic 3lb 10oz / 1.644kg to 8lb 8oz / 3.856kg

Height and body build are variable, with some adults short (5’ 1”/1.55m in a girl of 19 years; an adult man the height of a 12-year-old) while others are of average height (5’ 9”/1.75m in a boy of 16 years; 5’ 11”/1.8m in a boy of 15); however, the data supplied to Unique does suggest that on average height and stature are generally below average. There does not appear to be a clear link between growth delay before birth and childhood height, with examples of small -for-gestational-age babies growing into average-height children (Lloveras 2004) and others of babies of average birth weight later failing to thrive (Stumm 1999; Unique). Body build also varies from stocky to slight, with more children described as slight. We don’t know whether children with tetrasomy 9p continue to grow in their 20s, as some with trisomy 9p do.

“He is slight - to the amazement of those who know how much he can eat.” - adult

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

Many babies and children are late to achieve their `milestones` of sitting and walking and are helped by regular physiotherapy. There is a wide range of eventual ability, however, with some children acquiring mobility skills around the same age as typical children and others showing more obvious delay. Among 19 children from Unique, rolling over was achieved between 3 and 15 months, sitting between 4 months and 4 years, crawling or bottom shuffling between six months and 3 years, and walking independently between 12 months and 7 years.

Mobility is affected by abnormal muscle tone and many children either have low tone (hypotonia) or high tone (hypertonia). Babies with low muscle tone at birth feel floppy to hold and have obvious head lag. Low muscle tone generally improves with maturity but may still be present in adults. Regular physiotherapy helps, and the use of orthotics such as support boots may also help increase mobility.
Eventual walking style also varies. While some achieve total mobility and learn to climb stairs - at least with a rail, to run, ride a bicycle and to swim, others retain an uneven and uncoordinated walking style and some rely on wheelchair use for long distances and outdoors. In general, it appears that those least affected or unaffected in early childhood are most likely to achieve normal mobility and sporting prowess as adults, while those children who have obvious mobility problems early on achieve a more limited degree of mobility. But a child who walked first at 7 can walk long distances with other people as an adult and doesn’t use a wheelchair [Unique].

**Joint abnormalities**

Joint abnormalities are a known feature of tetrasomy 9p at birth, with extremely loose joints and dislocations (elbows, wrists, knees, hips) often observed (El Khattabi 2015; De Azevedo 2003; Tonk 1997; Leichtman 1996; Linuma 1994; Cavalcanti 1987; Shapiro 1985; Moedjono 1980). Children with very loose joints may need additional braces (supports, splints) before they are able to walk. In some cases, joints are unusually tight and may require surgery and tendon lengthening to extend their range of movement.

A wide variety of specific abnormalities of toe and foot position are also a common feature of tetrasomy 9p. These may include pes cavus (‘claw foot’), pes planus (flat feet), rocker bottom feet (the sole is curved without an instep, like a chair rocker), pes planovalgus (the feet are flat and stick out), pes equinovarus (club feet, with the foot turned inwards, the soles pointing towards each other), pes adductus (so-called ‘banana foot’, where the toes point inwards) and other less common positions. Babies born with feet affected in this way will receive specific physiotherapy which may avoid the need for corrective surgery and plaster casting. Treatment is tailored to the individual child and in some cases surgical correction will best enhance eventual mobility.

Some children have a degree of hip dysplasia, in which the hip joints are easily dislocated. This may be apparent at birth or develop later. In either case it is treated with splinting and if necessary immobilisation in plaster and possibly surgery (Eggermann 1998; Papenhausen 1990).

Some babies are born with or develop a spinal curvature, either curving sideways (scoliosis) or forwards (kyphosis). Underlying the curve may be abnormalities of muscle tone and in some cases the bones of the spine (vertebrae) may be fused together or incorrectly formed. The curvature can be treated with physiotherapy and exercises, or a support brace may be needed. If the curve becomes marked it is possible to straighten the spine using rods (Dhanda 2002; Stumm 1999; Verheij 1999; Dutly 1998; Melaragno 1992; Sjöstedt 1989; Balestrazzi 1983; Moedjono 1980; Unique).
Development: hand use and coordination (fine motor skills)
Development of hand use and hand-eye coordination are frequently delayed but the evidence from Unique is that adults are generally able to carry out daily personal care tasks. One family supplied a detailed timetable of their son’s fine motor development: used a spoon at 13 months; placed 3 bricks in a tower at 21 months; used a knife and fork at 27 months; bounced and caught a ball at 27 months; drew a circle at 36 months; drew a person at 42 months. As an adult, this young man is able to dress and care for himself but needs help with small buttons and shoe laces. Another young man in his twenties eats with a fork and spoon, and knows how to dress, but needs help.

The hands are frequently affected by tetrasomy 9p with common features such as bent and shortened fingers and thumbs, occasionally overlapping each other or joined by a bridge of skin and tissue, as well as abnormal or missing fingernails. The tips of the fingers may be noticeably shortened and even missing. The Unique experience is that these features do not generally affect the way a child uses their hands and only need correction when hand use is affected.

Development: toilet training
Data relating to the age at which children with tetrasomy 9p were toilet trained is limited; however, among 9/31 people in Unique, toilet training was successful between 2 years 3 months and six years, but not possible for all.

Learning
The range of learning ability is very broad. At one end of the spectrum are an adult with a professional career and children who attend mainstream schools, are able to follow the standard curriculum, sometimes with help for specific learning difficulties, and achieve a range of school-leaving qualifications. At the other end are children and adults with a moderate to severe learning disability. A statement or plan allowing for 1:1 support has proved invaluable for many children.

The evidence on learning comes chiefly from Unique and shows that in general
children with tetrasomy 9p have mild to moderate learning difficulties. Many learned to read and write between the ages of five and 11 years. Age of first reading does not necessarily predict eventual ability as one of the highest achieving adolescents was a relatively late reader. Specific areas of high ability and specific learning difficulties occur and a common theme appears to be a facility for visual learning.

- An adult man enjoys practical work and has a good memory for some things, but cannot read and has no interest in writing. He was at a special school from 2 to 19, then a residential college for three years and is now finishing a part time course at a local special needs college.
- A 19-year-old girl has a highly developed memory for people, upcoming events, lost or misplaced property and travelling directions. She is better able to learn practical tasks than academic tasks. She is extremely observant and interested in people. She can sign her name, copy most letters and write them with verbal prompts. She attended a mainstream primary and special secondary school.
- A 16-year-old boy who has attended a mainstream school with 1:1 support passed the United Kingdom school-leaver examinations in mathematics, science, art and design and shows particular strengths in subjects where word use is minimised. He has a talent for abstract art and impressionism.
- One 15-year-old shows an excellent - even remarkable - long term memory but has poor short term recall and working memory. He is a strong visual learner and is good at mathematics. He has dyslexia which prevents avid reading but he listens to stories such as Harry Potter. His drawing and writing are normal. He attends a private school for students with normal intelligence but learning disability.
- A 13-year-old girl, attending a mainstream secondary school, is reading books for 8-10 year olds and writing at a similar standard. Another girl, aged 10, has a very good memory and is able at English. She attends a special school where her learning is most helped by her determination, by observation of people and things around her and her good memory.
- A 6-year-old girl also has a very good memory and is willing to learn but lacks concentration and confidence. She reads school books, can write her name, some letters and some numbers and can draw people and butterflies. She attends a mainstream school with additional support.
Speech and communication

The ability to speak and converse generally reflects learning abilities, so children who need greater learning support tend to be those who start speaking later and develop less complex language. Children whose learning ability falls within the normal range may show little or no delay in initially acquiring speech and language and go on to develop complex conversational skills and a broad vocabulary.

Information provided to Unique indicated that most [16/17] children had delayed speech and this could be linked to hearing loss (see below) and low muscle tone. A number of parents reported that even where speech was delayed there was a big improvement in speech later in childhood. First words have generally emerged between nine months and four to five years and linked words and longer phrases by 10 years, but not everyone acquires speech. There are wide differences between individuals in understanding, with understanding and expression on a par in some children while in others expressive skills outstrip receptive language or vice versa. Where individuals have no speech or very few words, communication has still been successful through signing, gesture, facial expression and assistive technology.

Even among the fluent speakers, some lack of clarity has tended to persist with a small cluster of families remarking on their child’s disordered phonology and inability to discriminate between s, f, th and v sounds.

A mild to moderate hearing loss appears to be common. Hearing tests at birth are often normal, with hearing loss developing due to glue ear, made worse for a few children by unusually narrow external ear canals (Sepahi 2010; Tonk 1997; Melaragno 1992; Orye 1975, Unique). Glue ear is typically treated by inserting aeration tubes (grommets) into the eardrum and this surgical operation may need to be repeated. Normal hearing may not be achieved with aeration of the space behind the eardrum (middle ear) and hearing aids may help as a temporary or longer-lasting measure. As children are at risk of speech delay, parental concerns should be acted on early and home or school-based therapy provided.
Behaviour

The evidence from Unique shows that children and adults with tetrasomy 9p are loving, caring individuals and generally speaking have an open and sociable temperament. There is no obvious relationship between behaviour and learning ability, although those children with greater functioning difficulties will be in an environment where less is expected of them. Individuals do have difficulties in interpreting and responding suitably to social cues and this is most apparent in those who are in a mainstream environment outside their family. They may well be popular with their peers but find it easier to relate to people older or younger than themselves.

Within the family, children may experience difficulties with frustration and in accommodating their brothers and sisters, while some children may find it difficult to entertain themselves and require a greater degree of 1:1 attention. Early access to advice, input and therapy will help those families who find themselves in difficulties with their child’s behaviour. One child has a diagnosis of attention deficit hyperactivity disorder (ADHD) but methylphenidate (Ritalin) medication controls restlessness and inappropriate comments. Another child with frustration difficulties within the home has been helped by a behaviour chart and a clear reward system.

A loving, caring lad with an open and sociable temperament. Everybody loves him, but he does have a mind of his own and won’t be put on - age 26
A very outgoing personality who copes quite well socially. She can approach strangers but will withdraw or proceed depending on the reaction she gets. She does pick up on social cues and is very keen to help. She will initiate assistance and predict your needs - age 19
A likeable personality, very affectionate. Most of the time he is lovely and continues to be well behaved outside the family environment. He can be rather obsessive at times, e.g. tidiness, washing clothes etc. Socially, he is popular but his immaturity makes it difficult for him to have close friendships with people of his own age - age 16
A very sweet, loving child, he has an acute perception of people’s true selves - age 15
Socially, she gets on brilliantly with strangers; gets on OK with the family until she can’t do something she wants - age 10
Very friendly, loves to stop and chat with people. Happy and cheerful and her happiness rubs off on everyone - age 6

Autism

A 20 year old female who was diagnosed with mosaic tetrasomy 9p at the age of 6 years due to her facial appearance and developmental delays (including deficiencies in her speech and language skills and impaired social communication) was subsequently diagnosed with an autism spectrum disorder (ASD) [Chen 2012]. ASDs include autism and Asperger’s disorder and are associated with impaired social skills, problems with communicating, and a
need to carry out repetitive and restrictive behaviours (obsessive-compulsive disorder [OCD]). A single gene located on chromosome 9 at region 9p24 is thought to be linked to ASDs and OCD [Martinez-Jacobo 2015; Kantojarvi 2010]. There is anecdotal evidence from Unique of other people with tetrasomy 9p exhibiting ASD and OCD behaviours but a causal link has not been established, and some expert opinion doubts any link [El-Khattabi, personal communication].

Health concerns

**Eyesight**

Known difficulties include a squint (strabismus), including exotropia (divergent squint), frequently intermittent, and lack of stereoscopic vision (teaming of the eyes) causing loss of 3D vision and depth perception. Strabismus may be treated with patching, glasses, exercises or surgical correction. In at least one Unique child, the squint self-corrected by the age of six years.

There are six cases of marked short sight and one child and one adult are registered as partially sighted. Other children have sunken eyes; lazy eye (amblyopia); uncontrolled eye movements (nystagmus); an abnormal development of the iris; damage to the part of the back of the eye known as the chorioretinal area; a single eye [El Khattabi 2015; Lloveras 2004; Cazorla Calleja 2003; Dutly 1998; Tonk 1997; Papenhausen 1990; Balestrazzi 1983; Cuoco 1982; Garcia-Cruz 1982; Abe 1977; Orye 1975; Unique]. In at least one child the development of good vision was affected by raised pressure within the brain [Stumm 1999].

**Head and brain**

Many babies were born with a very large soft spot (fontanelle) or wide spaces between the bony plates of the skull. The front fontanelle was also often slow to close and in one child was still open at age 4 [Unique]. Additionally, some babies have an unusual head shape or size (‘strawberry skull’; asymmetric head shape; microcephaly – small head; macrocephaly – large head; brachycephaly – the head is disproportionately wide ear-to-ear compared to the measurement from front to back). One Unique baby was 2 years old before he was able to support his head.

In some babies and children, a structural abnormality of the brain was found, much more commonly among youngsters with a non-mosaic form of tetrasomy 9p. Structural anomalies such as enlarged ventricles (fluid-filled spaces) within the brain, absence or underdevelopment of the corpus callosum (the bundle of nerve fibres that links the brain’s two hemispheres) and Dandy Walker may be detected on prenatal ultrasound. The Dandy Walker anomaly is a cyst in the balance control part of the brain (cerebellum) that is involved with the fourth ventricle, one of the fluid-filled spaces within the brain. This may interfere with the body’s ability to drain cerebrospinal
fluid from the brain, resulting in hydrocephalus, a build-up of fluid within the brain (El Khattabi 2015; Nakamura-Pereira 2009; Lloveras 2004; Cazorla Calleja 2003; Stumm 1999; Andou 1994; Melaragno 1992; Balestrazzi 1983; Cuoco 1982; Garcia-Cruz 1982; Peters 1982; Ghymers 1973; Unique).

Some data suggest that the over-expression of genes located on 9pter-9q12 may be responsible for the abnormal migration of neurones (brain cells) during the development of the brain (di Vera 2008).

Other brain anomalies include underdevelopment of the grey matter both in the cerebellum and the cerebral hemispheres; lissencephaly (smooth rather than ridged brain surface); pachygyria (where the ‘hills‘ in the undulating landscape of the brain’s surface are unusually large); polymicrogyria (where the ‘hills‘ are many and small) (Cazorla Calleja 2003).

The most frequent problem that occurs after birth is hydrocephalus, usually requiring a shunt to drain the excess cerebrospinal fluid and relieve pressure on the growing brain. The build-up of hydrocephalus may occur even when a child’s head is unusually small (microcephaly). The experience of treatment for hydrocephalus is challenging for families, but one Unique family whose baby son had a shunt fitted at six months reported that at 12 months old he ‘has come a long way and is developing very well, even though he is still behind’. Despite the high rate of brain anomalies, only one child has been described as having had a seizure (not repeated) and among Unique members none has reported seizures (Andou 1994).

**Teeth**

Children with rare chromosome disorders are at risk for dental problems. In this group, 9/15 children were affected and one child with abnormal enamel has recently been reported (El Khattabi 2015; Unique). Both crowding (with malpositioning) and failure of milk teeth to fall out as permanent teeth came through were common and children had a high rate of dental extractions. One child lost her first milk tooth at nine years, seven months. In two children the milk teeth were late to emerge. A high standard of dental care is important to minimise damage by decay and erosion (by grinding) (Garcia-Cruz 1982; Peters 1982; Unique).

“Grinds his teeth, particularly when tired. A brace would have been useful to straighten his teeth, but the dentist and I can’t see him wearing one. He has no fillings, no extractions and no decay - but he doesn’t like sweets or fizzy drinks.”
- age 26
Palate

Abnormalities of the roof of the mouth are relatively common, affecting 32% of babies (El Khattabi 2015). Abnormalities can range from those invisible to the casual onlooker (a high palate, a divided uvula, the projection of soft tissue that hangs down from the back of the mouth) to an obvious defect with a divided upper lip and a large gap in the roof of the mouth. More serious defects were much more common in those with a non-mosaic tetrasomy 9p.

A cleft lip and palate is caused by an error in fusion when the fetus is forming. The lip and palate fuse from pieces that start on opposite sides of the head. The lip fuses around weeks 6-7 and the palate at around 12 weeks. A cleft occurs when the pieces come round but do not join. A cleft lip palate causes difficulties in feeding and speech production. Surgical repair eases these and may eliminate them.
Heart
A structural heart anomaly has been found in around one third of children and adults with mosaic tetrasomy 9p (El Khattabi 2015). The rate among Unique members was slightly lower at 26%, but half of these babies were born with complex, serious heart problems.

There were a wide variety of heart problems and outcomes. Among Unique members, in one teenager the heart is positioned to the right instead of the left of the chest (dextrocardia), without any effect on function or development; one youngster has insufficient mitral valves, a condition in which the valve between the upper left heart chamber and the lower left chamber does not close well enough to prevent back flow of blood when the ventricle contracts; this usually needs correction with surgery. A further youngster had mitral valve prolapse, in which the flaps of the mitral valve do not work well and allow back flow of blood from the ventricle to the atrium. This condition occurs in 1:20 people in the general population and often does not need treatment.

Among the cases reported in the medical literature, seven babies had a persisting feature of fetal circulation known as persistent left superior vena cava. This usually causes no problems but can be associated with other heart problems. In this group, five babies had additional heart problems; unfortunately, none of these babies survived the newborn period. Other babies had complex heart problems including holes between the upper and lower heart chambers (atrial septal defect/ ASD; ventricular septal defect/ VSD), narrowed or thickened heart valves and further persisting features of fetal circulation including most prominently a patent ductus arteriosus that were not compatible with life. However, not all babies with heart problems requiring surgical correction had a gloomy outcome. One Unique baby was born with multiple heart problems which were corrected surgically at one week of age and a baby with a VSD and patent ductus arteriosus repaired at four months was doing well at the age of three (Tang 2004; Lloveras 2004; Cazorla Calleja 2003; Dutly 1998; Tonk 1997; Papenhausen 1990; Calvieri 1988; Melaragno 1992; Orye 1975; Ghymers 1973; Unique).

Minor anomalies of the genitals
Among boys with a mosaic tetrasomy 9p, nine (out of 20) and three girls (out of 22) were affected. Four boys were born with undescended testicles (cryptorchidism). The testicles begin their descent from the abdomen during fetal life and have usually arrived in the scrotum by birth. In a significant number of boys without any chromosome abnormality, that journey is not complete by birth but is completed within the next few months. When descent does not occur, the testicles can be brought down in a surgical operation and anchored in the scrotum. Natural descent occurred during the first year of life in one boy. Two boys were born with a small penis (micropenis). One adult, otherwise normal, had no genital anomalies but low levels of sperm (oligospermia) (McAuliffe 2005;
Among those with a non-mosaic form of tetrasomy 9p, more babies were affected and generally more severely.

**Skeleton and bones**

A variety of unusual features of the skeleton have been reported, including underdeveloped shoulder blades, missing ribs in three babies; a prominent collar bone; underdevelopment of collar bones causing marked sloping of the shoulders; uneven skeletal growth with one side of the body larger than the other, a condition known as hemihypertrophy (El Khattabi 2015; Stumm 1999; Dutly 1998; Calvieri 1988; Balestrazzi 1983; Cuoco 1982; Garcia-Cruz 1982; Unique).

**Kidneys**

The kidneys were affected in more than one baby or child out of three with mosaic tetrasomy 9p. Among Unique members, only one child was affected, having repeated urinary infections as a child that needed preventive treatment with antibiotics. In other children the kidneys were small or large, but without functional implications. Among babies reported in the literature, cystic kidneys occurred once. Fluid-filled sacs form in the kidneys, usually during fetal life. A solitary cyst may not interfere with function unless it is large but multiple cysts may stop the affected kidney from working. A multicystic kidney may be removed if it is causing discomfort. The important thing is to ensure optimal function of the other kidney.

Hydronephrosis – enlarged kidneys – occurred in three cases and horseshoe kidneys in one. The bottom points of the two usually separate kidneys are joined, creating a U (horseshoe) shape. In itself this is not harmful and around one third of children with horseshoe kidney have no symptoms and may need no treatment. However, a horseshoe kidney can increase the risk of urinary tract infections. One child had a single kidney (El Khattabi 2015; Sepahi 2010; Tang 2004; Cazorla Calleja 2003; Dutly 1998; Melaragno 1992; Balestrazzi 1983; Ghymers 1973; Unique).

**Spine**

A sacral dimple (dimple or hole in the skin just above the crease between the buttocks) is also sometimes seen, but is six times as common in babies with non-mosaic tetrasomy 9p as in babies with the mosaic form. The sacral dimple may be shallow so you can see the base, but stools can collect there before your child is toilet trained, so keeping it clean and protected is important. A sacral pit may be deep and even connect to the spinal canal or the colon. If there is any concern about this, your baby’s spine will be imaged, usually with ultrasound or an MRI scan (Tonk 1997; Calvieri 1988; Unique).

See also spinal curvature, page 13
Skin lesions
Benign (non-cancerous) skin lesions (pilomatricomas) have been found in some people with tetrasomy 9p. These lesions may need to be surgically removed (El Khattabi 2015, Unique). One otherwise healthy 41-year-old man with skin lesions was only found to have mosaic tetrasomy 9p as a result of cytogenetic analysis carried out to investigate their cause (Papoulidis 2012).

Inflammatory myositis and lupus-like features
A 6 year old girl with mosaic tetrasomy 9p was recently reported to show signs of inflammatory myositis (chronic muscle inflammation accompanied by muscle weakness) and lupus-like features (an autoimmune condition which occurs when, for as yet unknown reasons, the immune system starts to attack and damage healthy cells, tissues and organs). It has been suggested that the additional copies of genes related to the correct functioning of the immune system that may be present in some cases of mosaic tetrasomy 9p, can lead to the immune system becoming over-active. Upon diagnosis appropriate treatment with corticosteroids and mycophenolate (mofetil) resulted in the total remission of all symptoms (Fremond 2015). One case of a confirmed autoimmune disorder has been reported to Unique.

General wellbeing
There is a report at Unique of a child with relapsing pain, fatigue and skin symptoms.

Other medical concerns
Missing gallbladder (Dutly 1998)
Umbilical hernia (Henriques-Coelho 2005; Dutly 1998; Eggermann 1998; Cavalcanti 1985; Unique)

Seen in non-mosaic form only
Under-developed lungs, possibly due to diminished fetal movement, sometimes with unusual lobe pattern and bronchopulmonary dysplasia (Henriques-Coelho 2005; Deurloo 2004; Dhanda 2002; Park 1995; van Hove 1994; Shaefer 1991)
Malrotation of part of the intestine (Dhanda 2002; Park 1995; van Hove 1994)
Diaphragmatic hernia (Henriques-Coelho 2005; Wisniewski 1978)
Underdeveloped bladder (Dhanda 2002)
Biliary atresia (Henriques-Coelho 2005) Inflammation of bile duct to the liver, causing blockage of the flow of bile and jaundice. The condition is treated through an operation called Kasai-portoenterostomy in which a loop of bowel is used to form a duct to drain bile from the liver.
Unique mentions other websites to help families looking for information. 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. It was compiled by Unique and reviewed by Professor Fionnuala McAuliffe, University College Dublin and National Maternity Hospital, Republic of Ireland and by Unique’s chief medical advisor, Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK. 2007 (PM) Revised by Unique and reviewed by Dr Laila El Khattabi, Cochin Institute, Paris, France 2015 V2

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