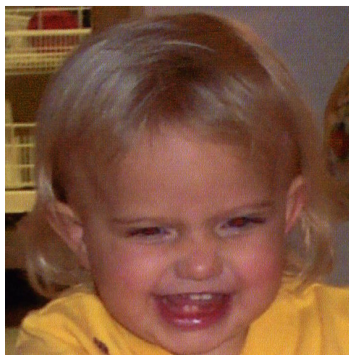


# 4q deletions between 4q11 and 4q22



## Sources

The information in this leaflet is drawn partly from the published medical literature. When it was written, around 20 people with the deletion had been described in the medical literature.

The leaflet also draws on information from *Unique*. At the time of writing, *Unique* had nine member families with a deletion from this region of chromosome 4q. The oldest child at the time was 17 years. Two families completed detailed questionnaires in 2006.

This does not make a large series but at the moment it is the best information available.

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 and 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 as well as on other factors that are not yet fully understood.

Knowing the chromosome make-up (known as the karyotype) is helpful in explaining the signs and symptoms that have already been found in an affected child. It is not so helpful when it comes to predicting the effects on 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 **proximal**. The area closer to the tip is called **distal**.

People with deletions of chromosome 4q between 4q11, 4q12 or 4q13 at one end and 4q21 or 4q22 at the other end (the bands marked  on page 3) have a proximal interstitial deletion. **Interstitial** means that one of the two chromosome 4s in the cells of the body has broken in two places, the intervening segment has been lost and then the 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**.

## Most common features

People with this deletion can be very different from each other, despite having apparently similar breakpoints in the chromosome. One of the most likely explanations for this is that breakpoints that appear to be the same are not, when the chromosome is viewed at higher resolution. To be more precise about the breakpoints, it is helpful to have molecular genetic tests as well as a conventional chromosome analysis. These are the features most commonly described in babies and children:

- Developmental delay
- Low muscle tone so the body feels soft and floppy
- A degree of learning difficulty with speech delay
- Growth delay
- Feeding difficulties
- Few major birth defects
- In some, seizures
- Areas of light-coloured skin without pigment and a white forelock of hair.

(Fujimoto 1998; Slavotinek 1997; U).

## Birth and the neonatal period

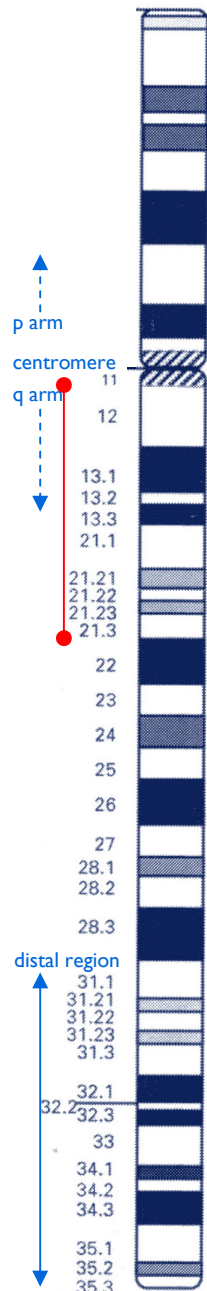
This depends chiefly on whether any of the baby's major organs are affected. If they are not, the newborn period usually appears to run smoothly, apart from feeding difficulties. However, babies with a congenital heart condition will need full clinical support (Strehle 2001; Slavotinek 1997; U).

## Appearance

If your child is small, this is the feature that is likely to make them stand out most. Relative to their length or height, most children have a large head. Facially, it is unlikely that they will look very different from other children as the cosmetic features that geneticists comment on are usually quite subtle. However, you may find that your baby does look somewhat different facially from other family members.

Typical facial features may include a square head with a high, domed or prominent forehead and a flat or prominent back of the head (occiput); obliquely slanting eyes; a tiny skinfold across the inner corner of the eyes; a broad or flat bridge to the nose and a nose that may be small and upturned; frequently, low set ears that may have an unusual shape;

## Chromosome 4



a small mouth with short upper lip or down-turned corners; a small or receding chin. The soft spot (anterior fontanelle) on the top of the head may be very large indeed and slow to close. It measured 6cm by 4.5cm in one five-month-old baby and in another 19-month-old baby still measured 2cm in each direction (Strehle 2001; Hsu 1998; Fujimoto 1998; Schinzel 1997; Slavotinek 1997; Curtis 1990; Mascari 1989; Yamamoto 1989; Beall 1988; Hoo 1986; McDermott 1980; Lacassie 1977; Funderburk 1974).

## Growth

From the experience of 21 babies, growth patterns before and after birth vary a lot between individuals. Bearing actual age in mind, weight at birth ranges between the lowest five per cent of the population and the top 75 per cent, although most babies have an average or somewhat below-average birth weight. Most babies and young children also put on weight and grow very slowly but individuals do vary. Two children are both tall and heavy for their age and others have an average height and weight for their age.

Among those children who are very short for their age, growth hormone levels and bone age have been assessed. Growth hormone levels have not been found to be abnormally low but in every child investigated, bone age was significantly reduced. A common finding is that head size is large relative to body size and weight, both at birth and in childhood (Nitsch 2005; Strehle 2001; Fujimoto 1998; Hsu 1998; Schinzel 1997; Slavotinek 1997; Curtis 1990; Yamamoto 1989; Beall 1988; Hoo 1986; Lech 1982; McDermott 1980; Lacassie 1977; Funderburk 1974; U).

## Food and eating

Some information on feeding is available for twelve babies. Feeding difficulties arose in most, which is unsurprising for babies who are born small and have a low muscle tone, affecting their ability to suck and co-ordinate the actions of sucking with swallowing. In some babies, the feeding difficulties were quite marked and two children are known to have needed a gastrostomy (a tube through which they could be fed direct into the stomach) although one needed this only for liquid feeds.

Reflux occurred in some babies, a condition where the feeds and stomach contents return up the food pipe (oesophagus) due to faulty action of the valve at the junction between the oesophagus and stomach. This condition can usually be controlled with careful positioning before and after feeds and with prescribed medication to keep feeds down and act against any acid attack within the oesophagus. If these measures are not enough, a surgical operation known as a fundoplication can be carried out to improve the action of the valve between the oesophagus and the stomach.

Two babies had severe cow's milk protein allergy requiring replacement with non-milk formula and of these babies, one had a severe anaphylactic reaction to both milk and soy proteins.

Only two babies had no feeding difficulties and of these, one was a baby with a small 4q12 to q13.1 deletion (Strehle 2001; Slavotinek 1997; Curtis 1990; Mascari 1989; Beall 1988; Hoo 1986; Funderburk 1974; U).

## Learning

Families can expect that their child will need extra support with their learning, but the extent of the support they need will only become clear over time. The only child with no known learning difficulties was a girl with a 4q12 to q13.1 deletion (Slavotinek 1997). From the sketchy evidence available from the medical literature, it seems that most children will have a moderate to severe learning disability. This means that they are quite likely to thrive best in a special school, although this depends very much on the arrangements available where you live.

One child was shown to have better motor than language skills at the age of four (Fujimoto 1998).

The *Unique* experience confirms this general picture but shows that children can be lively, eager and willing to learn at their own pace and that by adulthood some literacy and life skills can be acquired.

“ She loves to draw and look at books and has been painting with brushes since 20 months. She has just started working on numbers and counting. She is helped by her curiosity – she always points to things to ask what they are. She will look at all sides of toys and objects when something new is given to her. She learns very well and I: I has a long attention span – at 28 months

(Strehle 2001; Schinzel 1997; Curtis 1990; Mascari 1989; Yamamoto 1989; Beall 1988; Hoo 1986; Lech 1982; McDermott 1980; Lacassie 1977; Funderburk 1974; Henningsen 1969; U).

## Speech and communication

Speech and language are markedly delayed but there is not enough evidence to say whether the delay is disproportionate to the learning disability. Two children described in the medical literature had some speech, one a girl with a 4q12 to q13.1 deletion, the other child with a 4q12 to q21.1 deletion who had some words at the age of four (Fujimoto 1998; Slavotinek 1997).

*Unique's* experience is that a child with a 4q12 to q13 deletion spoke their first words at the age of 5 years; a child with a 4q12 to q21 deletion started to speak at 3½; another child with the same deletion had no words at the age of 6; and an adult with a 4q13 to q21 deletion had limited speech attributed to low muscle tone in the mouth and face. She could use both single words and linked phrases of two to three words, but preferred to use gestures. Her understanding was reported to be good and she could copy letters and words using a computer keyboard (U).

“ She has 6 months expressive language delay but her receptive language skills are age appropriate. To communicate, she uses signing, gestures, words and noises but with inflections in her tone as when she points at something, wanting to know what it is or what colour it is. Her first words came at 12 months and for a long time she said 2-3 words before she really started picking things up at 24 months. Now she uses lots of single words, and some phrases like ‘More snack please.’ She is also very co-operative, enjoying the interaction of talking - at 28 months

“ He communicates through crying and body language - at 5 years

## Mobility and activity: gross motor skills



**26 months old, with a 4q12q21.1 deletion**

Babies and children are likely to be delayed in reaching their mobility milestones but with encouragement, physiotherapy (physical therapy), practice, maturity and in some cases with supports and aids, they should achieve them eventually. However, this level of mobility may not be possible for all children.

Most children have hypotonia (low muscle tone, floppiness) and very lax joints also occur (Hoo 1986; Lacassie 1977; Funderburk 1974).

Of the two children described with a 4q12 to q13 deletion, one walked at 16 months, the other rolled at 8 months, sat at 10 months, crawled at 11 months and walked by the age of 2 years (Slavotinek 1997; U).

Among the children with a 4q12/13 to 4q21/22 deletion, one had only slightly delayed mobility skills. Of the others, sitting was achieved between eight months and almost four years; crawling by 25 months and walking with support between 18 months and seven years (Curtis 1990; Lech 1982; Funderburk 1974; U).

One child with a 4q13 to q21 deletion was found to have Charcot-Marie Tooth disease, a condition in which the muscles of the legs from the knees down and often those of the hands waste and weaken. This disorder is not normally associated with a 4q deletion (U).

“ Sitting, crawling and walking were all delayed but at 28 months she has no problems although she cannot run steadily yet. She can scoot or crawl up and down stairs but does not yet have the balance to walk up or down

“ He is not sitting, crawling or walking yet but he holds his head up - at 5 years

## Using their hands: fine motor skills

There is very little information on the fine motor skills that underlie hand use and hand-eye co-ordination. From limited information on three children, it appears that it is hard to predict an individual's rate of development. In one child of 28 months, no delay in these skills was found, while in a baby of five months these skills were especially delayed (McDermott 1980; U).

## Medical concerns

### ■ Heart

Among the 28 babies and children described in this leaflet, four had a diagnosed congenital heart defect and two further babies had a transient heart murmur but no heart defect. The conditions found included an atrial septal defect (ASD, a hole between the upper chambers of the heart), a ventricular septal defect (VSD, a hole between the two lower chambers) and two children had more complex conditions. One was Fallot's tetralogy, where the right heart is underdeveloped, there is a hole between the ventricles, the artery that takes the blood to the lungs has an unusually narrow entrance (pulmonary stenosis) and there is an unusual arrangement of the aorta. The other baby had a large ASD, a persistent ductus arteriosus (failure of a channel between the aorta and the pulmonary artery to close as expected soon after birth) as well as hypertrophic cardiomyopathy, a thickening of the heart muscles (Nitsch 2005; Strehle 2001; Hsu 1998; Curtis 1990; U).

### ■ Seizures

Six of the 28 children with this deletion (21 per cent) are known to have had seizures or seizure-like activity and one other has had an electroencephalogram (EEG, a test of the electrical signals in the brain) which suggested seizure activity. In two cases, seizures only occurred in young babies, in one on the first day of life and in the other at two months. In children taking anti-epileptic medication, the seizures were well controlled (Strehle 2001; Hoo 1986; Lech 1982; McDermott 1980; U).

### ■ Head and brain

Information on head size is available for 13 babies or children. Although head size may be small (microcephaly) compared with other babies, relative to their own body, the head is frequently large. In no case was the head relatively smaller than the body. Information is very sparse about children who have had a brain scan, and quite varied anomalies have been found: agenesis of the corpus callosum (absence of the broad band of nerve fibres that links the two hemispheres of the brain); enlarged ventricles, small cerebellum (the largest part of the hindbrain) and abnormal folding of the outer part of the frontal lobes, and rapid relative diminution of head size between birth and six months of age; atrophy of the temporal lobes (Nitsch 2005; Strehle 2001; Schinzel 1997; Curtis 1990; Beall 1988; Hoo 1986; U).

### ■ Hair, skin

A distinctive feature of some - but not all - babies and children with a 4q12 deletion is a white lock of hair at the front of the head, usually together with irregular

patches of non-pigmented pale skin over parts of the body. This may not be immediately apparent at birth (one family commented that their baby had extremely red skin at birth), it does no harm and the only points for families to watch for will be to use sun cream, especially on the non-pigmented skin in summer. Occasionally an area of light pigmentation will also be seen in the irises of the eyes. Among children without a white forelock, the hair has sometimes been described as fine or sparse (Fujimoto 1998; Slavotinek 1997; Yamamoto 1989; Hoo 1986; Lacassie 1977; Funderburk 1974; U).

### ■ **Mouth and palate**

Two babies were born with an unusually high palate. This can make feeding slightly more difficult, but most babies manage well. One baby had a tongue tie, released at birth in a small surgical procedure. Typically, the mouth is small and dribbling (drooling) may be a problem due to low muscle tone in the mouth area. Dribbling can be treated with skin patches containing hyoscine (Curtis 1990; Hoo 1986; U).

### ■ **Spinal curve**

Children with marked hypotonia are sometimes prone to develop a spinal curve. Very few children described in the medical literature have been followed for long enough to know whether this happens, although a spinal curve has been described in two youngsters, in one case before the age of four years. In one *Unique* member, a marked forwards and sideways curve developed by the age of 15 and needed surgical correction (Curtis 1990; Mascari 1989; U).

### ■ **Genital area and bottom**

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. This has been described in two boys with this deletion: one boy had a small penis and his anus (bottom) was abnormally positioned; the other boy had hypospadias (the outlet hole is on the underside). This condition can be corrected in a surgical procedure (Strehle 2001; Hoo 1986).

### ■ **Kidneys, bladder and urinary tract**

One baby was born with a missing right kidney (Yamamoto 1989).

### ■ **Hernias**

Two babies have been described in the medical literature with a hernia in the groin, requiring surgical correction (Strehle 2001; Beall 1988).

### ■ **Hands**

Typically, babies have small hands with tapering or stubby fingers and in some cases incurring fifth fingers. The arms may also be short (Schinzel 1997; Sijmons 1993; Beall 1988; Lech 1982; U). This feature is not universal: one child had normal sized hands (Curtis 1990).

### ■ **Limbs and feet**

Feet and toes are also typically small and the legs are often short. 'Rocker bottom' soles and prominent heels have been described. The toes may overlap, although this usually corrects itself at least partly once a child is walking. One adult had a clubfoot



(talipes) on one side and a claw foot (pes cavus) on the other, with legs of uneven length (Strehle 2001; Schinzel 1997; U).

### ■ Teeth

Delayed tooth eruption with imperfect enamel formation is strikingly common, noted by one in three families and researchers. Any of the teeth may be affected, including incisors and molars. First teeth have emerged between 18 months and two years and the enamel has been soft and thin, exposing children to the risk of caries and in some cases major dental surgery (Schinzel 1997; Slavotinek 1997; Hoo 1986; Funderburk 1974; U).

### Ears and hearing

A temporary hearing loss due to glue ear is common in all young children and particularly common in children with chromosome disorders. Treatment is straightforward through the insertion of aeration tubes into the eardrums, sometimes removing the adenoids with or without the tonsils at the same time. In addition to this type of conductive hearing loss, a more permanent deafness has been seen in two children with this deletion. Children with a permanent sensori-neural deafness can usually maximise their hearing with a hearing aid (Curtis 1990; U).

### Eyes and vision

The most common vision problem is a strabismus (squint), seen in two *Unique* members and two children described in the medical literature. Strabismus can normally be treated with patching, glasses and sometimes with a surgical operation. One *Unique* member also has an unspecified visual impairment and one baby has been described with an underdeveloped right eye and a developmental defect of the optic disc (the point where the optic nerve leaves the eye for the brain) (Slavotinek 1997; Curtis 1990; McDermott 1980; U).

### Experience with puberty

Puberty has only been described in one *Unique* member, a girl whose periods started at the age of 17.

### 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 deletion is then termed *de novo*. A check of the parents' chromosomes will show whether the deletion 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.

### 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 own chromosomes, the risk of having another affected child is higher.

### 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, causing an interstitial deletion.



26 months old, with a 4q12q21.1 deletion

# Support and Information



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

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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