

4q deletions between 4q21 and 4q31



Sources

The information in this leaflet is drawn partly from the published medical literature. When it was written, around 25 people with a deletion from this region of chromosome 4q had been formally described. The leaflet also draws on information from *Unique*. At the time of writing, *Unique* had ten member families with a deletion from this region of chromosome 4q. Three were adults, the oldest an adult of 29 years without developmental delay. Families completed detailed questionnaires in 2003 and 2006. The first-named author and publication date of references to the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed. References to the information held by *Unique* are marked U.


A chromosome 4q deletion is a rare genetic condition in which there is a missing copy of part of the genetic material that makes up one of the body's 46 chromosomes. Like most other chromosome disorders, this increases the risk of birth defects, developmental delay and learning difficulties. Whether problems develop or not and how serious they are depends very much on what genetic material is missing.

Knowing the breakpoints in the chromosome (shown in the karyotype) can be very helpful in explaining the signs and symptoms that have already been found in an affected child. It may not be so helpful when it comes to predicting the effects in an individual child, although it can suggest that some conditions may be more likely to occur.

What are chromosomes?

Chromosomes are the microscopically small structures in the nucleus of the body's cells that carry genetic information. They can be stained so that each has a distinctive pattern of light and dark bands when viewed at about 1000 times life size under a light microscope.

Chromosomes come in different sizes and apart from the sex chromosomes (two Xs for a girl and an X and a Y for a boy), they are numbered 1 to 22 approximately from largest to smallest. This means that chromosome 4 is one of the larger chromosomes.

Each chromosome has a short (p) and a long (q) arm, so people with a 4q deletion have lost material from the long arm of the chromosomes (at the bottom in the diagram on the facing page). The part of the arm that is closest to the centromere, where the short and long arms meet, is called the **proximal** part. The area closer to the tip is called **distal**. People with a deletion from chromosome 4q between band 4q21 at one end and 4q31 at the other end (marked  in the diagram on the facing page) have an interstitial deletion. **Interstitial** means that the chromosome has broken in two places, the intervening segment has been lost and the remaining sticky broken ends have joined up. Your geneticist or genetic counsellor can tell you more about the material that has been lost and where the breakpoints are in your child's chromosome.

4q21q22 deletions

Some people have a deletion limited to the 4q21q22 segment. *Unique* has a separate leaflet about this deletion called **4q deletions between 4q21 and 4q22**.

Main features

These are features that have been seen in others with a deletion between 4q21 and 4q31

- Developmental delay
- Low muscle tone from birth (congenital hypotonia), so the baby feels very floppy
- Heart anomalies
- Rieger syndrome (also known as Axenfeld-Rieger syndrome, see page 8). Dental development, the development of the front part of the eye and the skin around the umbilicus are affected. The syndrome can occasionally include a permanent sensorineural hearing loss
- Unusual shape or formation of the skull or face. Early fusion of some of the seams between the bony plates of the skull (craniosynostosis) may occur
- Skeletal anomalies
- Cleft (split) in part of the roof of the mouth (Lines 2004; Becker 2003)

Deletion 4q25q27 or 4q23q27

Nine patients described in the medical literature shared certain similarities. Four developed Rieger syndrome; six had developmental delay; six had finger/toe anomalies; five had hypotonia; five had a small lower jaw; four had seizures; four had congenital heart defects; and four had a cleft palate. *Unique* has an adult member with a 4q25q27 deletion who is unaffected; her son has a mild form of Rieger syndrome (Becker 2003; U).

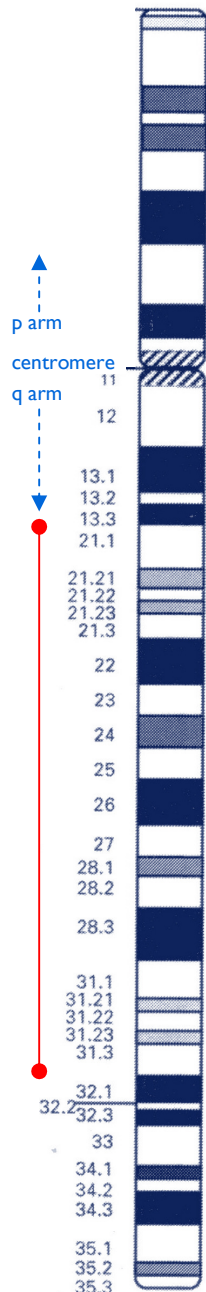
Pregnancy

In most cases, pregnancy has been described as uneventful and not giving cause for concern. The baby may be noticed at the mid-pregnancy scan or in the third trimester to be growing slowly (intrauterine growth retardation, IUGR) and in two instances, little fetal movement was felt (Hegmann 1996; Serville 1977).

Birth and the neonatal period

Some babies were delivered normally at term, but in many cases the baby's condition gave cause for concern in very late pregnancy or during delivery and a Caesarean section was performed. Although some babies did have a straightforward neonatal period, this was unusual and many needed support to start and maintain their breathing. Apgar scores (measures of a

Chromosome 4



newborn baby's wellbeing) were typically low at one and five minutes after birth and babies were usually relatively inactive and might have a weak cry. Although some babies were well enough to go home with their mother, it was not unusual for babies to spend their first weeks in special care, establishing independent breathing and overcoming early feeding difficulties as well as having the early investigations that would eventually lead to a diagnosis (U).

Appearance



Babies and children with a 4q deletion will have inherited family features. Doctors may point out what are known as 'dysmorphic features' which may or may not be obvious to a parent. Most of these are facial features of little or no consequence to the baby but they do help doctors to reach the correct diagnosis.

Typical features include a rounded, prominent forehead; wide set, small eyes that may have a tiny skin fold across the inner corner and may have hooded eyelids; a flat bridge to the nose at birth, although this may change during childhood, as it does in many babies without a chromosome disorder; a nose that

is typically short but broad and may turn up; ears set low on the side of the head that may be more simply formed than usual and may have narrow ear canals; a small mouth and a thin upper lip or a mouth with down turned corners; a small chin and lower jaw (micrognathia) that may be set back from the upper jaw (retrognathia). At birth, the soft spot on top of the head (anterior fontanelle) may be unusually large and may take longer than usual to close over. On the chest, the nipples may be small and unformed.

Hands and arms Researchers and families have reported something unusual about the hands in around half of children with a deletion between 4q21 and 4q31, although there is a lot of variety in the unusual features described. They include short arms and short fingers, broad, spade-like hands, incurving 5th fingers, slender, tapering fingers, a skin bridge between the 3rd and 4th fingers on one hand, broad thumbs, an extra skin crease on the first joint of the 5th fingers, overlapping fingers and small, deeply curved nails. Small nails and incurving 5th fingers seem especially typical of children with a 4q27q31 deletion.

Most of these features are cosmetic, but any difficulty they cause can be addressed with physiotherapy and if necessary with surgery, although this is rarely needed.

Feet and legs Unusual features of the legs and feet are as common as unusual features of the hands, especially among children with a 4q27q31 deletion. How serious the anomaly is varies widely, from short toe nails to missing toes in two cases. Toes may overlap each other or be joined by a bridge of skin and tissue. The toe nails tend to mirror the finger nails. In most children, this does not affect walking, but a small number of children have been born with a positional abnormality of the feet such as talipes equinovarus (club foot) which will usually need surgical correction before the child starts walking and a child with a 4q21.23q24 deletion was born with contracted joints and dislocated hips (Jacquemont 2006; Robertson 1998; Mitchell 1981; U).

Growth

Most babies were smaller than average at birth, but their weight came within the normal range and did not usually give cause for concern. There were exceptions, a small number of babies whose weight and length at birth put them in the lowest three to five per cent of the population. This was particularly common in babies with a 4q27q31 deletion and was also true of a baby with a small deletion within band 4q31. There were also babies whose weight at birth was well above average. This was true of at least two babies with a 4q25q27 deletion (Robertson 1998; Chudley 1988; U).

Feeding and eating

Experience suggests that newborn babies will usually need support with establishing and maintaining feeding. At birth they may not be able to suck strongly enough to feed effectively and they may have difficulty co-ordinating sucking with swallowing. The shape of the baby's mouth may not help: in many cases, the roof of the mouth (palate) is unusually high, it may be narrow and there may be a cleft (split) in the top of the mouth. A cleft seems to be more common in babies with a deletion between 4q21 and 4q27 than in babies with a 4q27q31 deletion and may be seen at the front of the mouth in the hard ridge behind the upper gums (alveolar ridge), in the hard or soft parts of the roof of the mouth, or in the uvula (the fleshy tissue that hangs down from the palate at the back of the mouth). In one baby a cleft was found in the voice box (larynx), between the throat and the airways leading to the lungs (Butler 1987).

Some babies may be able to feed from a bottle with an adapted nipple or with a plate on the roof of the mouth but most babies will need the extra help of a nasogastric tube or direct feeds into the stomach through a gastrostomy (G-tube, PEG) at first.

An extra difficulty for some babies is gastro oesophageal reflux, which occurs when the valve between the food pipe (oesophagus) and the stomach does not work effectively, allowing feeds and stomach contents to return up the food pipe. This can result in a baby inhaling some of the feed and this can cause a chest infection (aspiration pneumonia). Reflux may be controlled by correct positioning for feeds and sleeping, as well as giving small quantities slowly, and if this is not enough, thickened anti-reflux feeds or medication can help. If these measures are not enough, the valve between the food pipe and the stomach can be improved surgically in an operation known as a fundoplication.

The information from *Unique* shows that beyond babyhood, children do mature out of their feeding difficulties and learn to eat a range of normal foods but that psychological and behavioural issues around food and eating can be persistent.

Learning

Most children will need some extra support with their learning but this is not universal and the relationship between the amount of chromosome material lost and the level of learning difficulty that can be expected is not clear. Among *Unique*'s membership there is one adult with a 4q25q27 deletion who has no learning difficulties and at the time of writing was studying for a degree, and a young adult with a 4q24q26 deletion who completed regular, mainstream education despite mild but extensive learning difficulties. From the scant information available in the medical literature, it seems that there is a

broad range of eventual ability with most children experiencing mild to moderate difficulties although a minority will have more extensive difficulties.

In four cases where a developmental or intelligence quotient has been given, this was 60, 66, 80 and 90 (Motegi 1988; del Valle Torrado 1982; Ligutic 1981; U). Where a developmental age has been stated, this was 28-30 months at four years and 12-15 months at 42 months (Fryns 1992; Chudley 1988).

The following descriptions are of *Unique* members.

“ He has moderate learning difficulties. With numbers and counting his ability is poor but he is a lot better with things than with ideas. His strengths are music and a good memory. Repetition, determination and consistency help him to learn – 4q23q28 deletion, at 4 years

“ His difficulties are mild to moderate; he struggles with some counting but is very good with sequencing and times tables. He learns best when he is praised – 4q25q27 deletion, at 7 years

“ He is fantastic at recognising and knowing words and could read from the age of 6 although he has little understanding. His long-term memory is very good but short-term is poor. He finds numeracy hard but at 8 is finally getting there with simple additions and sums. His strengths are his confidence, reading and his very good picture memory. Overall, his difficulties are moderate to severe and he is achieving at the level of a 4 or 5-year-old - 4q25q28.2 deletion, at 8 years

“ She is just about writing her name but can't yet read. She has an excellent memory and remembers the strangest things – 4q27q31 deletion, at 5 years

“ She reads well and is starting to write although as she is deaf, communication is hard. She could recognise letters and numbers at five, started to role play at six, started to read and write at seven, is very good on the computer and uses words and symbols programmes very well and can type 30 to 40 words and read about 100 words from symbols – 4q27q31 deletion, at 11 years

Speech, communication and hearing

Virtually all the information available has come from *Unique*. This shows that a significant number of children have some degree of hearing loss which affects their speech development. Some children have very narrow ear canals which may even block, so that sound cannot get through (Mitchell 1981; U). Other children have a permanent form of hearing loss (sensorineural hearing loss); this appears to be most common among those with a 4q27q31 deletion but has also been found in a child with a 4q25q27 deletion and another with a 4q31.1q31.3 deletion (Robertson 1998; U). Additionally, some children develop the very common if temporary hearing loss caused by a build-up of fluid behind the ear drum within the middle ear that is usually treated by inserting hearing tubes (grommets) into the eardrum. Despite these high rates of hearing loss, most children develop some speech, although those with more severe hearing loss are likely to rely on signing and alternative means to communicate. Even in children with no diagnosed hearing loss, first words are usually late to emerge and progress to joined words and sentences is likely to be slow. Understanding may run ahead of expression if hearing is unaffected. However, a 12-year-old with a 4q21.23q24 deletion had normal verbal abilities (Jacquemont 2006; U).

- “ He has a vocabulary of 10 or more single words and some two-word phrases as well as vocal noises and can sign the word ‘more’. He started using words at the age of two and understands a lot more than he can express – 4q23q28 deletion, at almost 4 years
- “ His speech is delayed due to his hearing loss and he still has difficulties with understanding. He first spoke at the age of four and today uses sentences. Even now he cannot express emotions very well and this can lead to behaviour problems – 4q25q27 deletion, at 7 years
- “ He first started to babble at 11 months and now talks non-stop. He has some echolalia and his comprehension is poor so he needs to repeat instructions to himself - 4q25q28 deletion, at 8 years

Sitting, moving, walking: gross motor skills

It seems that most babies with this 4q deletion, although not all, have very low muscle tone at first and are delayed in reaching their developmental milestones. Supported sitting is usually possible for many months before independent sitting, and crawling may never occur because of low muscle tone in the upper body. All children known to *Unique* do walk and will eventually run, although some have an unusual gait and may have difficulties with co-ordination and balance. *Unique* sources show that the age range within which babies have learned to roll over was between six and 10 months; babies have sat between 7 and 18 months; crawled between 10 and 17 months; and walked between 17 and 26 months. Climbing stairs was generally achieved during the third year, but might be later (U).

Hand use: fine motor skills

A delay in holding objects, transferring them from hand to hand, letting them go and using them at mealtimes and in school was usual, although the information available from *Unique* suggests that eventually children can generally be expected to feed themselves and use an implement for writing as well as to operate a computer.

In individual cases, the pincer grip between the thumb and forefinger has been late to develop and low muscle tone in the arms and hands has made drawing and writing difficult. Children have learned to feed themselves using their hands between 8 and 12 months, held a cup or spoon between 2 and 3½ years and used a knife and fork around 6 to 7 years.



Medical concerns

■ Heart

A congenital heart anomaly has been found in almost half of all babies, although the majority of defects are minor and the rate among *Unique* members is very much lower than in the medical literature.

The most common anomalies noted have been interconnecting holes between the two sides of the heart, either between the upper chambers (atrial septal defect, ASD) or between the lower chambers (ventricular septal defect, VSD). A channel connecting the two main outflow vessels from each side of the heart known as the ductus arteriosus that usually closes around the time of birth is occasionally found still open (persistent ductus arteriosus, PDA). These defects may resolve in time but if they do not, they can be corrected surgically.

Less common problems include narrowing of the blood vessels taking blood from the heart and an enlargement of the heart muscle, usually caused by the heart working abnormally hard. In children with deletions of 4q between 4q21 and 4q31, these problems have appeared to be generally self-correcting.

■ Rieger syndrome

A form of Rieger syndrome (also known as Axenfeld-Rieger syndrome) is liable to be present when one copy of the *PITX2* gene, situated in the 4q25q26 band, is missing. Signs of this syndrome include abnormal dental development with small and missing teeth, defects in the front part of the eye and excessive skin around the navel (umbilicus). The heart, limbs and pituitary gland may also be affected and a permanent hearing loss has occasionally been found (Becker 2003; Lines 2002; Flomen 1997; Schinzel 1997).

■ Cleft

A cleft (split) in part of the upper mouth has been described as common in babies with 4q23q27 or 4q25q27 deletions, although none has been reported in *Unique*'s membership, so the frequency may be overstated (Becker 2003; U). If a cleft does occur, extra help will be given with feeding as well as speech and language therapy, which will continue after surgical correction of the cleft.

A cleft alveolar ridge has been seen in three children, all of whom had lost the 4q25q26 segment.

■ Head shape

At birth, a baby's head may well be an unusual shape and may be larger or smaller than normal. The soft spot on top of the head (anterior fontanelle) may be unexpectedly large and slow to close and the seam lines between the bony plates of the skull may also be open. It can also happen that one or more of the seam lines fuse early, so that the brain has little room for growth in this area (craniosynostosis). If this occurs,

a decision will be taken whether to monitor the growth of the head or to operate surgically to re-open the skull plates to allow better room for growth (Rose 1991; Butler 1987; del Valle Torrado 1982; U).

■ **Seizures**

Seizures or seizure activity on an electroencephalogram has been described in seven babies out of 34. In all babies who needed anti-epileptic medication, seizures were controlled on phenobarbitone. No children in *Unique* developed seizures.

■ **Genital area and bottom**

Minor anomalies in the genital area occur quite frequently in babies with a chromosome disorder, especially although not exclusively in boys. In babies with a deletion between 4q21 and 4q31, the hole for the bottom may be very close to the genitals, so that careful hygiene at nappy changing is especially important. In boys, the hole usually at the end of the penis may be found on the underside instead (hypospadias) and the testicles may be small and not descended into the scrotum at the time of birth. Surgical repair of hypospadias is usually carried out using tissue from the foreskin, so baby boys with hypospadias are usually left uncircumcised.

■ **Bones and skeleton**

Babies with a chromosome disorder are very thoroughly investigated and it is not uncommon to find abnormalities of the skeleton, such as an extra or a missing pair of ribs. These are not usually of any consequence and no treatment is needed. The vertebrae in the spine may also be found to be split (butterfly vertebra) or incompletely developed on one side, resulting in a wedge shape (hemivertebra). Butterfly vertebrae usually cause no problems, while hemivertebrae can be one cause of a spinal curve developing.

■ **Teeth**

Children with 4q deletions are likely to need specialist dentistry. Those with Rieger syndrome (see facing page) typically have small teeth with poor enamel formation, as well as some missing teeth. The teeth may come through late and in one child emerged already with caries. Among *Unique* children, overcrowding of the teeth in a small jaw has been a more common problem (Ligutic 1981; U).

■ **Eyes and vision**

In addition to the typical features of Rieger syndrome (see facing page), some children have other visual problems. The most common is a squint (strabismus), which may be corrected with a regime of daily patching. If this does not work, the eyes can be realigned surgically. Among four children with 4q27q31 deletions, two had upper eyelids they could not fully open (ptosis). If the eyelid obscures vision, it can be lifted in a surgical procedure. One child also had a condition known as Duane's retraction syndrome which prevents full swivelling of the eyes (Chew 1995; Mitchell 1981; U).

Behaviour



Children with even slight learning difficulties may have problems with behaving in a way that other people think is appropriate. They may be over-friendly and trusting or, on the other hand, uncommunicative and unresponsive. If things do not go their way, if they are bewildered or unduly hurried, they can react aggressively. At the same time, they can be loving and caring.

Although it is reasonable for families to be alert to unusual behaviour patterns in their child, overall there is no evidence yet that a chromosome disorder involving a deletion between 4q21 and 4q31 is associated with any particular behaviour pattern or style. The behaviour of one 12-year-old boy with a 4q21.23q24 deletion met the criteria for a diagnosis of autism (Jacquemont 2006; U).

Unique publishes a leaflet on **Challenging Behaviour** for families.

The descriptions that follow are of individuals at various ages.

- “ He can be hyperactive when he is tired at end of the day but is generally a very social and playful, happy boy who loves to dance and watch musical shows on TV or video – 4q23q28 deletion at almost 4 years
- “ He is currently undergoing tests for atypical autism. He has difficulties with socialising, hyperactive behaviour, aggression and obsessional behaviour. This has got worse over time and behaviour management teaching has not helped – 4q25q27 deletion, at 7 years
- “ He loves to be around adults and craves their attention. Other children can be scared of his odd behaviour and speech. He demands constant attention and when this isn't possible he can become very difficult. His concentration and attention are not good and he flits from one thing to another. He can get very anxious at times. He has seen two behaviour nurses and is now under the care of a psychiatrist – 4q25q28 deletion, at 8 years

Why did this happen?

A chromosome 4q deletion can occur as a result of rearrangements in one parent's own chromosomes or it can happen out of the blue, so the child with the chromosome disorder is the only person in the family with rearranged chromosomes. The disorder is then termed *de novo*. A check of the parents' chromosomes will show whether the disorder is *de novo* or not.

If the check reveals a structural rearrangement of one parent's own chromosomes, this is usually balanced so that all the chromosome material is present, and the parent is then almost always healthy.

Occasionally, one parent has the same chromosome deletion as their child. The parent may be unaffected by the loss of chromosome material or only mildly affected.

Can it happen again?

Each situation is individual and families should consult their genetics service to discuss their future plans.

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 4q deletion. Where a parent has a rearrangement of their chromosomes, the risk of having another affected child is higher. Where the parent has the same deletion as the child, the risk of passing it on could be as high as fifty per cent.

How did this happen?

Rearrangements occur in chromosomes as part of evolution. They affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. So there is no reason to suggest that your lifestyle or anything that you did caused the loss of chromosome material.

Changes to the structure of chromosomes such as 4q deletions occur most often during the cell divisions that lead to the creation of eggs or sperm. Each of the 46 chromosomes first doubles lengthwise into two strands that are held together at the point where the short and long arms meet, known as the centromere. The chromosomes then arrange themselves in 23 pairs, with pairs lying alongside each other. The two members of each chromosome pair 'recognise' each other because the DNA sequence ladder that comprises them is in a similar order. However, when a small region of DNA on a chromosome has a twin region of DNA located elsewhere on the same chromosome, the pair of chromosomes may not align correctly. Usually, after chromosomes pair, the members of a pair exchange segments of DNA with their pair-mates, in a process known as crossing-over (recombination). After this point, the chromosome strands repel each other but are held together at the cross-over points known as chiasmata. Deletions can arise during this process when the chromosomes have lined up incorrectly. An unequal cross-over means that the exchanges are not equal between the members of a chromosome pair. In this case, a piece of one chromosome can loop out and be lost from the middle of the chromosome (interstitial deletion) or from the end of the chromosome that then 'heals' (terminal deletion).

Support and Information



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Join Unique for family links, information and support.

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Facebook page for 4q deletions: www.facebook.com/groups/102813767091

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.

This updated information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr E-M Strehle, consultant paediatrician, and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, UK. 2006. (PM)

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