Understanding chromosome disorders

Unique

4q deletions from 4q31 and beyond

rarechromo.org

Sources

The information in this leaflet is drawn partly from the published medical literature.

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 abstracts and articles from *Unique*.

The leaflet also draws on *Unique*'s database. When this leaflet was written, *Unique* had 54 active members with a 4q deletion.

Thirty-three families completed a detailed questionnaire in 2006. *Unique* is extremely grateful to the families who completed the questionnaire.

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.

Usually, when more chromosome material is lost, the effects are more obvious. All the same, there are some people with small 4q deletions who do have serious medical concerns and, less frequently, others with large deletions who are healthy and develop fairly normally.

Knowing an individual's chromosome make-up (the karyotype) is 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, 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 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 page 3). The part of the arm that is closest to the tip and furthest from the **centromere**, where the short and long arms meet, is called the **distal** area. People with deletions of chromosome 4q beyond 4q31 have what a geneticist would call a distal deletion. When the deletion is close to the centromere it is called **proximal**. When the chromosome has broken in two places and rejoined, leaving a segment out, the deletion is termed **interstitial**. When there is just one break in the chromosome, the deletion is called **terminal** but this does not of course mean that it is life-threatening.

In this leaflet, terminal deletions are referred to in this way: 4q31.3qter. This shows that the breakpoint is at 4q31.3. Interstitial deletions are referred to in this way: 4q32q34 deletion. This shows that the two breakpoints are at 4q32 and 4q34 and the segment between these breakpoints is missing.

Main features

The most likely effects of a distal 4q deletion are:

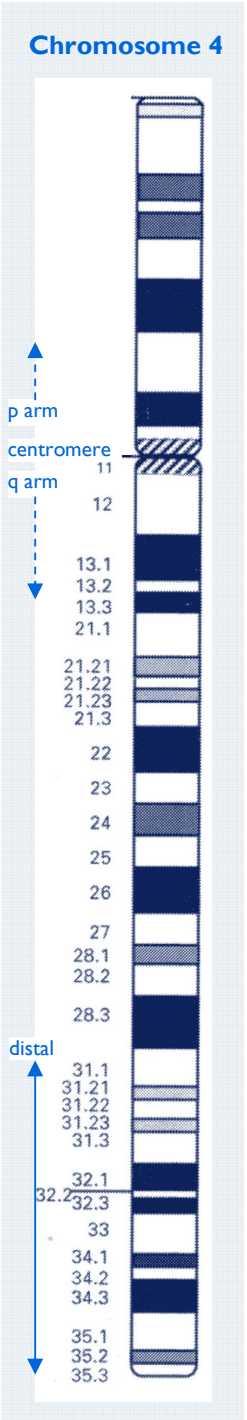
- A degree of developmental delay and difficulty with learning.
- A cleft in the palate (split in the roof of the mouth) and less commonly a cleft lip. This often occurs with a small, receding jaw as part of a condition known as the Robin or Pierre Robin sequence (see page 5).
- A structural heart anomaly. This may be slight and resolve naturally or more serious and require correction by surgery.
- Difficulties in co-ordinating the actions of feeding and swallowing.
- Unusual formation of the fingers and nails. The fifth finger is typically short, straight, pointed and has an odd nail. Other, more varied developmental defects of the hands are also common.
- Over- or underlapping toes.
- Characteristic facial features, particularly a short upturned nose and unusually formed or placed ears.
  (Lin 1988; Davis 1981; Mitchell 1981; Yu 1981; Townes 1979)

With a terminal deletion and breakpoint at **4q31** or **4q32**, other common features are:

- Birth weight normal or slightly low and slow growth after birth.
- Among boys, unusual genital features such as undescended testicles at birth and hypospadias (see page 12).
- Unusual facial features that may include a low bridge to the nose, wide set eyes and tiny skin folds across the inner corner of the eyes (epicanthic folds).

With a terminal deletion and breakpoint at **4q33** or **4q34**, the chance increases that any effects are mild. There are adults with a 4q34qter deletion who only discover their chromosome disorder when they pass it on to a child who is more obviously affected; others have difficulties more typical of a 4q deletion.

With a terminal deletion and breakpoint at **4q35**, there are children and adults with no known problems, others with minor behaviour difficulties and others with developmental delay and other difficulties more typical of a 4q deletion. (Mascarello 2003; Robertson 1998; Descartes 1996; de Michelena 1989; Fagan 1989; Lin 1988; Schinzel 1984; Tomkins 1982; Davis 1981; Mitchell 1981; Yu 1981; Townes 1979; U)



How important is the position of the breakpoint?

Molecular genetic technology can show the breakpoint in the chromosome more precisely than conventional chromosome analysis. In a child with a 4q deletion this can be helpful in revealing a very small amount of chromosome material missing from the region next to the tip of the chromosome, known as the subtelomeric region. This would be described as a 4q35 deletion.

Otherwise, this has not yet proved to be a very helpful test in 4q deletions because there appears to be no exact match between the specific material missing and features of the disorder. No 'critical region' for the typical features of the 4q deletion disorder has yet been identified (Robertson 1998).

How rare are distal 4q deletions?

They are almost certainly very rare, but an exact figure can't be given because of the possible numbers of people who are not affected by their chromosome loss and are never diagnosed.

Pregnancy

In most cases, pregnancy is uneventful and the baby is born around term with a normal or near-normal birth weight. A small number of babies do grow slowly in the womb but this is not typical and does not seem to be related to the position of the breakpoint (Aladhami 2000;).

How might a newborn baby be affected?

Typically, a new baby with a distal 4q deletion will be surprisingly unwell given their size and maturity. Many babies have great difficulty in feeding effectively at first and some have breathing difficulties. Babies with a heart defect are likely to be especially breathless and blue. All of these problems are less likely in a baby with a 4q34qter or 4q35qter deletion.

Appearance

Most babies with a distal 4q deletion look sweet and adorable and there may be little sign in their appearance 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 short, upturned nose with a low bridge; unusually shaped ears that may be set at an unusual angle or are lower on the head than expected; a slight upward slant of the eyes; and a thin upper lip. Babies with chromosome disorders (and some babies who don't have a disorder) quite often have a tiny skin fold at the inner corner of the eye known as an epicanthic fold and these appear to be more common in babies with a large 4q distal deletion than in babies with a small amount of material missing.

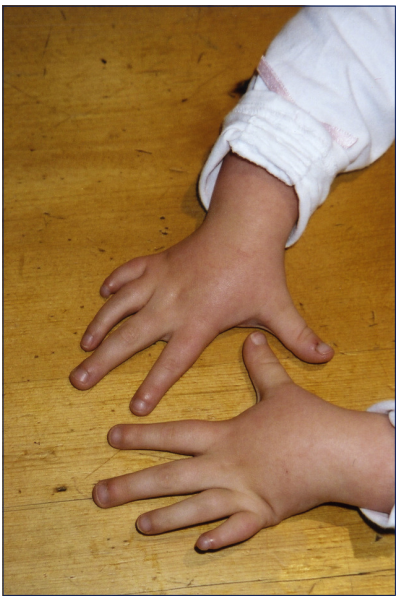
A highly typical feature of a 4q distal deletion is a small lower jaw that is often set back from the upper jaw. This is often part of a complex known as the Pierre Robin sequence (see page 5) (Keeling 2001; Aladhami 2000; Descartes 1996; Young 1982).

Pierre Robin sequence

As part of the Pierre Robin sequence, babies with a 4q distal deletion may well have a small lower jaw (known as micrognathia) that is set back from the upper jaw (known as retrognathia). This arrangement tends to displace the tongue backwards towards the throat where it can fall back and obstruct the airway (glossoptosis). Many babies will also have a cleft palate (a split in the roof of the mouth). 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 4q distal deletion, a cleft lip may also occur.

The Pierre Robin sequence is most likely to cause difficulties with breathing and feeding in babies. If your baby is affected in this way, the paediatrician and nurses will advise you how to minimise problems. Occasionally a surgical procedure may be needed to ease breathing. A cleft palate causes difficulties both in feeding and in speech production. Surgical repair of the palate eases these difficulties and may eliminate them altogether. In most children with Pierre Robin sequence, the jaw catches up in size by age 3 but in babies with a 4q distal deletion, catch-up growth does not always occur. One treatment option is surgery to bring the jaw forward, undertaken at a craniofacial centre. Dental development is usually affected by the small jaw and any cleft so that when teeth emerge, they may be small, crooked or missing. Occasionally children show additional features such as a very small or pointed tongue (Lin 1988; U).

Hands and fingers



Typically, people with a 4q distal deletion have small hands and apart from those with a 4q35qter deletion, the fifth finger of one or both hands has a characteristic form. It is short, with no creases at the joints, it does not bend and the nail is oddly formed, sometimes appearing on both the front and back of the finger. Other variants include a small, tapered fifth finger tip and small nail; a missing end joint; a clenched fifth finger; a pointed nail or a tiny extra nail. Even in those people who do not have the characteristic fifth finger, some other anomaly of the fingers, hand or arm is extremely common. This is particularly true when the breakpoint is between 4q31 and 4q33. Among the more serious anomalies that have been found in people with a distal 4q deletion are absence of the ulna (the inner, longer bone in the arm between the elbow and wrist), absence of the third, fourth and fifth fingers and the metacarpal bones in the hands that link these fingers to the wrist; and a split hand. Another serious problem that has been observed is a cleft between fingers four and five. Among people who are more mildly affected, examples

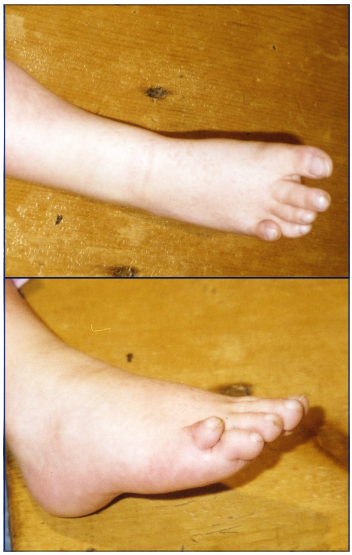
include an inability to fully straighten the arms at the elbow; missing nails and nail beds; and limited mobility of fingers three, four and five. Finally, both webbed skin between fingers two and three and incurving fifth fingers, characteristic of many chromosome disorders, have also been observed.

> “ His little fingers were stiff and looked as if they had been added after the rest of his hands had been made.

Duplicated fingers are not a feature of children with 4q distal deletions, but one child with an inverted duplication and distal deletion of 4q (material was missing from the end of the chromosome and a separate segment was duplicated) had a partially duplicated finger on the left hand.

When the anomaly is not severe and doesn't interfere with hand use, it can be left alone, but a finger that is present but non-functional may be removed (Keeling 2001; Aladhami 2000; Tsai 1999; Zackai 1999; Menko 1992; de Michelena 1989; Qumsiyeh 1994; Tomkins 1982; U).

Feet and toes



Typically, people with a distal 4q deletion have small feet, regardless of the breakpoint. Although there is no 'typical' toe formation, many have over- or underlapping toes, with the fourth toe most often underlapping the third or fifth toes. Some babies have a bridge of skin and tissue between two or more toes. The fifth toes may curve inwards and one baby had no bones in the fifth toes. The nails may be deeply curved, small or occasionally may be missing. In one child with an interstitial 4q31.1q31.3 deletion, the third toe on the right foot was missing and the head of the connected bone in the foot was underdeveloped; toes 1 and 2 were partly bridged by skin. So long as overlapping toes can be moved into a normal position, they can be treated either by splinting in soft plastic casing or by regular stretching. Once a baby is walking the toes will straighten to some extent (Keeling 2001; Robertson 1998; de Michelena 1989; U).

Growth

From a normal birth weight, babies with a distal 4q deletion tend to grow slowly. This is most pronounced in babies with a large deletion and can also occur in babies with a 4q34qter deletion but is less likely with a 4q35qter deletion. Three key measurements are taken during growth: weight, length or height and head circumference. In babies with a distal 4q deletion, the head circumference tends to be relatively larger than length or height and weight tends to be relatively the lowest measurement. There is little information available on eventual adult height but data from *Unique* show that there is a very broad range, with height in two adults with a 4q31qter deletion ranging between 4'9" (1.45m) and 5'10" (1.78m) (Aladhami 2000; de Michelena 1989; Davis 1981; U).

Feeding and eating

Many babies and young children need support at first with feeding. Initial feeding difficulties are almost universal in babies with a 4q31qter to 4q33qter deletion but also occur in babies with a 4q34qter or 4q35qter deletion and in babies with interstitial deletions.

In addition to the anatomical problems caused by the Pierre Robin sequence, particularly for those babies with a cleft palate, some babies have low muscle tone in the mouth and throat (oropharyngeal hypotonia) and have great difficulty in co-ordinating sucking, swallowing and breathing. Although these difficulties lessen with maturity and weaning from a purely liquid diet, there is a continuing risk of choking or 'floppy episodes' during feeds that mean that young children should be carefully supervised while feeding.

Gastro oesophageal reflux (where the stomach contents flush readily back up the food pipe) may also occur. Reflux can be eased by careful semi-upright positioning during and after feeds, raising the head end of the baby's cot and if necessary by prescribed medication that helps to keep the feed within the stomach. Babies who have continuing problems can have a surgical procedure called a fundoplication to improve the action of the valve at the junction of the foodpipe and stomach.

A high proportion of babies will need a period of feeding by nasogastric tube and it can be helpful to feed them direct into the stomach through a gastrostomy (PEG, button) (Fagan 1989; U).

> " She really enjoys her food now but as a baby had reflux with floppy episodes and would vomit after milk feeds. She used to go blue when feeding so I had to give her breaks. Once she was on solid foods and able to sit up she was much better – 4q31qter deletion, at 9 years.

> " Following long-term nasogastric tube feeding to the age of two, she was gastrostomy fed as her weight gain was poor and she was failing to thrive. She has started to eat now but still not 'normally' and the tube is still in place. It has been a long process teaching her to eat without gagging – 4q32q34 deletion, at 6 years.

> " She breastfed with no apparent difficulty for nine months. She did not want to wean and had no solid food until six months. When I tried to switch from breast to bottle at nine months, she had serious problems, could not suck on the bottle and began to get chest infections and pneumonias. She was found to be aspirating on all consistencies and was gastrostomy fed for 5 months. Now she is now eating and drinking normally but must drink a regulated amount using a straw or sippy cup – 4q34qter deletion, at 4 years.

Learning

Children with a 4q deletion are likely to need support with their learning and usually the larger the deletion, the more support they need. Youngsters with a 4q31qter or 4q32qter deletion typically need considerable support and this seems to be true of around half the youngsters with a 4q33qter deletion. However, there are exceptions and among *Unique* members there is a child with a 4q32qter deletion with no apparent

learning difficulties. With a 4q34qter deletion, some people have mild learning difficulties while others appear to have no difficulties at school. With a 4q35qter deletion, learning difficulties are less likely but may still occur both in children who inherit the incomplete chromosome 4 from one of their parents and in children where it has occurred for the first time in the family. There are fewer reports of children with interstitial deletions but the impression from the *Unique* series is that there is no direct link between the amount of chromosome material lost and the degree of learning difficulty. In particular, there are children with large interstitial deletions with one breakpoint at 4q32 who do not appear to have more than mild learning difficulties (Keeling 2001; Aladhami 2000; Fagan 1989; U).

4q31qter deletions

- He reads and writes; his long and short term memory fluctuate according to his oxygen levels and fatigue. Overall, he has the ability of an 8 year old and his strengths are his visual ability, a sense of humour, his courage, popularity, independence and gentle spirit. He has strong determination and a will to achieve – at 23 years.
- He cannot read, write or calculate but he has a good memory. Although he has no concept of time, he knows what sounds and voices go with which TV shows and when they come on – at 22 years.
- She has no interest in drawing and no imaginative play, instead using construction bricks to order and sequence. She cannot or will not write or read and has no concept of calculating but she does seem to remember things, people, activities and certainly places – at 9 years.
- Her memory is developing, with numbers and counting she is on track with her age group and is very determined – at 5 years.

4q32qter deletions

- He started to read and write when he was 5 and was calculating by 8. Although his ability with numbers is poor, he is obsessed with time keeping and has always had a great memory. His other great strength is his sense of direction – at 16 years.
- She started school with her normal year group and learned to read, calculate and write in her first year at school. She does not have a diagnosis of learning difficulty but we do believe she takes longer to pick things up – at 8 years.

4q33qter deletions

- She has a good memory and can count to 10 although she does not recognise number. Her strengths are her strong will, her determination, her amazing sense of humour, and her ability to tackle new situations even when they scare her – at 4 years.

4q34qter deletions

- He is excellent with numbers and counting and good at computers. Sometimes he struggles more with concepts than concrete ideas – at 12 years.
- He has trouble with writing, reading and calculating; his reading is not age appropriate but is improving. His difficulties are mild but he is determined to learn, asks many questions and is eager to know how things work – at 9 years.
- Her preliminary assessment found her to be in the low average range. She is

surprisingly keen on and good at nursery rhymes and singing in spite of her language difficulties. She can count from 1 to10; can sometimes identify three items and has a good grasp of abstract concepts she has experience of, such as dirty, clean, warm, dark, bright, happy, hungry, funny, sad, busy, fast and slow - at 3 years.

4q35qter deletions

❝ His writing is messy and he does find mathematics very hard – at 8 years.

Speech and communication

Generally, speech is affected in line with the level of learning difficulty and children with greater learning difficulties use less speech and simpler constructions. Understanding is also affected but children generally understand somewhat more complex speech than they can produce. Children with distal 4q deletions are generally communicative and even if they have no speech – which is quite unusual and only appears to affect children with the largest deletions - will generally use signing, gestures and vocal sounds to show what they want to say.

It has been suggested that in children with a distal 4q deletion, there is a specific problem with auditory processing, which means that they have difficulties processing and interpreting the sounds they hear. This is a complex problem that requires careful diagnosis to distinguish it from an underlying learning difficulty. In the view of the mother of an adult with a 4q31qter deletion diagnosed with a central auditory processing disorder, 'All children with this syndrome should receive testing for a severe language disorder; language function in these children often lags behind their cognitive ability. My son was using words from the age of nine months and today speaks in sentences. All the same, there is a huge difference between his understanding and his expression. He describes experiences in visual terms; for example, when his brother teases him, he describes this as *His candle gets brighter, but mine blows out.'*

Many children with a cleft or high-arched palate have repeated episodes of serous otitis media (glue ear) in early childhood and need repeated tube (grommet) insertion. Additional effects of a cleft or high palate include speech that can be nasal and hard to understand, accentuated in children with muscular weakness of the mouth and throat. All children with a distal 4q deletion should have access to regular, effective speech and language therapy. First words typically emerge between the ages of 2 and 3 years.

❝ She received speech and language therapy from 20 months onwards and thanks to this has made great progress. A year ago her speech showed delay but it is now age-appropriate and within the normal range. She spoke her first words from 22 months and now uses up to 8-word phrases. She has intelligibility problems but most people understand most of what she says. There was quite a pronounced difference between her receptive (stronger) and her expressive language skills but she has always had a very strong desire to communicate and now her expressive language is age-appropriate. Her receptive language, in particular her auditory processing, is probably less age-appropriate - 4q34qter deletion at 3 years.

❝ His expressive language is appropriate for his age and his receptive language is above his age range. He has delayed phonemic development and has only a limited repertoire of consonants and vowels as well as decreased strength, range of motion

and co-ordination of the oral musculature – 4q33q35 deletion at 2 years.

Sitting, moving, walking: gross motor skills

Delay in reaching developmental milestones can be an early sign of a chromosome disorder. In children with distal 4q deletions the picture is unusually varied. Typically, children have low muscle tone, lax joints, decreased strength, short arms and legs and delay in acquiring gross motor skills. All children described in the medical literature and known to *Unique* do walk, but many families describe their child's gait as like a toddler's and remark on the continued need for supervision on stairs. One *Unique* member with a 4q31qter deletion learned to sit alone at the age of 2, never crawled but scooted on his bottom instead, walked at the age of 6 and even as an adult has balance problems when climbing stairs. In contrast, some children, even those with large deletions, experience no or almost no floppiness as babies, sit, crawl and walk at the appropriate age and become very mobile children and adults.

- " She is especially good at sport – riding, tae kwan do, gym, anything linked with movement – 4q32qter deletion, at 8 years.
- " He still looks awkward when running and goes up and down stairs with two feet – 4q35qter deletion, at 8 years.

Using their hands: fine motor and co-ordination skills

Hand and eye co-ordination skills such as holding a bottle and playing with small toys may not develop in line with gross motor skills. A child who is late to walk may hold his bottle and pass toys between his hands at the expected age, while another child who walks on time may find it difficult to hold a spoon or pen. Overall, there appears to be fairly consistent delay in hand use and fine motor skills, regardless of the breakpoint.

Occupational therapy may help children to master and refine manual skills early, so that they can start school on a par with their classmates, able to hold a paintbrush, crayon and pencil, to feed themselves fairly neatly with a spoon, knife and fork and to manage the fastenings of their clothes for dressing and undressing. However, some delay should be expected and extra practice offered.

The role played by the typical 4q- hand anomalies in difficulties with manual skills has not yet been formally studied but it seems likely that any child with a 4q deletion will have particular difficulties and a limited range of grasp and grip positions.

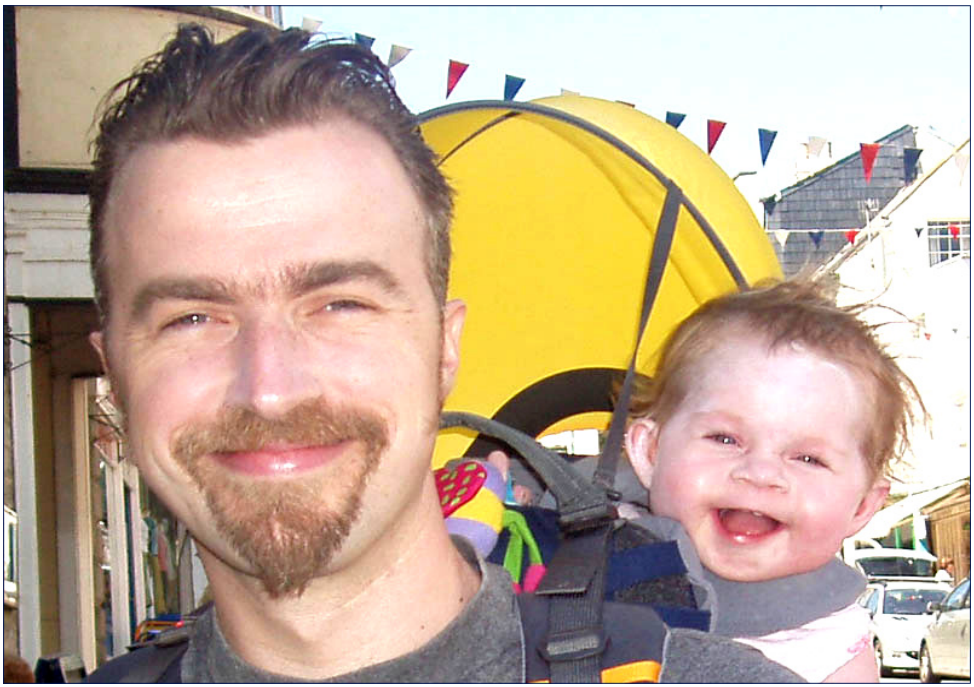
Medical concerns

Heart conditions

Heart conditions are found much more often in children with a distal 4q deletion than in children without a chromosome disorder. There is a very wide range, both in type and severity, and for this reason a child with a distal 4q deletion is likely to have a thorough cardiac examination.

If a heart condition is found, it may be treated with medication, it may be monitored to see if it improves naturally with time or it may need to be corrected with a surgical procedure. Sometimes more than one surgical operation is needed to correct the heart problem. *Unique* has members with a distal 4q deletion who are thriving very well after surgery for complex heart disorders.

No single heart condition is characteristic for distal 4q deletions. The range includes holes in the walls between the chambers of the heart (known as atrial septal defects or ASDs between the upper chambers and ventricular septal defects or VSDs between the lower chambers) or patent foramen ovale, where an opening between the upper chambers that normally closes after birth stays open; narrowing of blood vessels leading away from the heart (known as pulmonary stenosis when the pulmonary artery taking blood to the lungs is affected and coarctation of the aorta when the vessel taking blood round the body is affected); defective valves within the heart. Persistent ductus arteriosus has also been found, where a channel between the aorta and the pulmonary artery stays open instead of closing shortly after birth. One complex condition that has occurred is Fallot's tetralogy which involves both a hole between the two lower heart chambers (ventricular septal defect, VSD) and a narrow entrance to the vessel that takes blood to the lungs (pulmonary stenosis). Blood is diverted through the VSD to the aorta, reducing circulation to the lungs. Another complex disorder is known as atrioventricular canal and consists of a hole at the centre of the heart where the walls between the lower chambers meet the walls between the upper chambers. Both of these complex disorders can usually be improved by surgical correction. One child in the *Unique* series has hypertrophic cardiomyopathy (a thickening of the heart muscle that interferes with the heart's functioning); another has a complex condition including transposition of the great arteries, where the two main arteries are attached to the wrong pumping chambers (Keeling 2001; Schinzel 2001; Aladhami 2000; Tsai 1999; Grammatico 1997; Tupler 1992; de Michelena 1989; U).



***Unique* has members thriving after surgery for complex heart disorders.**

Lungs and breathing

Some babies and children with a distal 4q deletion experience obstruction of the upper airways. Unco-ordinated breathing plays a role in this and the tongue position caused by the Pierre Robin sequence is also a factor. In some children the upper airways, windpipe (trachea) and voicebox (larynx) are unusually formed and narrow or soft and liable to collapse (tracheomalacia, laryngomalacia), which adds to their difficulties.

Careful positioning for sleeping and slow, careful feeding should help and some children will have their tonsils removed. Oxygen may be needed, particularly at night, and surgical procedures may be needed to ensure an open airway. An aortopexy relieves external pressure on the soft trachea. A tracheostomy ensures an open airway (Stamberg 1982; Tomkins 1982; Mitchell 1981; U).

> " He had severe central and obstructive apnoea but did not present with the typical colour changes of a child deprived of oxygen. In my opinion, any child with this syndrome should be monitored on an ongoing basis for obstructive and central apnoea – 4q31qter deletion.

Babies who have gastro oesophageal reflux are also at risk of inhaling part of their feeds and setting the scene for pneumonia. As reflux may be 'silent', with no signs, monitoring will be necessary to show whether this is occurring (U).

Chest infections such as bronchiolitis are more common than in children without a chromosome disorder and tend to be more serious when they do occur. The recurrent breathing problems mean that many children are diagnosed with asthma, relieved by inhaled bronchodilator and anti-inflammatory medication.

> " She had both tracheomalacia and laryngomalacia and had episodes of pneumonia as well as very pronounced stridor. She has now had laser treatment on her larynx and an aortopexy to relieve the trachea and is in generally good health – 4q34qter deletion.

Calcium metabolism

Levels of calcium in the blood may be monitored because it is known that some children with a distal 4q deletion have very high circulating calcium levels and one or two have developed kidney stones as a consequence (Imamura 1998; Strehle 1998).

Minor genital anomalies in boys

It is relatively common for boys with chromosome disorders to have minor genital anomalies at birth. If necessary, these are usually easily correctable and then have no long-term consequences. Among the anomalies seen in boys with a distal 4q deletion are hypospadias, where the hole usually at the end of the penis is on the underside instead and undescended testicles (cryptorchidism) where the testes have not completed their descent from the abdomen into the scrotum before birth. Hypospadias can be corrected with a surgical operation and if the testicles do not descend naturally they can be brought down and anchored into position.

Seizures

There have been occasional reports in the medical literature and among *Unique* members of children having seizures but they have affected a minority of children and have usually been well controlled with medication (Sarda 1992; U).

Hearing

The typical shape of the roof of the mouth of a child with a distal 4q deletion makes it quite likely that they will develop the temporary form of hearing loss known as glue ear (serous otitis media). This can be relieved by inserting tiny tubes into the eardrums to let air into the middle ear. An additional problem for some children with a distal 4q deletion appears to be a central auditory processing disorder (see page 9).

Eyesight

Children with chromosome disorders are more likely to have eyesight concerns than other children but there is no specific vision problem that is typical of a 4q deletion disorder. Among *Unique*'s members are children who are very short-sighted, others who are very long-sighted, others with drooping upper eyelids (ptosis), and others who have no sight problems. In some children the optic nerve has an anomalous shape but this has not impacted on vision. One child has a coloboma (developmental defect) of the iris that does not affect vision. Disorders affecting the eyes that have been described in the medical literature include very small eyes (microphthalmia) and underdevelopment of the iris (the coloured part of the eye) (Jefferson 1986; Yang 1979; Kempen 1975; U).

Other concerns

A broad range of other features have been noted in other children and adults with a distal 4q deletion. These may be caused by their unusual chromosomes or be unconnected with them. They include kidney anomalies; a fontanelle (soft spot) that is late to close; absent thyroid gland; abnormal gallbladder; unusual position or double anus (U).

Behaviour

Many youngsters with a distal 4q deletion are described as open, pleasant, communicative and sociable. They can be kind and solicitous of other people's wellbeing. The challenges they face in their everyday lives may affect their behaviour, but there does not appear to be any behaviour pattern that is typical. In general, their behaviour reflects their learning ability and their ability to communicate with speech. At particularly difficult stages such as puberty, families may find behaviour management helpful. In *Unique*'s experience, medication has rarely proved necessary but can be helpful.

Some children show high levels of activity, a low attention span and some autistic behaviours, all fairly common in children with chromosome disorders who have learning challenges. This has led some researchers to speculate on the presence of genes for autism on 4q, but this suggestion needs further research. Families have seen marked behaviour improvements on prescribed medication, such as methylphenidate (Ramanathan 2004; U).

Adults without any medical or developmental problems due to their distal 4q deletion may still have behaviour difficulties. A *Unique* survey of parents with a 4q34qter or 4q35qter deletion diagnosed following the diagnosis in one of their children showed hard-to-handle behaviour and a particularly quick temper in 2/4 adults. In one case,

challenging behaviour in childhood was followed by violent behaviour in adulthood. In the other case, the father had a short temper and difficulty in dealing with authority.

> " I try to avoid confrontations and arguments as I can quite easily lose control and go into a rage. I've always been the same and have often wondered if my deletion is linked with my temper.

Similar problems with anger control are evident in some children with small deletions from near the end of the chromosome (U).

> " She is very loving and lovable – likes kisses, cuddles and attention. She only has tantrums if thwarted or when she is tired or hungry. Her behaviour can be quite challenging – she is strong-willed and not afraid to express her displeasure! But she is amenable to reason, she understands rules and can eventually be distracted. She does seem to need more attention, management, consistency and firmness than her sisters did but her life experiences have been different too – 4q34qter deletion.

> " She gets very frustrated when she cannot keep up with others and can be aggressive, especially to her younger brothers. She needs lots of 1:1 support and is difficult when she is tired or run down or if her routine changes – 4q32q34 deletion, at 8 years.

> " His lack of language has hindered his socialisation. He has had outbursts of kicking out but this has improved. Although he is a very strong-willed child, he is also very placid and happy-go-lucky – 4q32q33 deletion, at 6 years.

Mental health

Adults with learning difficulties are vulnerable to mental health problems but no study of adults with 4q deletions has been carried out. One study of people with mild learning difficulties and a diagnosis of a major mood disorder or schizophrenia did identify an adult with a very small 4q35.2qter deletion (Pickard 2004).

Independence

There are certainly adults with distal 4q deletions who lead independent lives, hold down good jobs and marry and have children. The chromosome diagnosis on its own cannot predict this but once a child's individual pace of development becomes clearer, it is easier to suggest forecasts.

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 parents have normal chromosomes but the child does not. It is then called a *de novo* rearrangement. A 4q deletion can also be inherited direct from either the mother or the father. The only way to know if the chromosome rearrangement is *de novo* or not is for the parents' chromosomes to be checked.

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. If the check reveals the same rearrangement as in the child, the parent may be entirely healthy and have no developmental problems or they may have signs that suggest a subtle effect.

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. In families where one parent has the same 4q deletion as the child, the risk of passing it on can be as high as 50 per cent.

How did it 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).

Parents with distal 4q deletions

Parents with a 4q34qter or 4q35qter deletion and various interstitial deletions including 4q33q35.1, 4q32q33 and 4q33q33 have passed their deletion on to one or more of their children.

Unique's 2006 survey of parents with the same 4q deletion as their child showed that most of the parents had no learning difficulties and they had not needed any extra help with academic work. Challenging behaviour was found in 2/4 adults, a high threshold for pain and a degree of clumsiness in one adult and flexible joints, a small cleft in the palate and copious dribbling in another. A study of five families with a 4q35qter deletion where the child was mildly affected showed that all parents were unaffected. Other studies have shown mild effects in parents (Mascarello 2003; Aladhami 2000; Gould 1999; Descartes 1996; Curtis 1989; U).

Support and Information

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Join Unique for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

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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