

Ring 9



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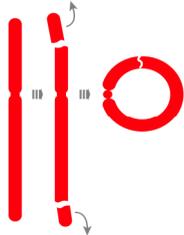
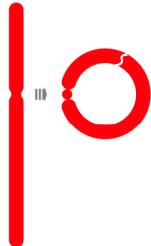
Ring 9 is a very rare chromosome disorder caused by an abnormal chromosome 9 that has formed a ring. The effects are variable, so people with ring 9 can be quite different.

What is a chromosome?

All our genetic information is carried in the cells of our body. Chromosomes are the structures that carry this information in the form of genes that tell the body how to develop and function. Chromosomes come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. Chromosomes are usually shaped like threads, with a short arm and a long arm. Occasionally the ends of a chromosome join to form a ring. Any of the 22 different chromosomes can form a ring and so can the sex chromosomes X and Y. The other chromosome in the pair is the usual thread-like shape.

How does a ring chromosome form?

A ring can form in different ways.

- Both arms of the chromosome usually break near the tips and the broken 'sticky' ends fuse. The broken fragments are lost, and with them any genes they may contain. For healthy development, chromosomes should contain just the right amount of material - not too much and not too little - so even a tiny piece of missing material can disturb development.
- Sometimes the tips of a chromosome fuse without losing any genes or other chromosome material. This way of forming a ring is believed to give rise to what is called **ring syndrome**. Ring syndrome is essentially the same, whatever chromosome is involved and most obviously affects growth. After conception, when the cells in the embryo that will become the baby are dividing and multiplying, the ring may not divide easily, and this can leave some cells with one ring, others with no ring, and others with two rings, entangled rings or double sized rings in a process known as dynamic mosaicism. The cells containing odd numbers of rings or no ring die off and the constant loss of cells is probably what causes very slow growth.
- Some rings are made in an even more complicated way, with part of the chromosome near the tip being duplicated (**dup** for short). The duplication can be in reverse order (inverted or **inv** for short) in the chromosome. At the same time, the tip is lost (deletion or **del** for short). This type of chromosome change, known as **inv dup del**, is not uncommon (Rossi 2007; Seghezzi 1999; Jacobsen 1973).

Sources & references

The information in this leaflet is drawn from the medical literature. By 2005, 23 cases had been reported, the oldest a man of 39 years. 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. The leaflet also draws on *Unique's* database. When this leaflet was written, *Unique* had twelve members with ring 9 (Purandare 2005; Smith 1989; *Unique*).

Looking at a ring chromosome

Chromosome analysis

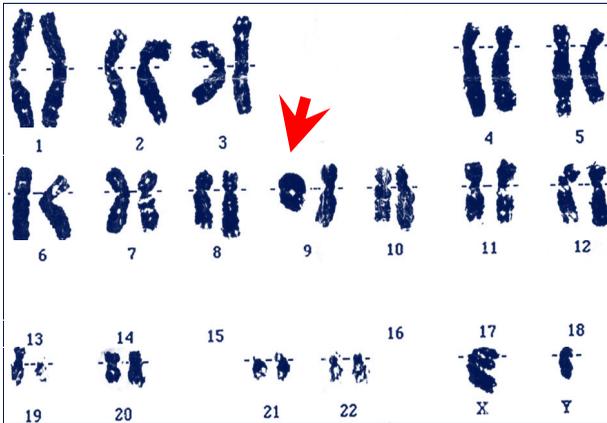
You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram of chromosome 9 to the right. The bands are numbered outwards starting from the point where the short and long arms meet (the **centromere**). Low numbers such as p11 or q11 are close to the centromere while high numbers such as p24 or q34 are almost at the tip.

Molecular and DNA technology

Some very tiny changes in chromosomes can't be seen even under the highest-powered microscope and are only found using molecular or DNA technology, in particular a technique known as array-CGH, that shows gains and losses of tiny amounts of DNA throughout the genome or another technique known as FISH, that allows chromosomes to be examined in greater detail. Inv dup del rings have only been identified so far using FISH or array-CGH.

The karyotype

Your child will almost certainly be given a karyotype, a shorthand notation for their chromosome make-up.



The karyotype is likely to read something like this

46,XY,r(9)

46 The total number of chromosomes in your child's cells

XY The two sex chromosomes, XY for males; XX for females

r A ring chromosome **(9)** The ring is a chromosome 9

46,XX,r(9)(p24q34)

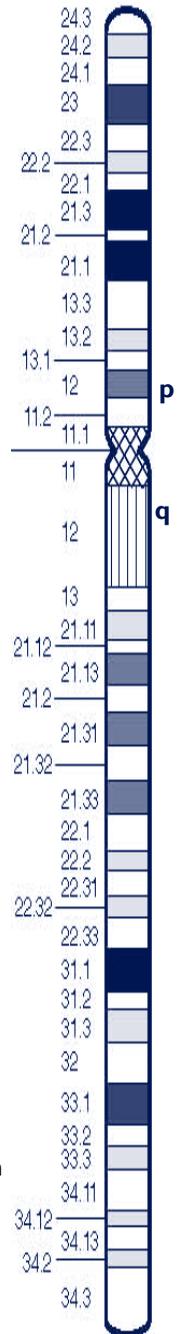
The breakpoints are in the short (p) arm (at band 24) and the long (q) arm (at band 34).

46,XY,r(9)(p24q34.3).ish r(9)(9ptel+,9qtel+, AHT-

FISH (.ish) using probes for the subtelomeres (the segment just before each chromosome tip) showed no loss of material and an all human telomere (tip) (**AHT**) probe showed that the telomere sequences were missing.

Chromosome

9



Does it help to know the breakpoints in the ring?

Knowing the breakpoints means that your geneticist or genetic counsellor can probably identify whether any genes are missing and whether there are extra copies of any genes. Genes act like a set of instructions that control the way our bodies develop, grow and work. Generally speaking, knowing which genes are missing or extra is very helpful when you want to know the overall effects of the ring chromosome. But there are still great differences between individuals – even individuals with apparently the same karyotype. It is very important to see your child as an individual and not to make direct comparisons with others with the same karyotype. After all, each of us is unique.

Why are people with a ring 9 chromosome so different from each other?

- The breakpoints may be different

Typically, the breakpoints in the short arm are between p22 and p24. Your child has then lost a similar amount of chromosome material to someone with a 9p deletion, a disorder also known as 9p minus. Typically, the breakpoints in the long arm are from q33 to q34, so your child has lost a similar amount of material to someone with a 9q34 deletion. *Unique* publishes leaflets on deletions from the short arm of chromosome 9 (**9p deletions**; **9p24 deletions**) and the long arm (**9q34.3 deletions**) which may help.

- There may be extra chromosome material as well as material missing

In some people, the ring chromosome contains a duplicated segment, so there is extra material and genes. A child with a large duplication of part of the short arm, including the 9p22 band, may share some features with people with a 9p duplication, also known as a trisomy. *Unique* publishes a leaflet on **Duplications of 9p** which may be helpful. A child with a duplication of a significant part of the long arm may share features with people with a 9q duplication (Seghezzi 1999; Wilmot 1988).

- There may be different ring arrangements in different cell lines

The karyotype quite often shows two or more different cell lines, one with a ring chromosome and others with different chromosome arrangements. When there is more than one cell line, it is known as **mosaicism**. It is harder to interpret a mosaic karyotype because of the intrinsic variety.

46,XY,r(9)(p24q34)[4]/46,XY[16]

This is a boy in whom 20 cells were tested. Four cells [4] showed ring 9 with breakpoints at p24 and q34 while sixteen cells [16] showed a normal karyotype for a boy or man.

In someone with mosaicism, many different chromosome 9 changes can be found: in addition to cells with a ring 9 and cells with normal chromosomes, you sometimes find cells with double rings made up from two chromosome 9s, cells with two or more rings, cells with rings that have opened up and ring fragments, as well as cells which are missing one chromosome 9. Commonsense might suggest that when a higher proportion of ring 9 cells or other unusual chromosome makeup is found, and a lower proportion of cells with normal chromosomes, the effects are likely to be more obvious. But this is not necessarily true. The frequencies of the different cell types in different tissues might vary considerably but usually only blood is studied.

- No chromosome material may be lost at all

In people with pure ring syndrome, the ring 9 is intact, with no material lost.

Are there people with a ring 9 chromosome who are healthy, have no major birth defects and have developed normally?

Yes, there are. In people with pure ring syndrome, no material is lost and even the tips of the chromosome are intact. Since all the genetic material is present, health and development are usually normal or nearly normal. The key effect is usually on growth, so that eventual height both as a child and an adult is unusually short. Some people with ring syndrome have streaks or patches of light or dark skin and this is a sign that there are some cell lines with a different chromosome make-up (Sigurdadottir 1999).



In people with pure ring syndrome, it is important to have the diagnosis confirmed using array-CGH or FISH. So long as all material near the tips (subtelomeric sequences) is present, normal or near-normal development may be expected. Sometimes all the telomeric sequences (the DNA from the very tips of each arm) are present.

How did this happen?

It is not known why ring chromosomes form in the first place but when parents' chromosomes are tested, they are usually normal. The actual cause of the ring forming is then not known and is best regarded as an accident that happened in cell division in the process of making sperm or egg cells. Ring chromosomes, like other chromosome disorders, affect children from all parts of the world and from all types of background. There is no reason to suggest that your lifestyle or anything that you did caused the ring to form.

Occasionally a structural abnormality is found in a chromosome 9 in one parent. In one father a pericentric inversion was found – a segment of one chromosome 9 including the centromere (the point where the short arm meets the long arm) had broken out, turned round 180 degrees and reinserted itself into the chromosome. Since all the chromosome material he needed was present, albeit in the wrong order, his development and health were unaffected. His son, however, inherited what is known as a recombinant chromosome, with part duplication of one arm and part deletion of the other in a ring format (Wilmot 1988).

Can it happen again?

Where both parents have normal chromosomes, it is very unlikely that another child will be born with a ring 9 chromosome or any other chromosome disorder. All the same, you should have a chance to discuss prenatal diagnosis if you would like it for reassurance.

In the rare instance where one parent has a change in chromosome 9, there is a much higher risk of having another affected child. Parents should meet a genetic specialist to discuss their individual risks and the options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is very accurate, although not all of these tests are available in all parts of the world.

What to expect

People with a ring 9 chromosome are likely to have certain features and effects in common with people with 9p deletions and 9q deletions. Those with a ring that contains a large duplication of 9p including 9p22 may have features of a 9p duplication.

See leaflets [9p deletions](#); [9p24 deletions](#); [9q34.3 deletions](#); [Duplications of 9p](#)

Feature	9p-	9q-	Duplication of 9p	Ring 9
Growth	Delayed	Delayed	Delayed; growth may continue into late adolescence & early 20s, allowing some catch-up	Delayed
Learning	Some support needed; disability	Some support needed; disability	Variable level of support needed	Support may be needed
Head size & shape	Keel-shaped (trigonocephaly)	Relatively small (microcephaly), narrow head (dolichocephaly)	Small, disproportionately broad head	Can be small and keel-shaped
Facial	Skinfolds across inner eye corners, arched eyebrows; small lower jaw; high palate; low set ears; short, upturned nose with flat bridge; short neck	Skinfolds across inner eye corners; low set ears; short, upturned nose with flat bridge	Prominent forehead with low hairline; deep, widely spaced and downslanting eyes; low, cup-shaped ears that stick out; a thick nose with a chunky tip; downturned mouth; short, broad neck	Typical are arched, thick eyebrows, upslanting eyes, a slightly receding jaw and mildly bulging eyes
Body	Wide spaced nipples	Hollow chest		
Hands & feet	Long middle joint of fingers & toes; flat feet	Club foot; single palm crease	Short fingers & toes with small or malformed nails. The 5 th finger may have a single crease or short middle joint and curve inwards. Thumbs, big toes and second fingers may have a short final joint	Variable
Neurology	Low muscle tone; seizure disorder	Low muscle tone; absent olfactory bulbs in brain	Seizures may occur	Abnormal tone; seizures may occur
Spine	Curvature		Spinal curvature, typically noticeable by the late teens	
Skin		Birth marks (capillary haemangiomas)	Harmless small fatty lumps beneath skin	Light & dark skin patches
Genitals	In boys, some anomalies and in extreme cases sex reversal	In boys, hypospadias; other minor genital anomalies	Minor genital anomalies including hypospadias, undescended testes & small penis in ½ boys	In boys, minor anomalies; more rarely obvious anomalies
Heart	Anomalies	Various conditions	Internal organs are usually normal and as a rule, people are healthy	In a minority, single to complex anomalies
Breathing		Soft windpipe		
Digestive	Feeding difficulties; reflux	Intestinal malrotation; GERD; feeding difficulties		Feeding difficulties & reflux are common

(Purandare 2005; *Unique*)

What is the outlook?

We can't be certain yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan.

Could your child with ring 9 syndrome have similarly affected children?

So far we haven't heard of someone with ring 9 having children of their own. So long as they are healthy and develop normally, it is possible that they could do so but the presence of a ring may cause problems in sperm and egg production which can then lead to reduced fertility.

Before trying to conceive it would be helpful for a couple to meet a genetic specialist to discuss individual risks and options for prenatal and preimplantation genetic diagnosis (PGD). See [Can it happen again?](#)



A child with ring 9

Development

While babies or children with an intact ring may show normal or near-normal development, reaching their baby 'milestones' at the expected time, other children will develop at their own pace, steadily but more slowly. It is not usually possible to predict an individual child's rate of development just from the karyotype - *Unique* records show great variability even among children with apparently the same karyotype. This judgment is usually best made from the child's own history.



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

Delay in reaching the developmental ‘milestones’ of sitting, becoming mobile and walking is common among children with a ring 9 chromosome and once on their feet many children continue to have an unusual style of walking. *Unique* records show that most babies needed support with a stander, walker or gait trainer before they became freely mobile and some relied on a wheelchair for outdoor use. This picture is not universal, however, and at least one adult *Unique* member had normal mobility in her early twenties.

Individual babies rolled over for the first time between 9 and 12 months, sat up from 14 months, became mobile (by rolling, shuffling or crawling – forwards or backwards!) between 15 and 22 months and were walking by 15 months to three years. However, individual children may not achieve these timeframes and may need much longer to become mobile.

One of the causes of the delay in mobility is abnormal muscle tone. This is most commonly low tone (hypotonia) but may show as increased tone (hypertonia). Hypotonia makes a child or baby feel floppy to handle and generally improves with physiotherapy and exercises but may never entirely disappear. Hypertonia is more likely to show as tight or clenched joints with a limited range of movement and a stiff posture; again, it generally improves with physiotherapy and occasionally surgery to release tight joints. At least one child was further hindered by uneven

foot length, requiring special boots.

Learning

People with ring 9 are likely to need continuing support with their learning, the possible exceptions being those with an intact ring. The medical literature shows a wide range of learning needs, with IQs suggesting a learning disability in the borderline mild/moderate to severe range. *Unique*'s experience broadly supports this, with individuals varying in their ability to handle formal academic skills. Some children do not read or write, while others acquire basic reading and writing skills, albeit somewhat later than other typically developing children. Writing ability tends to be undermined by residual hypotonia (low muscle tone) and the difficulties with coordination. Other skills, such as long-term memory, can be good. *Unique*'s experience is that most children attend a special school where their needs can be appropriately met, although this would not necessarily be the case for a child with little or no effect on learning.

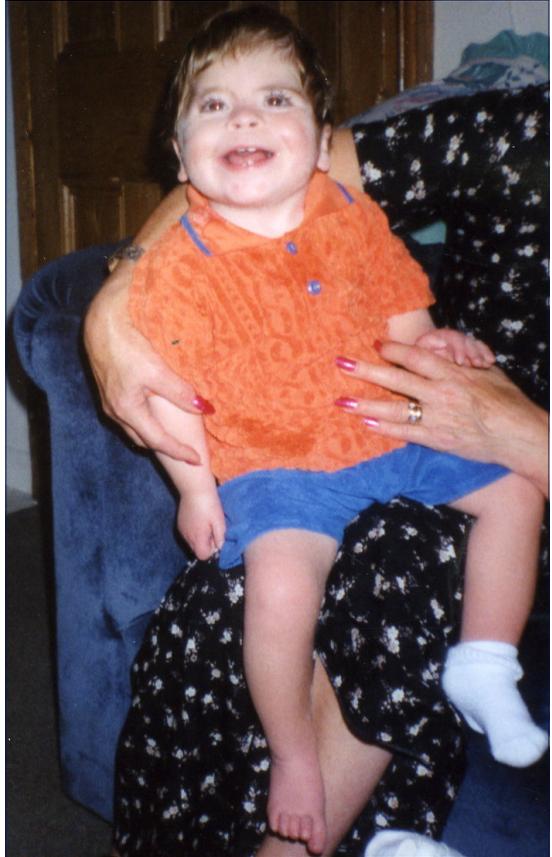
8 “ His memory is sometimes very good; he remembers people’s names from years

ago” – 14 years

“ He loves classical music. His memory is variable but he remembers people and places very well. He used to read 100 words and reads mostly picture books, transport and sport. His writing and drawing are rather poor due to his difficulties with coordination ” – 21 years

Speech and communication

Speech development and the emergence of words are noticeably delayed, but almost all children known to *Unique* have acquired some words or attempts at words, although this has not been possible in some cases in the medical literature. In most children, understanding appears to be better developed than speech but this typical pattern is reversed in one child. Most children take longer than normal to process language, leaving a break between hearing and responding. Responses may include gestures, different facial expressions, vocalisations, word-approximations, and in some children signing, single words and sentences. Although speech is delayed and children typically have difficulty with many of the sounds of speech, making what they say hard for



people not familiar with them to understand, the desire to communicate is usually strong. In just one child features of autism have been identified, with repetitive questioning, sentences and a long response time.

Children's first words emerged between 3 and 12 years and there appears to be a loose association between the age at which first words emerge and eventual fluency. In this situation intensive speech therapy has been helpful. Among adults, fluency varied between use of single words and short phrases (Purandare 2005; Zdansky 1977; Therkelsen 1971; *Unique*)

“ His language usually consists of single words of either vowels or consonants. He has difficulty with clarity with all sounds of speech ” – age 21

Behaviour

People with 9p deletions have been generally described as placid, happy and sociable - particularly with adults - and *Unique's* experience is that this is also true of those with a ring 9. Families describe their children as enjoying bubbles, balloons, hand-held windmills, lights, noisy toys and music, as well as pets. Adults are described as enjoying music and travel.

If children can't communicate their wishes or when a routine is unexpectedly broken, they may show challenging behaviour, with aggression and some self-harming, and if this occurs families are advised to seek help. Mood swings and temper outbursts have also been described in older children and teenagers. The medical literature shows that a minority of children have had restless behaviour and spells of confusion or even signs of hallucinations, treated with medication; however a high proportion of these children were cared for in residential homes after their families found their behaviour too hard to manage. *Unique's* experience is that these behaviours are not extreme and hard-to-handle youngsters have generally responded well to consistent behaviour management techniques and social skills training. Where behaviour management has not been successful, medication has been used with success. Any negative behaviours exist alongside positive traits, and children by and large remain loving and friendly (Purandare 2005; Fryns 1979; Zdansky 1977; Jacobsen 1973 ; Therkelsen 1971; *Unique*).

“ He likes cartoons, classical and rock music, travel (flying) and TV ” – 21 years

“ He only interacts with adults if he chooses to talk to them, depending what mood he's in ” – 14 years

Personal care

We don't know yet how much personal care individual children and adults with ring 9 will be able to carry out for themselves and how much help they will need. *Unique* records show great variations, with some youngsters toilet trained by three years while other adults have not achieved full control. Feeding, washing, dressing and personal care skills are generally very delayed, in part because of slow development of hand use and coordination, and youngsters will generally need considerable support from early intervention and occupational therapy services.

Feeding

While some babies feed without problem, a combination of low tone, incoordination and possibly palate abnormalities (a cleft or split in the roof of the mouth or an unusually high palate) can lead to early difficulties with latching on, sucking and swallowing. In addition, gastro-oesophageal reflux (also known as GORD or GERD), where feeds and stomach contents return up the food passage and may be vomited or inhaled, is fairly common. In the early days in hospital, tube feeds may be given to improve your baby's intake and occasionally it is helpful for a baby to be fed direct through a tube into the stomach (gastrostomy).

If your baby is very uncomfortable after a feed or brings up very much more of their feed than with normal possetting, discuss it with your health visitor or GP, as they

may have reflux. Babies with a high pain threshold – and this is fairly common among those with a chromosome disorder – sometimes tolerate very considerable discomfort without crying, so that reflux can remain ‘silent’. The concern here is that a baby with silent reflux may inhale part of their feed, causing repeated lung infections. If measures such as careful positioning after feeds, giving very small feeds and using prescribed medicines or feed thickeners do not control the reflux, it is possible to do a surgical procedure called a fundoplication to improve the action of the valve between the food passage and the stomach (Van Maldergem 1991; Manouvrier-Hanu 1988; Kasa 1988; Leung 1988; *Unique*).

Your baby may be slow to chew and move on to solid and finger foods but some families have accelerated this to relieve the hard work for their baby caused by sucking. Handling food and cutlery is likely to prove difficult because of low tone and incoordination and specially adapted cutlery and bowls are helpful.

Growth

Although growth is likely to be delayed, this is especially true of a child with pure ring syndrome and less so in those with other types of ring. In one child with ring syndrome, the growth failure was first noticed very early, at 4 to 6 months (Sigurdadottir 1999). Among others, *Unique* records and the medical literature show a range of heights in childhood and among adults and a range of builds, regardless of the apparent ring structure. Within *Unique*, adults vary between ‘very short’ and 5’ 4” (163 cm) and this variability is seen in children as well. Body build is variously described as ‘very skinny’, average to slim, ‘extremely well built, particularly shoulders’ and overweight. While a number of children described in the medical literature are in the smallest five per cent of the population for height, adults have achieved heights between 4’ 9” (144cm) and 5’ 2” (159cm) (Smith 1989; Therkelsen 1971; *Unique*).

Facial appearance



Children and adults with ring 9 may have some facial features in common with those with other chromosome 9 syndromes. The overall impression is likely to be that your child will not look much like others in your family and may look like others with ring 9 or another chromosome 9 syndrome. Most typically, babies resemble those with a 9p deletion in having a small head with a keel-shaped forehead, upwards slanting eyes, a wide nasal bridge, small skin folds across the inner corners of the eyes and a long upper lip (Van Maldergem 1991). Other facial features are not specific to the syndrome, but are quite typical. These include bushy, arching eyebrows that may meet in the middle; somewhat bulging eyes; and a small or receding lower jaw.

Skin

In mosaic cases, patches of lighter or darker skin may be found (Sigurdadottir 1999). There are a number of reports of children with unusually hairy appearance (Smith 1989; Dickerman 1983; *Unique*) and others with dry skin or eczema (Smith 1989; Jacobsen 1973; *Unique*).

Health matters

Some children are perfectly healthy, others are healthy apart from conditions that run in their family and are unlikely to be caused by the chromosome disorder (Smith 1989; Leung 1988; Fryns 1979; Jacobsen 1973; *Unique*). The conditions described below have been identified largely by medical researchers and geneticists who are more likely to publish work describing the abnormal than the normal.

■ Heart condition

In a minority of children with ring 9, a structural heart condition is found. Among *Unique* children, all heart murmurs generally turned out to be harmless and among children who do have a heart defect, none has had a heart condition that has needed surgical correction. More severe cases tend to be reported in the medical literature: in most cases, this is a simple hole between the upper (atrial) or lower (ventricular) sides of the heart or both, which may heal spontaneously in time or, if natural closure does not occur, be repaired surgically. Another common defect is persistent ductus arteriosus (PDA), a channel between the aorta and the pulmonary artery that takes blood to the lungs and which usually closes shortly after birth. When it stays open, the lungs receive more blood than they should and the heart has to work too hard. It can be closed surgically, sometimes using minimally invasive surgery by inserting a coil via an artery in the thigh. Tissue grows around the coil, closing the gap. A very small number of children have had a more complex heart defect, including a multiple defect known as tetralogy of Fallot, that was not successfully repaired (Purandare 2005; Manouvrier-Hanu 1988; Dickerman 1983; Inouye 1979; Fraise 1974; *Unique*).

■ Genital anomalies in boys

Some baby boys with 9p deletions and some with ring 9 are born with a genital anomaly. It is not yet known how commonly these occur, but reports from support groups suggest that they are less common than the medical literature might suggest (Ounap 2004; *Unique*).

Some baby boys have quite a minor degree of genital anomaly, while in others it is more obvious. The more obvious genital abnormalities are believed to be caused by the loss of two sex-determining genes close to the tip of 9p24.3, called *DMRT1* and *DMRT2*. We do not know why some boys are affected while others are not, but these genes may have a sensitive threshold above which normal male development occurs, while if the threshold is not met some anomaly occurs. Effects on the external sex organs can be fairly mild, including hypospadias, where the hole usually at the end of the penis is on the underside instead, and testes that are undescended at birth. Sometimes the effects can be more severe and include sex reversal, ambiguous or apparently female sex organs. The internal sex organs may

also be involved. These anomalies only affect baby boys. In baby girls, the external sex organs develop normally and experience so far shows that girls go through puberty in the normal way and at the normal age (Ounap 2004; Van Maldergem 1991; Nakajima 1976; Fraisse 1974; *Unique*).

If your baby has ambiguous genitals or sex reversal, as parents you can expect to be fully informed and supported. A decision about gender assignment will be reached in consultation with you and will depend in part on your baby's existing structures. A series of surgical operations and possibly hormone treatment may be needed. *Unique* does have experience of babies with sex reversal and can put families who would like contact in touch with each other (Stumm 2000; Raymond 1999; Metaxotou 1977; *Unique*).

■ Seizures and seizure-like episodes

A minority of children and adults with ring 9 experience seizures but these are generally well controlled with anti-epileptic medication. Two out of three *Unique* children with established seizures have outgrown them with no further need for medication. In others, seizures have persisted into adulthood (Purandare 2005; Smith 1989; Kasa 1988; Nakajima 1976; *Unique*).

In an attempt to establish a cause for seizures, as well as an electroencephalogram (EEG, tracing of electrical activity in the brain), imaging of the brain may be undertaken. In one case a child with infantile spasms was found to have an underdeveloped corpus callosum (the broad band of nerve fibres that links the two hemispheres of the brain), and in other babies there were non-specific changes including a smaller than expected brain size but no typical structural differences were seen and many children with seizures showed no abnormalities on brain imaging (Lanzi 1996; Manouvrier-Hanu 1988; *Unique*).

■ Digestive tract

Abnormalities of the gastrointestinal tract have been reported in some babies with ring 9 and a 16-year-old developed gastric volvulus as a result of intestinal malrotation. In volvulus, the intestine becomes twisted, causing an intestinal blockage. The twisting can cut off blood flow to the intestine and damage it. Treatment is determined on an individual basis but a volvulus is usually repaired as soon as possible by surgery. One *Unique* adult developed stomach ulcers as a teenager for which he was successfully treated with pantoprazole, a proton pump inhibitor drug (Purandare 2005; Leung 1988; *Unique*).

■ Infections

Frequent infections and infectious complications have been reported in the medical literature, with some babies experiencing repeated lung infections that have not responded to antibiotic treatment. Although in some babies gastro-oesophageal reflux may have contributed to lung infections, an underlying immune deficiency has been suspected; in others the possible cause was hypothesised to be deletion of the leukocyte interferon alpha gene (Lanzi 1996; Manouvrier-Hanu 1988; Dipierrri 1982; Portnoi 1982). However, apart from one adult with frequent urinary and ear infections, there is little evidence of this heightened rate of infections among the

Unique sample and a somewhat raised rate of infection is common among young children with any chromosome abnormality (*Unique*).

■ Cleft palate (split in the roof of the mouth)

A cleft 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. Defects in the roof of the mouth are common in children with and without a chromosome disorder. The hard palate at the front of the mouth may be split or the split may be found further back in the soft, fleshy tissue at the back of the top of the mouth. Occasionally the split is only seen in the tissue that hangs down above the tongue at the very back of the mouth (uvula, known as a bifid uvula when it is split). A cleft palate causes difficulties both in feeding and in speech production. Surgical repair of the palate eases these difficulties and may eliminate them altogether (Kasa 1988; Fryns 1979; Kistenmacher 1975; Jacobsen 1973; *Unique*).

■ Kidneys

Three *Unique* children out of eight had abnormal kidneys – either small, underdeveloped kidneys or a single working kidney along with severe reflux of urine within the kidney, requiring a vesicostomy. This is an operation to make an opening below the belly button (umbilicus). After the operation, the bladder will drain from the opening. The aim of the operation is to prevent urine from going back into your child's kidneys and damaging them. High blood pressure occurred both in new babies and in adults. One adult with a single functioning kidney and reduced function in the second kidney died of renal failure in her early twenties (Purandare 2005; Kasa 1988; *Unique*).

■ Spinal curvature

Scoliosis (a sideways curve in the spine) has been seen in a young child and an older girl of 16 with a ring 9 and members of *Unique*, one of whom was treated with expanding rods inserted into the spine (Purandare 2005; Jacobsen 1973; *Unique*).

■ Other

One child had a restrictive lung disease, abnormal blood vessels feeding the lungs and pulmonary hypertension – a raised blood pressure in the arteries that supply the lungs, carrying blood from the right ventricle. As the smaller blood vessels in the lungs become resistant to blood flow, the right ventricle must work harder to pump enough blood through the lungs. He needed a tracheostomy to aid his breathing (Purandare 2005); one child had extremely short forearms; the left radius (outer, shorter bone of the forearm) was missing and the right one was small; his thumbs were rudimentary (Inouye 1979); a baby was born with choanal atresia (the nasal passages are blocked by bone or tissue) (Dickerman 1983); one baby had a large umbilical hernia (Leung 1988).

■ Eyesight

Some defect of vision has been commonly found and although there is no clear pattern to the type of defect, children are likely to benefit from regular vision

screening. Of a total of 16, nine have no reported eyesight problems. Two children have an astigmatism, when the cornea (the clear cover over the iris and pupil) is abnormally curved. The effect on vision is to make objects appear blurred. Sometimes the brain can compensate for astigmatism although it may be too strong for this to happen without the aid of glasses. Two children have a visual impairment; one has an inward squint; two have errors of focusing, one with very short sight and another very long sight. One adult has very dry eyes and needs tear replacement; another is unusually sensitive to sunlight.

■ Hearing

Although two children have been reported with severe hearing loss (Purandare 2005), this has not been seen in other cases. Young children are generally prone to ear infections and a temporary hearing loss caused by a build-up of fluid behind the ear drum (glue ear) and it may be that children with chromosome disorders are more vulnerable to this type of conductive hearing loss. It is treatable with tubes inserted into the ear drum and generally resolves with age, vanishing by the age of 8 or 9. This type of hearing loss was common among the *Unique* sample.

■ Puberty

Among seven youngsters who have undergone puberty, everything proceeded as expected in six, while one boy had a very early puberty, with first signs from seven years and was shaving by the age of 10 (Purandare 2005; Fryns 1979; Jacobsen 1973; *Unique*).



Support and Information



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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 Rebecca Anderson, MS, CGC and Dr Stuart Schwartz, Department of Human Genetics, University of Chicago, Chicago, USA and by Unique's chief medical advisor, Professor Maj Hultén BSc PhD MD FRCPATH, Professor of Reproductive Genetics, University of Warwick, UK. 2008 (PM)

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