

*Unique*

Support and Information

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There is an e-group for families  
affected by a 4q deletion at  
<http://groups.yahoo.com/group/4qdeletion>



*Unique* lists other organisations' message boards and websites to help families looking for information. This does not imply that we endorse the content or have any responsibility for it.

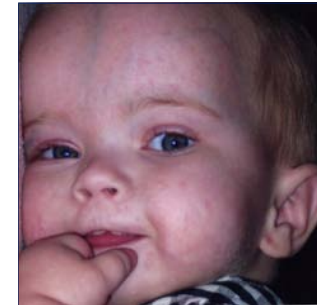
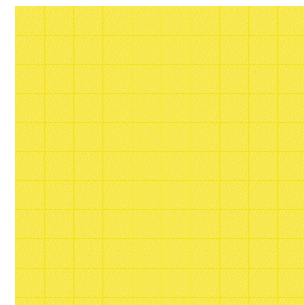
This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication and has been verified by Dr E-M Strehle, consultant paediatrician, and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, UK.

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# 4q deletions: between 4q21 and 4q22



## Sources

The information in this leaflet is drawn partly from the published medical literature. By 2006, more than 20 people with a deletion involving the 4q21q22 segment had been described in the medical literature with eight of the published cases strictly limited to the 4q21q22 segment. The leaflet also draws on information from *Unique*. When this leaflet was written, *Unique* had seven active member families with a 4q21q22 deletion. The oldest child at the time was 19 years. Five of the 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. References to the information held by *Unique* are marked U (Harada 2002; 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 very helpful in explaining the signs and symptoms 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).

People with deletions between 4q21 and 4q22 have lost material from the bands marked  in the diagram on the facing page. They may have lost a smaller or larger amount but it has recently been suggested that all people with the syndrome will have lost a minimum 'critical' region at 4q21.1q21.3 (Nowaczyk 1997).

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.



## Independence

Most children have difficulty in acquiring skills needed for daily living so it seems likely that they will need support throughout their lives.

## 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 (interstitial deletion) or from the end of the chromosome that then 'heals' (terminal deletion).

## Main features

These are features that have been seen in others with a deletion between 4q21 and 4q22:

- Delay in development
- Learning difficulties
- Low muscle tone, so a baby feels floppy to hold
- Short height but proportionately larger head size
- In some, heart conditions
- In some, seizures  
(Nitsch 2005; Harada 2002).

## Other features

- Genital anomalies in boys
- Microcornea. The transparent circular front part of the eyeball is unusually small. The eye itself may also be small
- Possibility of liver tumour  
(Nowaczyk 1997).

## Pregnancy

Pregnancy is generally uneventful. A minority of babies show growth delay which may be picked up in mid to late pregnancy but this is the exception rather than the rule. Babies with 4q21q22 deletions typically have short arms and legs and this may be noted if the femur (thigh bone) is measured during pregnancy.

## How might this affect a newborn baby?

Some babies are distinctly unwell at birth while others manage reasonably well. Some babies have very low Apgar scores (a measure of general wellbeing) at birth and have difficulty in establishing independent breathing. Some spend their first weeks of life in special care, although the *Unique* series shows that the great majority do well afterwards. Others are well at birth with high Apgar scores (Jacquemont 2006; U).



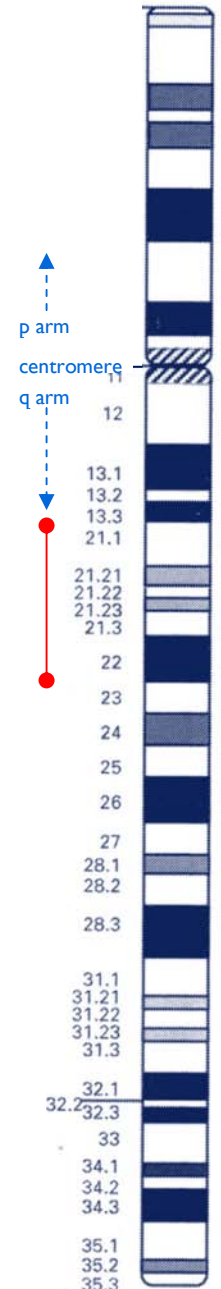
At 7 months

## Appearance

There may be little sign in the appearance of a baby with a 4q21q22 deletion of the underlying disorder. 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 head that is relatively large. The soft spot on the top (anterior fontanelle) can be unusually wide open at birth, measuring 6cm by 10cm in

## Chromosome 4





one newborn baby. Most typically, the forehead is rounded and prominent (frontal bossing), and the back of the head may also stand out (prominent occiput). The ears may be set low on the side of the head and be simply or unusually formed. The eyes may be set wide apart and can be unusually small. Typically, the nose is small, with a wide, flat bridge and may be upturned, the mouth is small and the upper lip is short and thin. The chin and lower jaw tend to be small (micrognathia) and may be set back against the upper jaw (retrognathia). The neck and the chest may be short and in some babies the nipples are underdeveloped (Nowaczyk 1997; U).

## Growth

The birth weight of babies with a 4q21q22 deletion is extremely variable, with published weights at term ranging from 1700g (3lb 12oz) to 4082g (9lb 4oz). The birth weights of babies in the *Unique* series were close to average for gestational age. Length at birth was also variable but usually fell within the normal range.

There appears to be no consistent growth pattern after birth either: some babies grow well, others more slowly. The medical literature reveals short stature in four children and a drop-off in length from the 50<sup>th</sup> centile at birth to the tenth centile by the age of eight months in a fifth baby. Among *Unique* children, growth delay, satisfactory growth and irregular patterns of growth are all documented. A 19-year-old girl reached a height of 157 cm (5' 2").

Some children have short arm and legs relative to their body size as well as small hands and feet and this may be one of the distinctive features of people with 4q21q22 deletions.

A study of a six-year-old girl with severe growth failure and a 4q21.1q22.2 deletion highlighted four bone-related genes in 4q21q22 – *BMP3*, *PRKG2*, *MEPE* and *IBSP* – which could be related to severe growth retardation, delayed bone age and short limbs (Jacquemont 2006; Harada 2002; Suwa 1998; Nowaczyk 1997; Abuelo 1988; U).



At almost 3½ months.  
At birth, this baby's feet fitted into dolls' shoes.

## Feeding and eating

Babies will usually need support and extra time with feeding, although feeding problems are not usually severe and some babies manage very well. Some of the typical problems that families encounter are the baby's difficulty in co-ordinating the actions of sucking, swallowing and breathing (oropharyngeal inco-ordination) and a tendency for feeds to be brought back up the food pipe from the stomach (gastro

## ■ Eyesight

Children with chromosome disorders generally have a high rate of eye problems. Among those with a 4q21q22 deletion, immaturity of the visual pathways, strabismus (squint) and both long and short sight have been described (Jacquemont 2006; U).

## Behaviour

There is no known typical behaviour pattern for children with this deletion but the general impression from families of affected children is that they have a pleasant, sociable disposition.

Among older children the picture may change and challenging behaviour has been seen, getting markedly worse around puberty. However, this responded well to medication which was eventually safely withdrawn once puberty was past. An adult has been described with autism (Jacquemont 2006; U).

- “ The sweetest, calmest, most tolerant baby I've ever seen who scarcely ever cries. As her developmental abilities have progressed, she does get frustrated but even this is muted compared to most babies.
- “ A very happy boy who makes our life happier.

Asked what their babies enjoyed doing, parents said:

Face to face play, a parent singing, laugh-and-learn toy puppy, bright toys and especially bright lights and loud sounds – 10 months

Playing with toys and people; loves music - 13 months

Listening to music or singing, practising pulling herself up; anything with lights and sound; looking in a mirror – 26 months



(hypospadias). This has been seen three times in boys described in the medical literature; in one boy the testicles did not descend into the scrotum (Jacquemont 2006; Suwa 1998; Nowaczyk 1997).

#### ■ Kidneys

Two babies were born with small cysts in their kidneys. As the gene *PK21* for polycystic kidney disease type 2 has been mapped to 4q21q23 it has been suggested that only having one copy of this gene may lead to renal cyst formation. However, none of the *Unique* series has been found to have kidney cysts (Velinov 2005; Nowaczyk 1997; U).

One *Unique* member (out of six) has Fanconi syndrome, causing an impairment in the tubular function of the kidney that causes certain compounds to be excreted instead of being absorbed into the bloodstream. This is possibly caused by the loss of a gene or genes at 4q21.

#### ■ Liver

One baby with a 4q21.22q23 deletion developed a liver tumour at the age of four months. The 4q21q22 segment includes a gene for liver cell cancer, so children in whom this region is deleted should be followed up for liver tumours (Harada 2002).

#### ■ Other organs

One baby was born with no parathyroid glands and an underdeveloped thymus and one child in the *Unique* series has a very small pituitary gland. An adult was born with Meckel's diverticulum, an abnormality of the intestine (Jacquemont 2006; Abuelo 1988; U).

#### ■ Bones and skeleton

Apart from shortened bones in the arms and legs, the most common anomalies are either an extra set of ribs or a missing pair. This does not affect a child's quality of life and treatment is not necessary. A spinal curvature has been seen in a 20-year-old man (Jacquemont 2006; Nowaczyk 1997; U).

#### ■ Teeth

Occasionally children have teeth that are imperfectly formed, positioned or have defective enamel or pitting. It has been suggested that absence of the *DSPP* gene at 4q21.3 may be responsible for some of the dental defects (Jacquemont 2006; Harada 2002).

#### ■ Hearing

Three of the 15 children described are known to have a permanent hearing loss and one other child has the type of conductive hearing loss caused by glue ear. In one child the ear canals are so narrow as to be blocked. This relatively high rate of hearing impairment means that children's hearing should be carefully monitored from birth and professional advice sought on using hearing aids to maximise hearing during critical periods of language acquisition (Harada 2002; U).



oesophageal reflux, also known as GERD). Babies may suck too weakly to meet their own nutritional needs and need their feeds supplementing with high-energy formula. With increasing maturity babies usually learn to suck more efficiently. A baby with a 4q21.1q21.3 deletion nursed from birth, fed entirely from the breast from 2.5 months and sucked strongly enough on her own to make the milk flow from 4 months. Giving feeds through a nasogastric tube or through a tube direct into the stomach (PEG, gastrostomy) can help as a temporary measure.

Giving small feeds with the baby in a semi-upright position and laying him in his cot with the head slightly raised may help to ease reflux. If simple management steps do not help feeding enough to ensure a steady, if small, weight gain, there is a range of medical and surgical options. Reflux can be treated with prescribed medications and formula that both help to keep the feeds down and to counteract acidity within the oesophagus. In severe cases a surgical fundoplication can help. The top of the stomach is wrapped around the bottom of the oesophagus and stitched in place. At the same time the hole in the diaphragm through which the oesophagus passes is tightened (Nowaczyk 1997; U).

#### Learning

It seems likely that the great majority, if not all, children with a 4q21q22 deletion will need support with their learning and the information at *Unique* suggests that many will need very considerable help. It is uncertain whether the amount of chromosome material lost impacts directly on the child's learning ability but it is very likely that a child will need special education (Nowaczyk 1997; U).

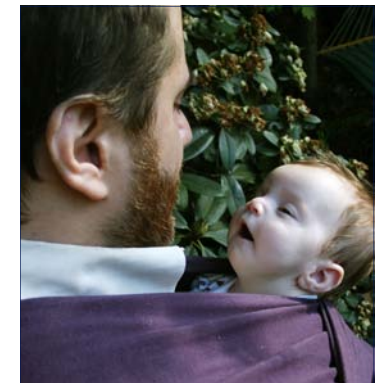
“ Her strengths are that she is good natured and patient and has started to show determination – at 2 years

#### Speech and communication

As usual with chromosome disorders, there is a range of ability among individuals and it is probable that children's speech and language develop in line with their ability to learn, although some children also have a hearing impairment to overcome. Vocalisation tends to develop late in babies and although sounds may progress to babble, the evidence suggests that in children with this deletion speech may not emerge. Instead, children will use alternative means of communication such as pointing with their eyes, gesturing, making vocal noises, using pictures and sometimes sign language (U).

“ All her noises are quiet and low pitched and we don't think she can hear herself – at 10 months

“ I believe that speech-language pathologists (therapists) should be involved from birth to maximise essential language and brain development — a parent.



At 2 months, in typical posture — pushing her head back to look at whoever is carrying her.

## Sitting, moving, walking: gross motor skills



Almost one year old.

At birth, most babies are unusually floppy (low muscle tone, hypotonia) and as they mature, they typically reach their developmental milestones after other babies. One baby in the *Unique* series was born with slightly contracted elbows, which improved over time. Babies in the *Unique* series first rolled over around the age of eight to nine months and achieved being able to stay in a sitting position from 10 months to 3 years, although they might still need support. Mobility was achieved around or soon after the second birthday and one child was walking by the age of four years. This means that babies should be offered physiotherapy (physical therapy) from early babyhood to give them the best chance of learning to move and walk independently (Nowaczyk 1997; U).

Typically, children with 4q21q22 deletions have small, short feet. Occasionally two toes will be webbed or will overlap each other. These features should not delay walking and overlapping toes may improve once a child is on their feet.

One parent's tips to promote gross motor development:

- Consider physical therapy (physiotherapy) from a young age
- A shallow baby bath placed in a normal bath helped leg development through splashing with her feet
- The Bumbo baby sitter helped develop better trunk strength. Your physical therapist (physiotherapist) can advise on seats for your baby

## Using their hands: fine motor skills

The evidence from *Unique* is that fine motor skills develop earlier than movements that involve the whole body and in some young children may be age appropriate, with young babies playing with small toys between six and 16 months and learning to finger feed, hold their bottle or cup and clap their hands in their first or second year. The age at which babies mastered holding an implement such as a spoon ranged from 18 months to three years and it could be a further few months before they were able to bring the spoon to their mouth (U).

Typically, the hands of a baby or child with a 4q21q22 deletion are small and the fingers are usually short (although long fingers are occasionally found). The fifth fingers sometimes curve slightly inwards, occasionally the fingers overlap and the fingernails can be sharply curved. These differences are cosmetic and should not affect the child's ability to use their hands.



## Medical concerns

### ■ Heart

A significant minority of babies with a 4q21q22 deletion are born with a structural heart anomaly. For this reason, all affected babies will have a thorough cardiac examination – even though, in most, no abnormalities will be found.

Five babies out of 15 have been found to have a heart anomaly, in each case involving a hole between the two sides of the heart. In three babies a significant hole was found between the two lower pumping chambers of the heart (ventricular septal defect, VSD) and in two of them there was also a hole between the two upper chambers (atrial septal defect, ASD) while one baby had a single large ASD. In one baby an opening between the two upper chambers known as the foramen ovale that is open during fetal life but closes around birth stayed open instead.

These types of heart anomaly are among the most common and may resolve spontaneously in time. If they do not resolve and lead to an abnormal blood flow through the heart that has an impact on the baby's quality of life, they can be surgically corrected, although this has not been necessary for any of the *Unique* children. One *Unique* baby had a large ASD successfully closed at the age of 18 months (Jacquemont 2006; Genesio 2005; Suwa 1998; Fagan 1989; U).

### ■ Brain

The brain in babies who have a scan has usually been structurally normal, although in two babies the band of nerve fibres that connects the hemispheres on each side of the brain (corpus callosum) was either missing or underdeveloped. In three babies there was a degree of retained fluid within the brain tissues (hydrocephalus) but not so severe that a shunt was required to drain it. One child in the *Unique* series had a delay in the natural maturation of the nerve fibres (delayed myelination) and in two children a degree of atrophy (wasting) was seen. A gene for Parkinson disease known as SNCA is found in the deleted 4q21q22 segment, but it is not yet certain whether this will add to the neurological symptoms (Jacquemont 2006; Genesio 2005; Harada 2002; Nowaczyk 1997; Abuelo 1988; U).

### ■ Seizures

A small minority of children are known to have developed seizures, one at birth, another at three months and the third at nine months. In one child the seizures became hard to control but otherwise the seizures were reasonably controlled with medication (Suwa 1998; U).

### ■ Lungs and breathing

Babies with silent, undiagnosed gastro oesophageal reflux may be at risk of inhaling some liquid from their feeds into their lungs and setting the scene for a chest infection to develop. This occurs quite commonly in children with chromosome disorders but has only been described in one child with a 4q21q22 deletion. Repeated attacks of pneumonia may be the first clue to the reflux and once the underlying cause is treated, they should cease (U).

### ■ Genitals

It has been suggested that boys with a 4q21q22 deletion may typically be born with a small penis or that the hole usually sited at the end is on the underside instead