

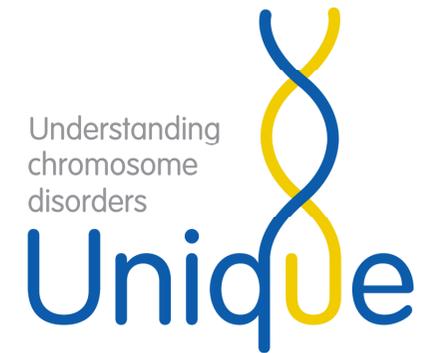
Support and Information



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Duplications of 3q

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Duplications of chromosome 3q

A duplication of 3q is a rare genetic condition caused by having an extra part of one of the body's 46 chromosomes. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Extra material is likely to disturb development but how obvious and serious the disturbance is depends on the amount of duplicated material, on which part of the chromosome is duplicated and on what genes are disturbed.

Chromosomes are the structures in the nucleus of the body's cells that carry genetic information in the form of genes, telling the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. Most chromosomes have a short (p) arm (at the top in the diagram on the next page) and a long (q) arm (at the bottom).

Most people have the duplication of 3q in all cells analysed. In a few people, the extra material is only found in some of the cells and the other cells have normal chromosomes. This type of change is called **mosaicism**. Generally speaking, people with a mosaic duplication of 3q are somewhat more mildly affected. But many outcomes in people with a chromosome disorder are not certain and this is even truer in people with a mosaic chromosome disorder.

Looking at 3q

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 3 on the next page. The bands are numbered outwards starting from the point where the short and long arms meet (the **centromere**).

A low number such as q11 is close to the centromere. A higher number such as q28 is close to the tip (the **telomere**). Sometimes a high resolution chromosome test called an array or microarray is used to find chromosome deletions or duplications that are too small to be seen with a microscope.

Sources & references

The information in this leaflet is drawn from what is known about around 50 people with a duplication of 3q. Thirty-three people have been described in the medical literature with a pure duplication of 3q without known loss or gain of material from any other chromosome arm. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain most articles from *Unique*. The leaflet also draws on *Unique's* database. When this leaflet was written, *Unique* had 19 members with a pure duplication of 3q.

Very many more people have been described in the medical literature with loss or gain of material from another chromosome arm as well as the 3q duplication. As these people do not show the effects of a 'pure' duplication, they are not considered in this leaflet. For families with a child with a combined duplication and deletion, *Unique* holds a list of cases, including *Unique* members, which is available on request.

Can it happen again?

The possibility of having another pregnancy with a 3q duplication depends on the parents' chromosomes. If both parents have normal chromosomes, the duplication is very unlikely to happen again.

If either parent has a chromosome rearrangement involving 3q, the possibility of having other affected pregnancies may be increased, depending on the precise rearrangement. Parents should meet a genetic counsellor to discuss their specific recurrence risks and options. Preimplantation genetic diagnosis (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 conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Prenatal testing is very accurate, although not all of these treatments and tests are available in all parts of the world.

Could my child with a 3q duplication have similarly affected children?

A few people have passed a small duplication on to one of their children. A father with a 3q22.1q24 duplication passed it on to his daughter, one mother passed a 3q25q26.2 duplication on to her son and another mother passed a 3q21q23 duplication on to her daughter. All these parents were healthy (although the father had seizures as an adolescent) and had at most a mild learning difficulty. The effects on the children were not completely known but in one case the child was more severely affected than his mother (Rizzu 1997; Williamson 1981; *Unique*).

In each pregnancy, someone with the duplication theoretically has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the duplication. Their ability to look after a child is very likely to be closely related to any learning difficulty they may have themselves.

Growing up with a 3q27q29 duplication

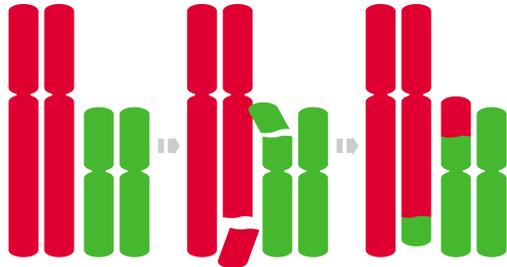


Left to right: 2 years; 4.5 years; 7 years; 9-10 years; 15 years

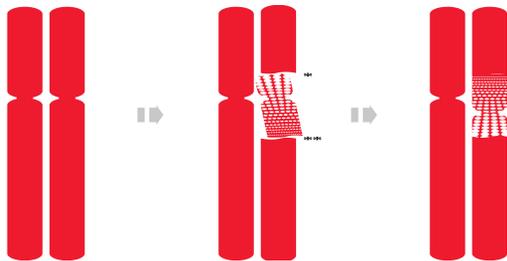
“ At 17, he enjoys TV, videos, movies, the cat, hanging out with friends at school, respite care and computer games. He has been assessed as coping well in a familiar environment but has difficulty adjusting to increased responsibility and conceptual/practical difficulties. He has a lovely singing voice and is now doing work experience at the town library. However, even though he is functioning at a relatively high level, he still has significant behavioural issues which will always be problematic for him socially.

How did the chromosome duplication arise?

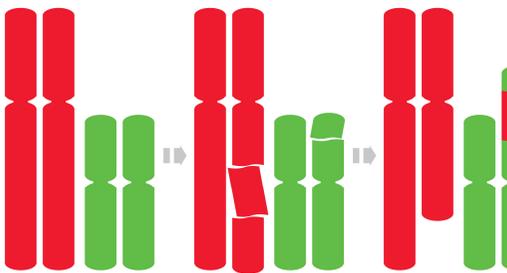
A blood test to check both parents' chromosomes is needed first. Most 3q duplications are the result of a rearrangement in one parent's chromosomes (Yatsenko 2003). This is usually a rearrangement known as a **balanced translocation** in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no difficulties with health or development, although they may have fertility or childbearing problems. Balanced translocations are



A balanced translocation



A pericentric inversion



A balanced insertional translocation

not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers. Other changes sometimes found in parental chromosomes are a **pericentric inversion** within chromosome 3 in which a piece of the chromosome including the centromere has broken off, swivelled round 180 degrees and reinserted itself into the chromosome at the same breakpoints or an **insertional translocation** in which a piece of 3q has inserted itself into another chromosome. The eggs or sperm of someone with any of these changes risk containing too much chromosome material. If the duplication is due to a pericentric inversion, there will be a loss of material from the short arm (3p) as well.

Some 3q duplications occur when both parents have normal chromosomes. The term that geneticists use for this is **de novo (dn)**. De novo 3q duplications are thought to be caused by a change that occurred when the parents' sperm or egg cells were formed. We know that chromosomes must break and rejoin when egg and sperm cells are formed but this only occasionally leads to problems.

What is certain is that as a parent there is nothing you did to cause the 3q duplication and nothing you could have done to prevent it. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. It is no-one's fault.

Is there a dup 3q syndrome?

If you search on the internet, you will find references to a dup 3q or duplication 3q syndrome, consisting of a low frontal hairline, excessive hair growth, joined eyebrows, hand and foot abnormalities, defects of the internal organs, especially the heart, and urinary tract anomalies as well as learning disabilities, delayed development and a normal birth weight (van Essen 1991; Wilson 1985; Steinbach 1981). Many geneticists have tried to identify a 'critical' region' within 3q that causes this 'syndrome'. However, the evidence that this syndrome exists is not secure. It was first described when chromosome analysis was much less precise than it is today and many cases supposed to show the syndrome had other chromosome changes as well.

It is more helpful to compare your child with others who have similar or the same chromosome breakpoints. When you do this, you will see that some effects are very broadly similar and this leaflet tells you what is known about these. Comparing your child's karyotype with others, both in the medical literature and within *Unique*, can then help to build up a general picture of what to expect. For example, generally speaking children with a duplication of the last five bands of 3q, between 3q27 and 29, do not have major internal organ anomalies or severe learning disabilities (Yatsenko 2003) and those with a duplication of the last band, 3q29, typically have mild to moderate learning difficulties and some unusual facial features (Battaglia 2006). You will probably also notice that many cases have anomalies that are relatively common in other chromosomal disorders, such as low muscle tone, delays in development, failure to thrive and anomalies affecting the appearance of the hands and feet. But there will still be differences between your child and others with an apparently similar karyotype. In addition to the chromosome 3 duplication, the genes on other chromosomes and environmental factors also influence development. It is important to see your child as an individual and not to rely on direct comparisons with others. After all, each of us is unique.

The karyotype

Your geneticist or genetic counsellor will be able to tell you about the breakpoints in your child. Your child will almost certainly be given a karyotype, a shorthand notation for their chromosome make-up. It is likely to read something like this

46,XY,dup(3)(?q28q29)de novo

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

XY = The two sex chromosomes: XY for males; XX for females

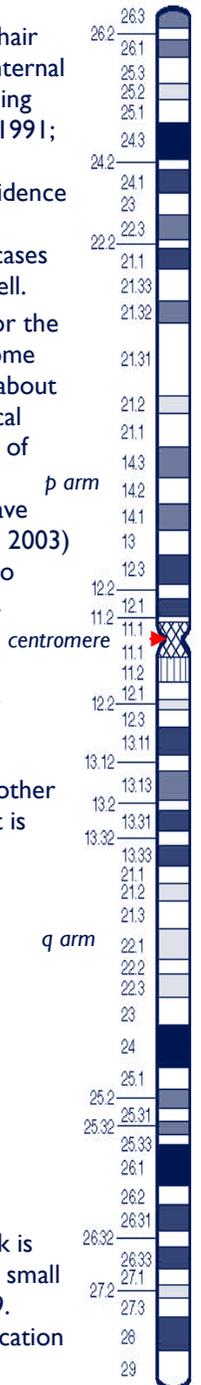
dup = A duplication, or material has been repeated

(3) = The duplication consists of material from chromosome 3

(?q28q29) = The chromosome has broken in two places. The first break is thought (?) to be at q28 and the second break is at q29. There is only a small amount of extra material in the duplication between bands q28 and q29.

de novo = The parents' chromosomes have been checked and no duplication or other abnormality found. The duplication has not been inherited.

Chromosome 3



Are there people with a 3q duplication who are healthy, have no major birth defects and have developed normally?

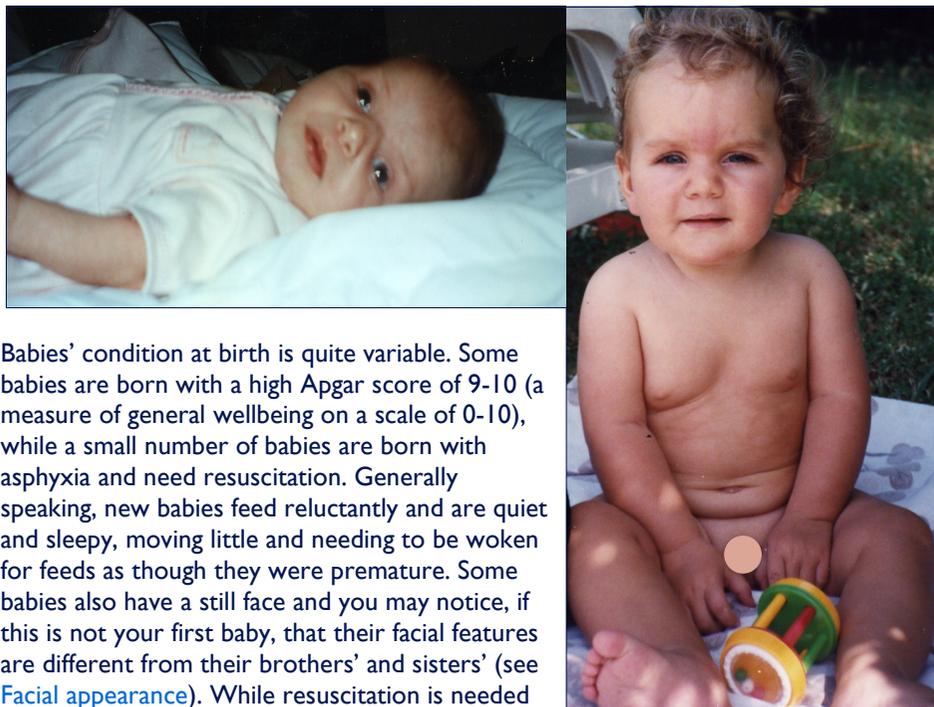
Everyone known about so far with a 3q duplication is affected in some way. However there is a great range of different effects and some people with small duplications are very mildly affected. This is true of a 28-year-old man with a duplication of 3q22.1q24, a woman with a duplication of 3q25q26.2 and a mother-daughter pair with a 3q21q23 duplication (Rizzu 1997; Williamson 1981; *Unique*).

Generally speaking, it seems that children with small duplications are more mildly affected as are those with a mosaic form of the duplication.

What is the outlook?

The outlook is determined largely by any defects in the major internal organs, especially the heart (Tranebjaerg 1987). Historically, babies with heart defects have not thrived as well as those born with a healthy heart, but improvements in children's heart surgery have increased survival and mean that you cannot always judge the present by looking at the past. Infections have also played an important role in survival (Battaglia 2006).

Your baby



Babies' condition at birth is quite variable. Some babies are born with a high Apgar score of 9-10 (a measure of general wellbeing on a scale of 0-10), while a small number of babies are born with asphyxia and need resuscitation. Generally speaking, new babies feed reluctantly and are quiet and sleepy, moving little and needing to be woken for feeds as though they were premature. Some babies also have a still face and you may notice, if this is not your first baby, that their facial features are different from their brothers' and sisters' (see [Facial appearance](#)). While resuscitation is needed more often in babies with a serious heart defect, it is also sometimes needed for babies with a healthy heart and some babies spend days or occasionally weeks in special care. This is an anxious time for parents, especially as medical staff may now seek the underlying cause for your baby's problems and take a blood sample to examine the chromosomes.

Among the more serious problems are abnormally small eyes (microphthalmia), missing eyes (anophthalmia) and small or elongated optic nerves, which interfere with the transmission of visual information to the brain (Moreira 2005; van Essen 1991; Wilson 1985; *Unique*). A number of babies were also born with cataracts (Vianello 1987; Gustashaw 1985; Moreira 2005; Wilson 1985; Schwanitz 1977; *Unique*) and others had damage to the optic nerve at the point where it leaves the eye as well as more complex eye defects (glaucoma) (Madan 1992; Sod 1978). One *Unique* youngster who is blind in one eye has keen vision in the other eye. Recently there have been attempts to identify critical regions for eye anomalies and *SOX2*, a major gene for anophthalmia, has been mapped to 3q26.3q27 (Fantes 2003).

Treatment of cataract depends among other things on its size but usually involves surgical removal of the cloudy lens, following by optical correction with a clear lens or glasses. Treatment of glaucoma depends on whatever your child's ophthalmologist considers to be the cause. In both cases, treatment may bring excellent results but in some cases, some loss of vision may occur. The experience of *Unique* is that many children have been helped by specialised vision services and teaching.

Hearing

The most complete information on hearing comes from *Unique*. Of the 19 *Unique* members, eight - regardless of the position or extent of the duplication - have had the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear) often associated with frequent ear infections. Children normally outgrow this naturally but if it is severe or persistent, tubes may be inserted into the eardrum to aerate the space (the middle ear) behind it and improve hearing. In this group, however, there are three children whose ear drums did not heal after their tubes were removed or fell out and remained perforated. While other children wear hearing aids (if they will tolerate them) some of these children could not do so because of the risk of introducing infection through the eardrum (*Unique*).

Descriptions in the medical literature are not clear enough to allow certainty over whether a permanent sensorineural deafness occurs in children with a 3q duplication. However, hearing aid use suggests that in some children this may be the case (Konstantareas 1999; Schwanitz 1977; *Unique*).

Teeth

Generally speaking, children with chromosome disorders appear to have more dental problems than others. Problems seen in this group that are not specific to the 3q duplication include grinding and a high rate of cavities because children are unwilling to have their teeth cleaned regularly. Information on nine children in the group shows that in one child with a cleft soft palate and a duplication of 3q25q28, the two middle right teeth in the upper jaw were fused; two children have under- or overbite, caused by a mismatch between the teeth of the upper or lower jaw; in two children the teeth emerged unusually early (van Essen 1991; *Unique*).

Clinical follow-up

Regular kidney investigations (ultrasound scans) have been recommended due to a theoretically increased risk for renal cancer (Bonné 2004).

and another chromosome change and a 'critical region' has been suggested at 3q29. However an omphalocele has been seen in only one baby with a 'pure' 3q duplication and in no *Unique* members (Yatsenko 2003; Wilson 1985; *Unique*). Surgery is usually performed shortly after birth to return the organs to the abdomen and close the opening in the abdominal wall in a single or a staged operation.

Other babies with a 3q duplication were born with intestinal malrotation, a related developmental anomaly of the digestive tract (Kadotani 1979). As the intestine returns to the abdomen in the 10th week of gestation, it turns twice and is fixed into its normal position. Incomplete rotation without fixation is known as intestinal malrotation. The bowel may twist on its own blood supply, causing a condition known as volvulus. Intestinal malrotation can cause abdominal pain, malabsorption and malnutrition and growth disturbance. Some people with malrotation have no symptoms or problems but if the intestine or blood supply is obstructed, surgical repair is needed.

■ Bones and skeleton

One child was born with the bottom three vertebrae missing and the base of the spine fused to the pelvis. Nerves to the bladder and bowel were also missing, so that the bladder did not empty fully, raising the risk of infection (*Unique*). A baby was born with underdeveloped top (first) ribs and missing bottom (12th) ribs (Wilson 1985). One child was born without the usual arrangement of tendons attaching the shoulder blades to the rib cage, so they stand out noticeably (*Unique*). A baby was born with an unusual step-like protrusion from the back of the skull known as bathrocephaly (*Unique*).

■ Other problems

Other anomalies have been seen: an enlarged spleen, underdeveloped thymus gland and lungs (Wilson 1985); an enlarged liver and spleen (Steinbach 1985); a narrowed anus (Gustashaw 1985). One child with a 3q25.31q27.1 duplication developed a type of bone tumour known as fibrous dysplasia which was removed but recurred (*Unique*) and another child became hypothyroid, needing thyroxine replacement (*Unique*). One baby was born with facial paralysis (*Unique*).

Eyesight



People with a 3q duplication are at risk for serious vision problems. Despite this apparently alarming statement, twice as many people have perfectly good eyesight as have a vision defect. What is more, while some people do have a serious defect, others have more minor problems. Among the less serious problems are blocked tear ducts, leading to constant eye watering and raising the risk of infection (*Unique*), and problems with muscle alignment, leading to a squint (strabismus) (Madan 1992; *Unique*). Both of these problems can be corrected with fairly minor surgery, and eyesight should then be normal. A marked narrowing of the horizontal opening of the eyelid (blepharophimosis) has also been seen (van Essen 1991); if this interferes with vision it can be surgically corrected.

A few babies have been born with a minor defect overlying the spine, such as a hollow at the base of the spine (sacral dimple) or a deeper pit or hole (Meins 2005; Moreira 2005; van Essen 1991; Gustashaw 1985; Sod 1978; *Unique*). If the dimple is shallow and the end can be seen and it is in the crease between the buttocks, it is not usually a sign of any underlying problem. All the same, poo from a dirty nappy can lodge inside, so it is important to keep it clean and cover it well with barrier cream. An ultrasound or MRI scan can show whether the pit is deep or connects with the spinal canal. A sacral dimple is sometimes called a pilonidal dimple.

Facial appearance



Different boys:

14 years,
3.5 years,
22 years
and
4.5 years

A large number of unusual facial features have been noted by geneticists in reports on babies and children with a 3q duplication. Your baby or child may have just one or two or sometimes more of these features and you may find that he or she looks more like others with a 3q duplication than like other members of your own family. The key features noted include: hair growth on the face (hirsutism), especially the sides of the forehead; thick or bushy eyebrows that meet in the middle; a broad base to the nose; a small ('pug', 'boxer'), upturned nose; widely spaced eyes (hypertelorism) that may slant upwards, with skinfolds across the inner corner (epicanthic folds) and long eyelashes; low-set and unusually-formed ears; small skin tags or holes in front of one or both ears (preauricular tags/ holes); a small lower jaw (micrognathia); a short neck, with sometimes an apparent skinfold at either side (Rossi 2002; Rizzu 1994).

However, not all youngsters have any of the reported features; some have an entirely normal facial appearance (Lopez-Rangel 1993).

Hands

Your child's hands may look somewhat unusual. Most typically, one or more fingers or the thumb are held in a 'fisted' position and one finger may overlap another; the hands may be small and the nails thin and small or sharply curved (van Essen 1991); the fifth fingers on one hand or both may curve inwards (clinodactyly) (Roberts 2006; Moreira 2005; Gustashaw 1985; Williamson 1981; Yunis 1979; Sod 1978; *Unique*). In individual children, anomalies have included a duplicated or broad thumb tip (Pires 2005; Schwanitz 1977); odd finger sizes and a finger-like thumb (*Unique*); individual deformed or twisted fingers (*Unique*); fingers joined by a bridge of tissue or skin (Schwanitz 1977; *Unique*); extra fingers (*Unique*). Other functionally unimportant features include a single crease across the palm (Wilson 1985); multiple crazed palm lines (*Unique*); and short, broad or tapering fingers (Meins 2005; Rizzu 1997).

Fingers that are clenched at birth may gradually straighten with maturity and with exercises that you are shown by your physiotherapist or occupational therapist. Splinting may be helpful and occasionally surgery may be needed to give your child the fullest range of movement possible.

“ She only opened her hands properly when she was 19 months old and still has problems with dexterity - 10 years



Left hand and foot of a boy with a mosaic 3q23q29 duplication

Hands and feet of a girl with a mosaic 3q24qter duplication

Feet

Many babies with a 3q duplication are born with their feet held at an unusual angle. Additionally, toes may overlap, there may be a large ‘sandal’ gap between the first and second toes or two or more toes may be webbed with tissue or skin (Meins 2005; Rossi 2002; Sod 1978). Further difficulties with foot position may emerge once a child is mobile on their feet, and individual children may walk with their feet splayed out and roll their ankles inwards (*Unique*).



Left talipes, treated with four surgical interventions, in a girl with a mosaic 3q24qter duplication (see above)

At 2 years

At 2 years, 7 months

At 7 years

Treatment for an abnormal foot or walking position is individually tailored and aims to straighten the foot so that it can grow and develop normally. First-line treatment is non-surgical and may include manipulation, casting, taping, physiotherapy and splinting, followed by bracing to prevent relapse. Ankle or foot supports are often prescribed, as well as special footwear. Surgery is considered if non-surgical treatments are not completely successful. The foot position may relapse as the child grows and develops, making further surgery necessary.

most common and a few boys have hypospadias, where the hole that is normally at the end of the penis is located on the underside instead. Minor genital anomalies are common in boys with a chromosome disorder and there is no ‘critical region’ for them on 3q. All the same, boys with small duplications between 3q26 and the tip of the long arm have not been seen with undescended testicles, although isolated hypospadias has occurred in a boy with a small duplication at 3q28 and 3q29.

Hypospadias is usually repaired surgically using tissue from the foreskin. Treatment for undescended testicles depends on the suspected cause and is usually needed if the testicles do not descend naturally in time. Generally speaking, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy. Girls do not generally show any genital anomalies, although one girl with a mosaic 3q24qter duplication developed a benign tumour in the reproductive tract (Müllerian papilloma) which was removed surgically (*Unique*).

■ Infections

Babies and young children with a chromosome disorder generally have a higher rate of childhood infection including ear and chest infections than children with no disorder and this is true of those with a 3q duplication. Episodes of pneumonia may be triggered in young babies by milk or reflux inhalation and can be a constant winter feature in early childhood. Infections can be serious and have been a cause of death in some children. Ear infections may be picked up late in a child with a high pain threshold (*Unique*).

“ More ear infections than most but not picked up quickly due to high pain tolerance - 3q26.3q27 duplication, at 4 years

“ On antibiotics at least once a month for urinary tract, ear or eye infections - mosaic 3q24qter duplication, at 10 years

■ Kidneys

Five children with a 3q duplication described in the medical literature and one *Unique* member have had kidney anomalies. However, the types of anomaly have been varied, ranging from double arteries to cysts, and enlarged or very small kidneys with nephritis (kidney inflammation) leading to chronic kidney failure; a further *Unique* member has somewhat enlarged tubes leading from the kidneys to the bladder (ureters) (Moreira 2005; van Essen 1991; Wilson 1985; Steinbach 1985; Stengel-Rutkowski 1979; *Unique*). All these children except one *Unique* member have a duplication of bands 3q26 and 3q27 which may represent a ‘critical region’ for kidney anomalies.

Some physicians recommend kidney screening as there seems to be an increased risk of renal cancer in people with changes in chromosome 3, but again *Unique* has seen no cases of renal cancer (Bonné 2004).

■ Omphalocele

An omphalocele is a sac containing part of the bowel that protrudes at birth through a hole in the abdomen near the base of the umbilical cord. It is assumed to arise due to full or partial failure of the normal developmental process by which the midgut protrudes, turns and then returns to the abdominal cavity and the hole is closed around the umbilical ring. This rare anomaly has been seen in 12 babies with a 3q duplication

■ Brain

In eighteen of the 52 babies and children with a 3q duplication some unusual structure or size of the brain has been shown. The brain itself may be somewhat smaller than expected, or parts of the brain may be an unusual size – such as the corpus callosum (the band of nerve fibres that links the left and right hemispheres) or the vermis (a narrow, worm-like structure between the hemispheres of the cerebellum – the area at the base of the brain that plays an important role in the integration of sensory perception and motor control). One child with a 3q21q27 duplication had a Dandy-Walker malformation, involving the cerebellum; another baby with a 3q21q24 duplication had a small cerebellar vermis, absent corpus callosum, mildly enlarged ventricles and an enlarged cisterna magna (one of the spaces in the brain that acts as a reservoir for cerebrospinal fluid). In other children, the fluid-filled ventricles within the brain may be larger than usual or they may be asymmetrical. In one child with a small duplication at the tip of the 3q arm at 3q29, an Arnold-Chiari malformation (an abnormality of the base of the skull allowing varying degrees of intrusion of parts of the brain and brainstem into the spinal canal) was found (Roberts 2006; Moreira 2005; Pires 2005; Madan 1992; van Essen 1991; Mandava 1990; Naritomi 1989; Wilson 1985; Yunis 1979; Schwanitz 1977; *Unique*).

Your paediatrician or neurologist is best placed to suggest what the implications of a structural brain anomaly will be. In terms of treatment, if the anomaly causes raised pressure within the brain, it is possible to insert a shunt to drain excess fluid.

■ Feet

While most babies with a 3q duplication are born with normally shaped and positioned feet, around one baby in five is born with their feet held in an abnormal position. Talipes (clubfoot) usually affects both feet. Treatment is individually tailored and aims to straighten the foot so that it can grow and develop normally. First-line treatment may be non-surgical and include manipulation, casting, taping, physiotherapy and splinting, followed by bracing to prevent relapse. Surgery is considered if non-surgical treatments are not completely successful. The foot position may relapse as the child grows and develops, making further surgery necessary. In children with a 3q duplication, this is especially likely as children may well have unusual muscle tone – too floppy, too tense and contracted or a mixture of both. The experience of *Unique* members suggests that muscles in the lower leg contract, requiring surgical release, and a minority of children also have problems with rolling ankles.

If a 'critical region' exists for talipes, it appears to lie between 3q25 and 3q26.3 (Rossi 2002; Rizzu 1997; van Essen 1991; Sod 1978; Schwanitz 1977; *Unique*).

Other babies are born with slightly unusual feet that do not, however, need treatment or adaptation. Most typically, feet are short and broad, there may be a wide ('sandal') gap between the first and second toes and other toes may be widely spaced, overlap each other, be joined by a web of skin or be odd sizes. Nails may be oddly formed ('in layers').

■ Minor genital anomalies

Of 20 boys with recorded information on genital formation, nine have a minor developmental anomaly. Testicles that have not descended at birth (cryptorchidism) are

Feeding

Many newborn babies will have difficulties feeding and beyond the newborn period, *Unique* has information on feeding histories from 12 children. These show a range of challenges, from relatively minor difficulties with latching on to breastfeed to outright failure to thrive, managed by long-term insertion of a gastrostomy feeding tube direct to the stomach. While there is a trend for greater feeding difficulties among those children with larger duplications, some children with small duplications have also had significant feeding difficulties. Many babies and children do have a low muscle tone (hypotonia), which makes feeding and sucking difficult. Breastfeeding may be achievable, but some babies find the effort too much and thrive better on bottles with teats suitable for premature babies; others need to be fed by nasogastric tube for a short while until they learn to feed from a bottle or the breast. Progress to sipping, chewing and solid foods tends to be delayed and among older children the problem of overfilling the mouth and failing to chew has been seen.

Unique data show that some babies and children have gastro oesophageal reflux (where feeds and stomach contents return into the food passage and are often vomited or may be inhaled, causing chest infections known as aspiration pneumonia) but this is generally controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head end of the bed for sleeping. If these measures are not enough, prescribed medications or anti-reflux milk are usually enough to keep feeds down. Reflux has also been diagnosed among older children and may go unrecognised and undiagnosed because of children's decreased response to pain.

Constipation has also been seen among older children and in at least one case did not respond to increased fluid, fibre or medication, so that an antegrade continence enema (ACE, a tube leading from outside the stomach to the bowel) was placed to allow regular flushing of the bowel (*Unique*).

“Tends to favour very cold water over all other flavours and textures - 3q21q26.2 duplication, at 7 years

“Over the past two years has regularly complained of feeling sick. Tests showed the most acute gastro oesophageal reflux - 3q25qter duplication, at 14 years

Growth

Failure to thrive is believed to be typical of babies with a 3q duplication (Rossi 2002). However, in many cases growth has not been tracked through childhood and there is virtually no information in the medical literature on eventual adult heights. Birth weight in one baby with a complete 3q duplication was very low (1.87kg, 4lb 2oz) (Wilson 1985) but this was not the case in another baby with a mosaic complete duplication (3.29kg, 7lb 4oz) (Stallings 1997). Among babies with partial duplications, there is great variability, from babies born at term weighing around 4 kg (8lb 13oz) to others weighing around 1.67kg (3lb 11oz) at 36 weeks. Even where the duplication appears to be the same, birth weights can be very different.

Range of birth weights at or near term: 4.677kg (10lb 5oz) to 2.07kg (4lb 9oz)
Data held by *Unique* confirms this variability. It also shows that growth can pick up dramatically once feeding and digestion problems have been solved. One child had a marked growth spurt after coming off methylphenidate (Ritalin). Heights among adolescent and adult *Unique* members range up to 5 feet 6 inches (1.68m).

- “ Top 90% for height and skinny-looking: normal for family - *3q26.3q27 duplication, at 4 years*
- “ Very small in stature. She is the size of a typical 3 year old. She has long skinny legs, a short stocky body and a normal sized head for a child of her age - *3q21q26.2 duplication, at 7 years*
- “ Strong build but legs below the knees look like two sticks - *mosaic 3q24qter duplication, at 10 years*
- “ Short until 8 years then with growth spurts would grow 2 to 3” a year. Growth has since slowed and is 5’ 6” (1.68m) tall - *3q25.31q27.1 duplication, at 15 years*
- “ A lot taller than other children. Her weight is high as well - *3q21q23 duplication, at 16 years*

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



At 5 years

At 7 years

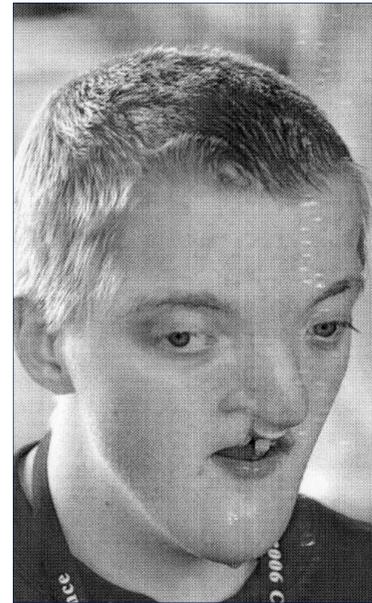
Delay in reaching the developmental ‘milestones’ of sitting, becoming mobile and walking is typical. This means that your baby will make progress, generally following the normal developmental sequence, but progress will come slower than normal. How much slower depends chiefly on your baby’s innate abilities, but also on opportunities, on stimulation and to some extent on therapeutic interventions. It is hard to predict eventual mobility, but

while in some it is normal, other children may need a wheelchair long term.

From *Unique’s* experience, head control is achieved around or after six months, rolling over from nine to 19 months, sitting without support from 12 to 30 months, becoming mobile from 15 months to three years and walking from 18 months to 10 years. Not all babies crawl: some shuffle on their bottoms or roll over and over, while others crawl backwards. Walking may remain unsteady for a long while after it is first achieved. Achievements such as climbing stairs may not be possible for all, but in a child who walked at 30 months was achieved at 33 months. Walking over uneven ground may also prove a particular challenge and never prove possible without support. One of the causes of the delay in mobility is low muscle tone (hypotonia). This makes a child or baby feel floppy to handle and generally improves with time. It may also resolve with physiotherapy and exercises. In some children, muscle tone increases, so that muscles remain unable to stretch. If this gives rise to toe-walking, a surgical intervention known as heel-cord lengthening may improve your child’s gait.

- “ Enjoys running, throwing and occasionally catching balls, loves water and swimming - *3q26.3q27 duplication, at 4 years*
- “ When outside, we always hold her hand - *at 10 years*
- “ Unsteady and tires easily, uses a wheelchair on long trips - *at 14 years*
- “ Normal mobility - *3q25.31q27.1 duplication, at 15 years*

divided (cleft) upper lip. Why some babies with 3q25 duplication are affected while others are not is uncertain – even the baby with the largest duplication of 3q – the entire arm – had a normal palate and upper lip (Wilson 1985). What is clear, though, is that babies whose duplication does not include band 3q25 are most likely to be born with a normal palate and upper lip (*Unique*).



A cleft is caused by an error in fusion when the fetus is developing. 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 palate 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); in babies with a 3q duplication this is most likely when the first breakpoint is no closer to the centromere than 3q25 (Schwanitz 1977; *Unique*).

A cleft palate causes difficulties both in feeding and in speech production. Surgical repair of the palate eases these difficulties and may eliminate them.

- “ He has a high palate and this, combined with hypotonia, makes for feeding problems. Food gets stuck in his mouth and has to be scraped out so he doesn’t choke. He also has a split uvula - *3q25.31q27.1 duplication, at 4 years old*

■ Seizures and seizure-like episodes

No seizures or seizure-like episodes have been reported in 42 babies and children. Seizures have been reported in ten people, including five out of 17 *Unique* members. The seizures occur regardless of the size or position of the duplication and no ‘critical region’ makes them more likely. One adult with a 3q22.1q24 duplication had seizures from 12 to 16 years but these had not recurred by the age of 28 (Williamson 1981). In six of the children with seizures who had imaging of the head and brain, a brain anomaly was found (see page 14). In two *Unique* children the seizures were the first sign of a chromosome disorder. Both of these children have a very small duplication near the tip of 3q. In all the *Unique* children for whom we have information, seizures were well controlled with standard anti-epileptic medication.

- “ Chloe continues to have smaller, less severe seizures with occurrences of pneumonia and other viral infections. We give her the prescribed medication clonazepam each night at bedtime to help her sleep and that seems to have decreased the severity and the frequency of the seizures drastically - *3q21q26.2 duplication, at 7 years old*

Health matters

■ Heart

Three quarters of babies with a duplication of 3q – regardless of where the breakpoints are – were born with a healthy, normal heart and are not known to have experienced any heart disease. Thirteen babies of the 52 described were born with a heart defect, but these defects were extremely variable both in severity and type. One baby was born with a persisting hole from the fetal circulation (patent foramen ovale) that did not need treatment, but was monitored (Meins 2005). Four babies were born with a hole between the upper or lower chambers of the heart, or both (atrial septal defect (ASD); ventricular septal defect (VSD)). In both an ASD and a VSD, some blood flows through from the left to the right side of the heart, increasing the blood flowing to the lungs. Treatment for an ASD depends on the type of defect, whether it closes spontaneously and its size and can include taking medication to help the heart to work better, control of potential infection to the inner surfaces of the heart and surgical repair with stitches or a special patch. Specific treatment for VSD is determined individually. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow (Pires 2005; van Essen 1991; *Unique*).

One baby was born with a narrowing (coarctation) of the aorta, the vessel that takes the blood from the heart to the rest of the body. This forces the left side of the heart to pump harder to push blood through the narrowing. Treatment is tailored to the individual child but if necessary the narrowed section can be surgically removed or made larger. Another baby was born with a double aorta, needing surgery (Sod 1978; *Unique*). One baby had a valve defect (Steinbach 1981), while others had more complex problems, including the collection of anomalies known as tetralogy of Fallot. In recent decades, surgical repair has become increasingly possible for babies with complex heart defects (Gustashaw 1985; Wilson 1985; *Unique*).

There has been speculation in the medical literature about a 'critical region' of 3q for heart problems, but as more babies have been diagnosed, it has become clear that most have no heart defects and that there is no single band of 3q that, when duplicated, is responsible for causing a heart defect. While it is true that most of these babies with a heart defect have a duplication of at least band 3q25, one baby with a valve anomaly had a duplication of the end of the arm from 3q26 and another with tetralogy of Fallot had a duplication near the tip of the long arm between 3q27 and 3q29 (Steinbach 1981; *Unique*).

“ His aortic valve insufficiency has not affected him in any known way although he has been told not to do push-up exercises - 3q25.31q27.1 duplication, at 15 years old

“ He took medication for two years and his ASD healed spontaneously with time. It caused very slow feeding for the first two years of his life - 3q13.3q25.3 duplication, at 23 years old

■ Cleft palate, lip or both

Most babies are born with an intact roof of the mouth (palate) and a normally formed upper lip. However, around one baby in three with a duplication of the 3q25 band, which appears to be the 'critical' area, is born with a split (cleft) in the palate or a

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

Most children, though not all, experience quite considerable delay in controlling their hand use. They may show a weak hand grip, drop things or knock them over easily and find manipulating small objects a particular challenge. In *Unique's* experience, slow-developing children may continue to need help to feed, dress and care for themselves throughout childhood and even as adults, and may master activities such as cutting, drawing and writing only with hand-over-hand assistance. Some children, probably a minority and most typically those with small duplications beyond 3q25, do achieve relative independence in these activities.

In terms of self care, it may not be appropriate for parents to expect toileting to occur at the same age as other unaffected children. Data from *Unique* suggest that bladder and bowel control may be achieved in children with a small duplication from or beyond 3q25 at three to four years, while in others control may only be achieved later, if at all.

“ Fine motor skills wonderful - 3q26.3q27 duplication, at 4 years

“ Can dress self with help, but prefers not to - 3q25qter duplication, at 14 years

Learning



Many children, although not all, will need extra support with learning. How much support will be needed usually only becomes apparent over time, and not enough experience has yet built up in youngsters with a 3q duplication to make reliable predictions. However, it seems likely that some children with a mosaic duplication and some others with relatively small duplications may learn at a fairly normal pace. There is evidence that youngsters with the following duplications have had at most mild learning difficulties: 3q21q23; 3q22.1q24; 3q25q26.2; 3q25.1q26.1; 3q25.31q27.1 (Rizzu 1997; Lopez-Rangel 1993; Williamson 1981; *Unique*). Others with effects that appeared mild in early childhood included a one-year-old boy with a 3q12q23 duplication (Gamerding 2006). However, even youngsters with a moderate learning disability are capable of considerable subtlety and complexity in their learning.

One boy with a 3q27q29 duplication has an exceptional memory for names, faces and places and specific strengths in reading (Harry Potter books). He finds writing difficult due to poor motor skills but can count money, read the time and, at 17, is learning to email and to speak Italian (*Unique*). This general learning profile is similar to one in a girl with a mosaic duplication of 3q24 (*Unique*).

Other youngsters will need more extensive support and skilled one: one teaching to

develop and maintain the skills they need for daily living, and for them the focus of education should be on living skills rather than academic achievements.

There is some research interest in the *NLGN1* gene that is involved in making points of contact between different nerve cells in the central nervous system as one gene that may be involved in learning disabilities in 3q duplications (Meins 2005). However, identifying a gene cannot yet improve therapy and it is most fruitful for families to ensure that their child is regularly and thoroughly assessed and then placed in a calm, stimulating and supportive learning environment where his or her strengths and abilities - such as memory, application or musicality - are recognised and built upon and weaknesses - such as motor skills - minimised.

“ An exceptional musical memory – he hears a song once and can repeat the tune. He is also more able at puzzles and shapes. He is determined and quite organised and loves books, especially shape books – dad reads three a night. He can draw a circle face with two eyes and a straight mouth - *3q26.3q27 duplication, at 4 years*

“ He can spell his own name on the computer and knows how to load and shut it down, can also load some games, use a mouse, create pictures and recognise his own printed work - *at 14 years*

“ An exceptionally good reader and reads a lot. Can write (in print) just about anything but has difficulty with the proper way to make some letters - *at 15 years*

Speech and communication

Information on speech and communication is available on only 17 youngsters and in many cases the information is sketchy. This shows that some speech developed in 10 children but had not emerged in the other seven, followed up to between 15 months and 23 years. The children most likely to develop recognisable speech are those with a small duplication from 3q25 or beyond and possibly also those with a mosaic duplication (*Unique*). Among *Unique* members who are verbal are youngsters with duplications of 3q21q23; mosaic 3q23q29; mosaic 3q24qter; 3q25.1q27; 3q26; and 3q26.3q27. The medical literature also records verbal skills in youngsters with duplications of 3q26.2q27 (Holder 1994); 3q25q26.2 (Rizzu 1997) and 3q25.1q26.1 (Lopez-Rangel 1993). Among those without speech, communication devices are popular and some use is made of sign language as well as gestures and expression.

A small minority of babies is born with a cleft in part of the roof of the mouth (cleft palate); even after repair, this can affect the quality of speech sounds and so compounds the difficulties that children face. Other children may have a high or short palate that results in velopharyngeal insufficiency (incomplete closure of air spaces at the back of the throat) and a nasal quality to speech or a snorting sound when trying to make explosive sounds such as *p, b, g, t* and *d*.

“ He cannot yet express himself fully; he has a small vocabulary but is progressing all the time. Uses long phrases - *at 7 years*

“ She started to speak at approximately 8 months and hasn't stopped since - an awful chatterbox - *at 10 years*

“ He tends to run words together; understands well but expression is a problem especially when upset or angry. He talks constantly, always asking questions. Final sounds can be lost; if we don't understand often he'll spell the word - *at 15 years*

Behaviour

Unique has fairly detailed information on the behaviour of eight youngsters with a 3q duplication. This is too small a number for a definitive picture to emerge but may afford other families helpful insights into their own child's behaviour.

Most children are described by their families as being friendly and sociable, even to the point of approaching strangers to cuddle them. A few children show more reserve and can seem aloof, or friendly only to those they know well. Confronted with the challenge of frustration, behaviour can deteriorate sharply and children typically respond by throwing, kicking, hitting, banging or grinding their teeth. One family noted that the poor behaviour associated with frustration vanished with the emergence of speech, although their son sometimes shouts and swears when angry but only at home with the family. Another family took a conflict de-escalation course. One teenager was taking risperidone to calm his behaviour by 16 years. Two very young children had episodes of self-harming and screaming, but these improved with age. Children were felt to need high levels of attention, in part because they have little or no sense of danger, yet love to play with water, but also because they cannot hurry or be hurried.

In terms of enjoyment, children have a wide range of unusual or more everyday pleasures, from touching people's hair or heads, music, bowling, swinging, a ball pit, singing, computer games, trains and anything with buttons, to doing real things like washing up and hoovering as well as dancing and watching others dance.

Sleep problems occurred in seven out of eight and were treated with behavioural means as well as prescribed medication and melatonin.

“ Hugely infectious laugh – others can't help but laugh when he does - *3q26.3q27 duplication, at 4 years*

“ She loves other children, the bigger the better. She loves to be gently wrestled with and tossed on the couch - *3q21q26.2 duplication, at 7 years*

“ A happy kid with a great sense of humour - *mosaic 3q23q29 duplication, at 7 years*

“ Has a great sense of fun and can be very funny - *mosaic 3q24qter duplication, at 10 years*

“ Does not interact appropriately – touches everyone and kisses them, will also hit or push them if he wants them to move - *3q25qter duplication, at 14 years*

“ Very efficient helper who carries out jobs well even when not asked to - *3q25qter duplication, at 14 years*

“ He was a very gentle, sweet baby and had a very endearing personality throughout his early childhood. As he got older his behaviour became more challenging and difficult. Over the years autistic traits have become more obvious. He tends to talk loudly and is defiant when told what to do. Loud outbursts of verbal abuse and swearing often ensue. On occasion he has hit a teacher, slammed doors, broken the emergency window in the school bus ... Many offences were impulsive with much contrition later. From 13, I battled on alone after stimulant medication made things worse. Since a crisis last year he has been on a low dose of risperidone with some regular behavioural therapy and has thankfully settled down - *3q27q29 duplication, at 17 years*

