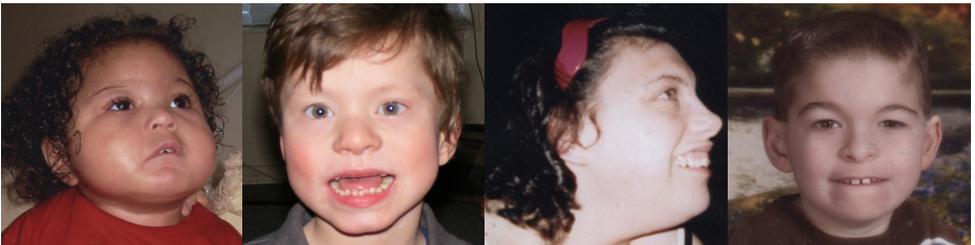




Understanding Chromosome & Gene Disorders

# 1q4 deletions: from 1q42 and beyond



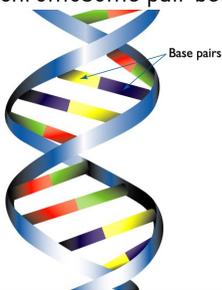
[rarechromo.org](http://rarechromo.org)

## 1q deletions: 1q42 and beyond

A 1q4 deletion means that the cells of the body have a small but variable amount of genetic material missing from one of their 46 chromosomes – chromosome 1. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having parts of chromosome 1 missing may increase the risk of birth defects, developmental delay and learning difficulties. However, the problems vary and depend very much on what and how much genetic material is missing.

## Background on Chromosomes

Chromosomes are structures found in the nucleus of the body's cells. Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one half of each chromosome pair being inherited from each parent.



Each cell usually contains a total of 46 chromosomes made up of 23 pairs. Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest (chromosome 1 is the largest chromosome). Each chromosome has a short or petit (p) arm (shown at the top in the diagram on page 3) and a long (q) arm (the bottom part of the chromosome).

1 base pair = 1bp  
1,000 base pairs = 1kb  
1,000,000 base pairs = 1Mb

Chromosome 1 is the largest chromosome and represents about eight per cent of the total DNA in cells. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.

## Chromosome Deletions

A sperm cell from the father and an egg cell from the mother each carries just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently than usual. People with a 1q4 deletion have one intact chromosome 1, but a piece from the long arm of the other copy is missing or deleted. Although the exact numbers and types of genes that are affected by the deletion is often not known, since some genes are missing there can be effects on a person's learning and physical development. Therefore it is believed that most of the clinical difficulties are probably caused by having only one copy (instead of the usual two) of a number of genes. We are still learning the about the specific jobs or functions of the genes in these regions. Also, it is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

The first published description of a person with a 1q4 deletion was in 1976. There have since been over 50 cases reported in the medical literature worldwide. The deletion occurs in equal frequency in males and females.

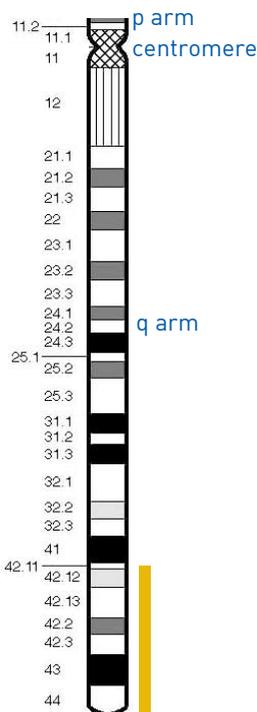
A 1q4 deletion is sometimes called a terminal (the tip of the long arm of chromosome 1 is included in the deletion) 1q deletion or 1qter deletion or, if it can't be seen down a microscope, 1qter microdeletion (Mankinen 1976; Hiraki 2008).

## Looking at 1q

Chromosomes can't be seen with the naked eye but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands that look like horizontal stripes under the microscope. By looking at your child's chromosomes in this way, it is possible to see the point (or points) where the chromosome has broken and to see what material is missing, if the missing piece is large enough. However, because the amount of material missing is often quite small, in this type of routine analysis your child's chromosomes may have looked normal. Consequently there are certainly people with a 1q4 deletion who have not yet been diagnosed. New, more sensitive, molecular techniques such as fluorescent *in situ* hybridisation (FISH) testing or array comparative genomic hybridisation (array-CGH) may be necessary to confirm or detect 1q4 deletions or microdeletions.

The vast majority of 1q4 deletions are terminal. However, some deletions are interstitial. This is where a piece of the long arm of chromosome 1 is missing, but the end of the chromosome is still present. In the diagram of chromosome 1 on the right the bands are numbered outwards starting from where the short and long arms meet (the centromere). A low number, as in q11 in the long arm, is close to the centromere. Regions closer to the centromere are called proximal. A higher number, as in q43, is closer to the end of the chromosome. Regions closer to the end of the chromosome are called distal.

The region 1q4 includes all of those bands in the long arm that begin with 'q4' and therefore include the bands q41, q42.11, q42.12, q42.13, q42.2, q42.3, q43 and q44. This leaflet is specific for bands from q42 to the tips of the chromosomes and does not include breakpoints within band q41 or closer to the centromere.



## 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 (<http://www.ncbi.nlm.nih.gov/pubmed/>). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from two surveys of members of Unique conducted in 2004 and 2008, referenced Unique. When this leaflet was written Unique had 47 members with a pure 1q4 deletion without loss or gain of material from any other chromosome. These members range in age from a small baby to an adult aged 31 years.

Many more people, described in the medical literature and 16 members of Unique, have a loss or gain of material from another chromosome arm as well as a 1q4 deletion, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a 'pure' deletion, they are not considered in this leaflet. Unique holds a list of these cases in the medical literature and the karyotypes of those in Unique; this is available on request.

## Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point(s) where the chromosome has broken in your child. You will almost certainly be given a karyotype which is shorthand notation for their chromosome make-up. With a 1q4 deletion, the results are likely to read something like the following example:

### 46,XX,del(1)(q43)

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(1)	The deletion is from chromosome 1
(q43)	The chromosome has one breakpoint in band 1q43, and material from this position to the end of the chromosome is missing

### 46,XX,del(1)(q42.13q44)dn

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(1)	The deletion is from chromosome 1
(q42.13q44)	The chromosome has two breakpoints, one in band 1q42.13 and one in band 1q44, and material between these two breakpoints is missing
dn	The deletion occurred <i>de novo</i> (as a 'new event'). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 1q44. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

In addition to, or instead of a karyotype you may be given the results of molecular analysis such as FISH or array-CGH for your child. In this case the results are likely to read something like the following example:

### 46,XY.ish del(1)(q44)(D1S3738-)

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes, XY for males; XX for females
.ish	The analysis was by FISH (fluorescent <i>in situ</i> hybridisation)
del	A deletion, or material is missing
(1)	The deletion is from chromosome 1
(q44)	The chromosome has one breakpoint in band 1q44, and material from this position to the end of the chromosome is missing
(D1S3738-)	The deleted part of chromosome 1 includes a marker called D1S3738

### arr[hg19] 1q43q44 (237,433,883-249,212,668) x1

arr	The analysis was by array-CGH
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted
1q43q44 237,433,883-249,212,668	Chromosome 1 has two breakpoints, one in band 1q43, and one in band 1q44. The base pairs between 237,433,883 and 249,212,668 have been shown to be deleted. Take the first long number from the second and you get 11,778,785 (11.8 Mb or 11,800 kb). This is the number of base pairs that are deleted means there is one copy of these base pairs, not two – one on each chromosome 1 – as you would normally expect.

## Most common features

Every person with a 1q4 deletion is unique and so each person will have different medical and developmental concerns. Additionally, no one person will have all of the features listed in this leaflet. However, a number of common features have emerged:

- Hypotonia (floppiness or unusually low muscle tone) in newborn babies
- Seizures, commonly starting in the first three years of life
- Children will need support with learning, the amount of support needed by each child will vary
- Feeding difficulties
- Short stature or small size
- Heart conditions, though the majority of reported cases are minor and often resolved naturally without surgical intervention
- Microcephaly (an unusually small head). However, the baby's head may appear to be in proportion to the rest of the body
- Structural anomalies of the brain, most commonly the underdevelopment of the nervous tissue that connects the two hemispheres of the brain (corpus callosum)

## Does the breakpoint matter?

In some ways it does. It is true that babies who lose a large segment of the chromosome have a generally harder time. Yet children with deletions in band 1q43/44 that are so tiny that they cannot be seen under a microscope (a submicroscopic deletion or microdeletion) can be affected in the same way as children with large deletions, albeit often less severely. This suggests that the gene-rich tip of the chromosome, missing in all individuals with terminal deletions, is responsible for many of the effects of a 1q4 deletion (see [Ongoing research into 1q4 deletions](#) page 20) (de Vries 2001; Gentile 2003; Van Bon 2008; Unique).

## Breakpoints in Unique families

Bracketed numbers show numbers of families on the Unique database (2008). In addition, members of Unique have a 1q4 deletion as well as a duplication of another chromosome. The other chromosomes involved are: 3, 8, 9, 12, 13, 14 and 16.

These breakpoints are recorded for members of Unique with a 'pure' terminal 1q4 deletion:

1q42 - qter [2]  
1q42.12 - qter [1]  
1q42.3 - qter [2]  
1q43 - qter [15]  
1q44 - qter [12]

These are the breakpoints recorded for members of Unique with interstitial 1q4 deletions:

1q42q44 [1]  
1q42.1q42.3 [2]  
1q42.1q44 [1]  
1q42.11q42.3 [1]  
1q42.13q42.3 [1]  
1q42.13q44 [1]  
1q42.3q43 [1]  
1q43q44 [2]

# Are there people with a 1q4 deletion who are healthy, have no major medical problems or birth defects and have developed normally?

In a few people with very small deletions, the 1q4 deletion appears to have a more mild effect. A 40-year-old mother of two boys was unaware that she had an interstitial deletion of 1q42 until the deletion was detected in both of her sons. She had an absent corpus callosum and was of small stature but was otherwise physically unaffected by the deletion and had none of the characteristic facial features. She was less academically successful than her parents and brothers, leaving school at 16 years and subsequently being employed as a childcare assistant and a hospital care worker (Puthuran 2005).

A 7-year-old girl with an interstitial deletion of 1q44 had learning difficulties but walked at 12 months and developed normal speech. She had microcephaly but otherwise had no health problems. Her mother also had the same deletion and was healthy with no learning difficulties (van Bon 2008).

## What is the outlook?

At present it is difficult to predict the long-term outlook for children with 1q4 deletions because in many cases this chromosome disorder has only fairly recently been diagnosed with certainty and very few adults (both in the literature and at Unique) have been described. Nonetheless, it is fair to say that most children will need lifelong care and specialist medical support and will only achieve limited independence. However, many research reports describing 1q4 deletions focus on children with very large deletions who generally have a harder time. The Unique experience is of a larger number of children with deletions nearer the end of the chromosome, at bands 1q43 and 1q44, whose outlook appears better (see [Breakpoints in Unique families](#) page 5) (Unique).

*“ She may sound like she has lots of health problems but she lives life to the full and brings so much happiness, joy and love to everyone that meets her. ” – 3 years*

## Growing up with a 1q4 deletion



As a baby



3½ years



10 years

*“ During some hospital admissions, we saw that blood test results noted a Pelger-Huet anomaly. On researching what this meant, we found a link to 1q42.12 deletions whereas our daughter’s deletion was 1q42.13q42.3. We requested a retest and were given a new diagnosis of a 1q41q42.2 deletion. ”*

Many years ago, the standard technology used to identify chromosome deletions, called karyotyping, involved looking at the banding patterns of stained chromosomes under a microscope. This technique is less accurate than the molecular tests that are now more commonly offered to families. This family received important and new details of their child’s deletion following an array test, which helped to explain a specific health concern. If your child’s deletion was identified by a chromosome staining technique, you may wish to contact your genetics department and request a more detailed and accurate test.

## Pregnancy

Many mothers carrying babies with 1q4 deletions experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, pregnancy complications are not uncommon in mothers carrying a baby with a 1q4 deletion. Of the 17 families who have told us about their pregnancy experiences, ten babies were small for gestational age or were described as having intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed resulting in babies that are smaller than expected for the number of weeks of pregnancy. Concern about IUGR for two babies resulted in induction of labour between 36 and 38 weeks. A number of parents also had unusual findings when undergoing ultrasound scans: a kidney anomaly was detected in one baby; enlarged cerebral ventricles (regions within the brain) were seen in another baby and one baby was shown to have a clubfoot (Unique).

Only one family known to Unique discovered the 1q4 deletion before their baby was born. However, there is also one example in the medical literature of prenatal diagnosis of 1q4 deletions by amniocentesis performed after an increased nuchal thickness and other anomalies were detected during an ultrasound scan. Conversely, fetal blood samplings, performed after fetal anomalies were seen on ultrasound scans, failed to detect a 1q4 deletion in three babies (all of whom had submicroscopic deletions of 1q4) (Rotmensch 1991; de Vries 2001; Roberts 2004; Hill 2007; Unique).

## Growth and feeding

Babies tend to be small and underweight at birth. Reports in the medical literature have suggested that babies with larger deletions have a lower birth weight, ranging from an average of 2.5 kilos (5lb 8oz) for babies with a 1q42 deletion to 2.9 kilos (6lb 6oz) for those with a 1q43 deletion. However, evidence at Unique does not appear to support this. Regardless of the breakpoint, birth weights recorded at Unique show a considerable variation with an average of 2.64 kilos (5lb 13oz). Around half of the Unique babies were at the low end of the normal range, although the other half had a low birth weight (below 2.6 kilos or 5 lb 12oz) at term (Schinzel 2001; Unique).



5½ years

**Range of birthweights at Unique (at or near term):**  
1.559 kilos (3lb 7oz) to 3.798 kilos (8lb 6oz)

Feeding difficulties are a major area of concern for families, particularly as babies usually start out small and underweight. The hypotonia that is common in babies with a 1q4 deletion can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft or high palate can also find the action of sucking and swallowing difficult. Seven of the 12 mothers surveyed by Unique attempted to breastfeed their babies, although only one established successful breastfeeding. However, a number of babies were bottle-fed expressed milk. Three of the 16 babies surveyed benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat). As these babies matured enough to suck effectively, the NG-tube could be removed and breast or bottle feeding established. A further three babies who initially benefited from

temporary NG-tubes later needed gastrostomy tubes (a G-tube, feeding direct into the stomach) in order to meet their nutritional needs (van Bon 2008; Unique).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). In the Unique survey, over 70 per cent of babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Unique).

Constipation is common among children with chromosome disorders and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake. A number of babies and children with a 1q4 deletion suffered from constipation. It is important that parents discuss the possible causes with their health visitor or doctor, who may recommend adapting a child's diet or giving stool softeners such as Movicol, or laxatives such as Lactulose and Senna.

Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of finger feeding may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems. Children often continue to be slow, fussy eaters although some children develop large appetites and a love of food (Unique).

*“ At 6½ years she still only eats blended food. She identifies lumps of food in her mouth immediately and spits out the food. She doesn't know how to chew. ”*

*“ She is a slow and fussy eater. She is sensitive to the temperature, texture, amount and timing of food. ” – 12 years*

## Appearance

Children with 1q4 deletions sometimes have facial features in common. Typically, babies have a small head (microcephaly) with a prominent forehead and sometimes a ridge down the centre where the skull plates have fused. They may have a round face with full cheeks and unusually-formed, low set ears. They have a flat bridge to the nose, which is short and broad. They may have deep set eyes or widely spaced eyes (hypertelorism) or there may be an extra fold of skin covering the corner of the eye (epicanthic folds). They often have a thin bow shaped upper lip with a small, receding lower jaw (micrognathia). A short neck is also common. However, many children look little different compared to other children and may closely resemble their siblings or parents (Unique).

Many of the facial features are present in all those with a 1q4 deletion regardless of whether the deletion is large or small. On the other hand, certain features such as a low set ears, micrognathia, hypertelorism and epicanthic folds are not frequently seen in those with small submicroscopic deletions (van Bon 2008).

The characteristic facial appearance may change over the years. The round face and flat nasal bridge seem to disappear over time and are not apparent in adulthood.

Microcephaly is often the only remaining characteristic facial feature (Gentile 2003; van Bon 2008; Unique).

*“ She has a small head and widespread nose and a prominent forehead. She is still a pretty little girl. ” – 3½ years*

## Learning

Learning difficulties and intellectual disabilities are common in children with a 1q4 deletion with most children severely affected and a small minority profoundly affected. As always, there is individual variation, and a few children with small deletions have moderate or even mild learning difficulties. However, most children will need considerable support and benefit from early intervention programmes and may thrive best in a special learning environment. Indeed the vast majority of Unique children attend a special education school, although a small number attend mainstream school, often receiving 1:1 help in the classroom or benefiting from an attached special needs unit (Unique).



12½ years

Children are typically good-natured and determined, qualities that serve them well in maximising their abilities, so that some children learn to draw simply and write their own name and other simple words. A few children learn to recognise their name and a small minority master reading. The hypotonia (low muscle tone) that affects many children, can make writing or drawing difficult and some children find using a keyboard to write easier than a pencil or pen. Children generally struggle with abstract and mathematical concepts but some have a good memory. A number of children are described as being easily distractible or having a short attention span which can make learning more of a challenge. Many parents note that the most successful methods for learning involve learning through play, making

learning fun and lots of repetition. Children with 1q4 deletions seem to share a love of music and singing (Baker 2002; Daniel 2003; Unique).

*“ She can paint and scribble on her own. ” – 3 years*

*“ He is in a mainstream class at school and receives teacher aide assistance. He is behind his peers in most classroom/outdoor physical activities but he tries hard and we’re more than happy with his progress. He loves to read! ” – 9 years*

*“ Her memory appears to be quite good for things she likes. She can recognise her own name and some short words. She loves music and learns through repetition. ” – 11 years*

*“ She appears to remember places and people she knows well. ” – 25 years*

## Speech and communication

Speech appears to be a problematic developmental area in children with a 1q4 deletion and speech skills are likely to be significantly delayed or absent. A few children learn to use words and even short sentences, but this is not possible for all. Some Unique children master sign language, but most children communicate their needs by eye contact, pushing and pulling, gestures and vocal noises. In many children receptive language seems to be better than expressive language skills - many children understand far more than they are able to express. This is shown by their ability to understand words and follow instructions and respond when told to do tasks (Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which in addition to insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with certain sounds (Unique).

“ She is very vocal and can sign a few requests. ” – 3 years

“ She can say her name and ‘mama’ but doesn’t say them unless prompted. ” – 3½ years

“ He makes various sounds and can say five words clearly and in context most of the time. ” – 5 years

“ She uses two signs very consciously (‘finish’ and ‘drink’). She will reach for things and push food/drink away when she does not want any more. She has about 20-30 words that she can repeat and has a few words she uses actively and (often) relevantly. ” – 6½ years

“ His biggest difficulty is now his speech delay – he can talk but has difficulty with forming some sounds. Others find him difficult to decipher but those who are close to him are fairly ‘tuned in’. He can put 5-6 words together now but sentence structure is not appropriate – eg he will ask, ‘Where is you?’ ” – 9 years

“ He is non-verbal but uses signs, gestures, vocal noises and a computerised output device to communicate. ” – 10 years

“ She uses gestures and has approximately 20 signs and some speech. ” – 11 years

“ She has four Makaton signs. ” – 25 years

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

The hypotonia that affects between 80 and 90 per cent of those with a 1q4 deletion means that it may take a little longer for them to roll over, sit, crawl and walk and reach other developmental milestones. The Unique experience is that babies start to roll between 2 months and 3 years (average 14 months); sit between 8 months and 4½ years (average 22 months) and crawl between 12 months and 4 years (average 28 months). Some children, however, do not crawl but instead move

around by bottom shuffling. Many children need support (such as a standing frame, walking frame and/or leg braces) while learning to walk. A number master independent walking, although this is not possible for all. Those Unique children who learned to walk independently did so between 18 months and 7 years (average 34 months). Children often walk slowly and some will continue to need a wheelchair for long distances (Unique).

The hypotonia often improves as children mature; however, early physiotherapy and occupational therapy benefit most children. Other activities such as swimming and hydrotherapy have helped some children. Physical activities enjoyed by the more physically able Unique children include swimming, horse-riding, playing football, trampolining and dancing (Unique).



6 years



6 years

“ She can sit up on her own for one minute and she can get into the crawling position. She stands in a standing frame for up to one hour. ” – 3 years

“ She can sit and roll around the floor but can't crawl or walk at present. ” – 3 years

“ She has just started to crawl at 3½ years. She used to be extremely floppy but much improved now. ” – 3½ years

“ She crawls around quite fast and can climb onto low objects (eg a low sofa but not up on a dining chair). She also cannot climb stairs. She walks with the support of one hand but is not able to get up or down

by herself. Her favourite activity is swimming. ” – 6½ years

“ He has an unsteady walking gait (because of his feet abnormalities) and prefers to sit on the floor in a 'W' formation rather than in a chair. ” – 9 years

“ He walks and he also has a sort of shuffling 'run'. He can use stairs holding onto a rail. ” – 10 years

“ She bottom shuffles most of the time. She has a walker which she is strapped into and she gets around very well. ” – 11 years

“ She is not mobile without a K walker. She has never crawled or walked alone. ” – 25 years

## Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Hypotonia can also affect fine motor skills in children with a 1q4 deletion and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch screen computer can often be easier. Many children have occupational therapy in order to help improve these skills but difficulties with fine motor skills often persist (Unique).

As a result of these difficulties, children are likely to continue to need help with dressing and undressing. They will also require assistance in tasks such as brushing teeth and washing. Toilet training is also likely to be affected. The information at Unique shows that consistent toilet training has been achieved by only four children and was mastered between 2½ years and 8½ years. Some other children have acquired bowel but not bladder control (Unique).

“ She grasps things with an open hand – she has no real pincer action yet. ” – 3 years

“ He began using his hands at 13 months and now at 5 years old he plays with toys.

“ He still has difficulty with doing buttons/unscrewing lids etc. He was out of nappies at about 4. Still occasionally wets the bed at night. ” – 9 years



2½ years

“ He was very late holding his bottle and most other fine motor activities. He can use a spoon and fork somewhat but prefers to use his hands. ” – 10 years

“ Her fine motor skills are better than her gross motor skills. She is quite clumsy. ” – 11 years

“ She has no co-ordination. ” – 11 years

“ She has good fine motor skills. ” – 14 years

“ She was not able to hold a bottle until 2 years. She wears nappies 24/7 and has no self-help skills except holding a cup with a spout to drink. ” – 25 years

## Medical concerns

### ■ Seizures

Seizures have been reported in 35/41 (85 per cent) people with a 1q4 deletion in the published medical literature, and similarly in over 80 per cent of Unique families. Typically seizures developed between the ages of six months and three years, although two Unique newborn babies experienced a seizure immediately after birth. Seizures occurred irrespective of the breakpoint. In five children first seizures were associated with a childhood infection or fever. One child had a single febrile convulsion at age 3 and has since remained seizure-free (Vaughn 1996; Gentile 2003).

In most children seizures were reasonably well controlled with antiepileptic medication but in five children (out of 28) the seizures were not fully controlled. One adult of 20 became seizure-free after the age of 17 (Halal 1990; Murayama 1991; Unique).

### ■ Heart problems

Heart (cardiac) conditions have been described less often in the medical literature than among Unique families. Out of 37 children, a heart condition was mentioned in 18 (49 per cent) in the literature, whereas 86 per cent of Unique families reported a heart condition (Hiraki 2008; Unique).

The most common conditions seen in Unique children were holes between the upper or lower chambers of the heart (ventricular septal defects (VSD) or atrial septal defects (ASD)) which were present at birth. In many children these defects heal (close) naturally without surgery. Persistence of prenatal cardiac structures such as persistent ductus arteriosus (PDA) has also been reported, which again often resolves without the need for surgical intervention. Two Unique children had pulmonary stenosis (a narrowing of the blood vessel leading from the heart) or sub-aortic stenosis (a narrowing of the area below the aortic valve (the valve that allows blood into another blood vessel leading from the heart)). In both pulmonary and sub-aortic stenosis the heart has to work harder to pump blood. Two further Unique children had Fallot's tetralogy, a complex heart condition (involving both a VSD and pulmonary stenosis) that required surgical correction (Unique).

Heart conditions occur irrespective of breakpoints, affecting those with breakpoints in 1q42, 1q43 and 1q44 as well as those with interstitial deletions (Hiraki 2008; Unique).

## ■ Brain

Central nervous system (CNS) anomalies have been reported in almost 90 per cent of those with a 1q4 deletion. The most common problem is agenesis of the corpus callosum (ACC). The corpus callosum is the largest connective pathway in the brain. It is made up of more than 200 million nerve fibres that connect the left and right sides (hemispheres) of the brain. ACC is a birth defect in which the corpus callosum is partially or completely absent, resulting in poorly connected or disconnected brain hemispheres. Each hemisphere of the brain is specialised to control movement and feeling in the opposite half of the body, and each hemisphere specialises in processing certain types of information (such as language or spatial patterns). Thus, to co-ordinate movement or to think about complex information, the hemispheres must communicate with each other. The corpus callosum is the main, although not the only, connector that allows that communication (Gentile 2003; Puthuran 2005; Hiraki 2008).

Almost 70 per cent of Unique children were diagnosed with a corpus callosum abnormality. Diagnosis is made by viewing the brain, usually by a magnetic resonance image (MRI) scan or a computerised axial tomography (CT or CAT) scan or, much less frequently, by a prenatal ultrasound scan. Research into the impact of ACC is in the early stages, and those with ACC show individual differences. However, research indicates that ACC can be associated with microcephaly, delays in reaching developmental milestones (such as sitting, walking), feeding problems, low muscle tone, speech and language delays and behavioural issues. ACC has been reported in those with breakpoints in 1q42, 1q43, 1q44 and those with interstitial breakpoints (see [Ongoing research into 1q4 deletions](#) page 20) (Puthuran 2005; Hiraki 2008; Unique).

Children may also have ventricles, the normal fluid filled spaces within the brain, that are larger than normal. Other brain anomalies that have been reported, albeit much less frequently, include hydrocephalus (excessive fluid in the brain, often called 'water on the brain') and delayed myelination (insulation of the nerve fibres). One Unique child has Dandy Walker syndrome, a fluid filled cyst in part of the brain. Dandy Walker syndrome together with 1q44 submicroscopic deletion has been reported in the published medical literature (van Bever 2005; Hiraki 2008; Unique).

## ■ Kidneys and urinary tract

Kidney problems may occur, although they are usually minor. Among Unique children around 20 per cent are affected, and the most frequent problem is kidney reflux (where urine flows upwards from the bladder back to the kidney). One Unique child affected by kidney reflux underwent ureteral re-implantation. This surgical procedure is performed when the ureters (the two tubes that carry urine from the kidney to the bladder) do not join the bladder in the correct place which can cause kidney reflux. The procedure disconnects the ureters from the bladder and reconnects them in the correct place (Hiraki 2008; Unique).

One child with a 1q42 deletion had only one kidney and one child with a 1q43 deletion had a 'horseshoe' kidney (the two kidneys are fused together to form a 'horseshoe' shape) (Unique).

## ■ Vision

Vision problems are common in children with a 1q4 deletion. More than 60 per cent of Unique families were affected in one way or another. The most common feature was a squint (strabismus) where one or both eyes turn inwards, outwards or upwards. Other problems reported were long sight, short sight and astigmatism (the cornea, the clear cover over the iris and pupil, is abnormally curved resulting in blurred vision).

These problems are often mild and can be corrected with glasses (Unique).

A number of other problems have been reported in only one child. One Unique child was thought to have hypoplastic optic discs when a baby but the problem seemed to resolve by the age of 6 months, one had possible cortical visual impairment (the visual systems of the brain do not consistently understand or interpret what the eyes see) and another, with an interstitial 1q deletion, is blind in one eye (Unique).

Duane retraction syndrome (a congenital eye movement disorder) has been reported in one person with an interstitial deletion of 1q42.13q43 (Kato 2006).



11 years

## ■ Hearing

Hearing problems can affect children with a 1q4 deletion. A number of children have recurrent ear infections. Almost half of those surveyed by Unique had a build up of fluid in the middle ear called glue ear. Glue ear usually resolves as children get older and the ear tubes widen and become more vertical resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary.

However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum (Unique).

One Unique child had narrow ear canals and was initially assessed as being severely or profoundly deaf. Her hearing has steadily improved and she no longer requires a hearing aid and can hear well. Another Unique girl is deaf in one ear and has hearing problems in the other but will not tolerate wearing a hearing aid (Unique).

## ■ Hands

Many children with 1q4 deletions have unusual hands including small hands, an incurving little finger (clinodactyly), tapering fingers, shortened thumbs or fingers that are fused together (syndactyly). In general, the hand anomalies do not greatly affect the function of the hands, although they can lead to problems with fine motor skills (Hiraki 2008; Unique).

## ■ Feet

The feet of those with a 1q4 deletion are often not perfectly formed. Evidence from the literature and Unique suggests that almost 70 per cent of children have a foot anomaly. A number of children are flat-footed: the arch of the foot has collapsed resulting in the entire sole of the foot coming into contact with the ground. Other anomalies include talipes (clubfoot), 'rocker bottom' feet (the arch of the foot is unformed, leaving the sole curved), feet that turn inwards, feet that roll inwards and overlapping toes.

Some children who have clubfoot may need surgery to correct the unusual positioning of their feet, although for other children plaster and splints may be sufficient. Generally the foot anomalies may mean that children require special insoles or inserts in their shoes or special supportive footwear (Hiraki 2008; Unique).

## ■ Skeleton

Various skeletal problems can occur in those people with a 1q4 deletion. Dislocation of the hip, in which the ball at the top of the thighbone (femur) does not sit securely in the socket in the hip bone (pelvis) can occur and affected more than 20 per cent of those who took part in the Unique survey. In the majority of affected children the dislocation was congenital (they were born with either one or both hips dislocated). Treatment of the dislocation depends on the child's age. In a newborn or very young infant, for example, a soft positioning device called a Pavlik harness will keep the hip bone in the socket and stimulate normal hip development. If that method doesn't work, or for an older child, surgery to reposition the hip may be necessary. Following either treatment, the child may wear a cast and/or braces for several months. This will help keep the hip bone in the socket while it heals (Hiraki 2008; Unique).



6 years

Some people develop curvature of the spine (scoliosis). Four of those who took part in the Unique survey had scoliosis: three had mild scoliosis and the fourth had more severe scoliosis which necessitated wearing a back brace and having spinal rods inserted surgically for support (Unique).

## ■ Minor genital abnormalities

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. The most common problems are cryptorchidism (undescended testes), and hypospadias (which occurs when the hole usually sited at the end of the penis is on the underside instead). In the case of cryptorchidism, the testicles can be brought down by a straightforward surgical operation. In the case of hypospadias, depending on how mild this is, it may need no treatment or require corrective surgery to re-site the hole. A less common finding was micropenis (a small penis) (Hathout 1998; Puthuran 2005; Rice 2006; Unique).

Girls may also have minor genital anomalies. The most frequent genital anomaly in girls is unusual labia that may be underdeveloped or large (Hiraki 2008; Unique).

## ■ Palate

A cleft palate (opening in the roof of the mouth resulting from the palate not forming correctly during development) has been reported to affect some children with a 1q4 deletion. The evidence at Unique is that clefts are much more common in children with a breakpoint in 1q42 or 1q43, with only one child with a 1q44 deletion (out of a possible 13) reporting a cleft. Likewise, in the published medical literature there is only one report of a child with a 1q44 deletion (out of a total of six reported cases) with a cleft palate. This limited evidence suggests that children with a breakpoint closer to the end of the chromosome may have a lower risk of a cleft. Further research and/or greater numbers of affected children are needed to support (or refute) this assumption (Hiraki 2008; Unique).

A number of children, all with breakpoints in 1q43 or 1q44, are reported to have a high palate (Unique).

Both cleft and high palates can contribute to the early feeding difficulties seen in children. A cleft or high palate may also make speech more difficult.



4 months

## ■ Skin

Eczema is a type of allergic reaction that seems to be common in children with 1q4 deletions, affecting around 60 per cent of children in the Unique survey. In mild forms the skin is dry, hot and itchy, whilst in more severe forms the skin can become broken, raw and bleeding. Parents have found that gentle moisturising creams and emollients can help keep it under control, with steroid cream employed in more severe cases. Eczema is often worse during the summer months and many children outgrow it (Unique).

## ■ Breathing

Breathing problems can affect children with 1q4 deletions. Around 40 per cent of those surveyed by Unique had apnoea (pauses in breathing). For the vast majority of children the apnoea episodes occurred in the newborn or babyhood period (infant apnoea) and ceased as they grew into toddlers. The apnoea is often associated with seizures. The Unique experience is that most children start breathing again on their own with no need for intervention. Simply touching or repositioning may raise the baby's alertness and stop the apnoeic episode. Where intervention has been necessary it has involved suction to clear the airways or delivery of oxygen. One child suffering from sleep apnoea had an apnoea monitor during his first year (Unique).

A minority of children (around 20 per cent of those surveyed by Unique) suffered from asthma although the majority were only mildly affected and it often improved with age (Unique).

## ■ Hernia

Hernias are sometimes seen in children with 1q4 deletions. Both umbilical and inguinal hernias have been reported. An umbilical hernia is a soft, skin-covered bulge at the belly button (umbilicus) that can look bigger when the baby strains or cries. The bulge contains a small piece of abdominal lining and sometimes part of the abdominal organs. It is caused by incomplete closure of the ring of muscle that the umbilical cord passed through in early life. Umbilical hernias are often quite small and may resolve naturally by the age of 3 or 4 years. Some babies have a larger hernia or one that does not disappear, in which case it can be surgically stitched in a small operation. An inguinal hernia is one where the bulge is tissue from the intestines and is located in the lower abdomen (groin). An inguinal hernia may also require surgery (Unique).

## ■ Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. A number of Unique children have teeth that are slow to erupt.

One Unique child had two bottom teeth missing (in both deciduous (milk) and adult sets of teeth). Another Unique child has two lower front teeth that share the same root (Unique).



3 years

## Behaviour

Children with a 1q4 deletion are typically happy, sociable and affectionate with an easy disposition, although they tend to be passive. However, they are as vulnerable to frustration as other children with a communication difficulty and a small minority succumb to temper tantrums and aggression that can present carers with challenges. One Unique girl (aged 7) can be violent and difficult to control. Many parents report that children with challenging behaviour have responded well to standard discipline techniques such as ignoring unwanted behaviour and rewarding them with cuddles and attention when they stop (van Bon 2008; Unique).

Other behavioural problems reported in the medical literature include an 8-year-old boy with an interstitial 1q43q44 deletion who showed stereotypic behaviour with teeth gnashing and groaning, and had little interaction with his surroundings and a 12-year-old boy who could be aggressive and had a decreased pain threshold (Sanford-Hanna 2001; van Bon 2008).

Additionally, behaviour within the autistic spectrum has been reported both in the published medical literature and in a very small minority of Unique children. The autistic tendencies that have been noted include avoiding eye contact, failing to show interest in other people, expressing little emotion, rarely crying and repeating movements like head shaking or wringing their fingers. Another feature seen in many within this group of children is a resistance to change. Parents find that a daily routine where the child understands what happens and when can help children to feel safe and secure (Halal 1990; Murayama 1991; Unique).

*“ She is a good baby and smiles a lot. ” – 4 months*

*“ She is a very happy, contented child. She rarely cries and is well behaved. ” – 3 years*

*“ She is very good and placid. She loves music. ” – 3½ years*

*“ She has a big personality and is always happy and content. She loves people and adores music. ” – 3 years*

*“ She’s a lot of fun to be around. ” – 5 years*

*“ People love him because he is so adorable and loving. Because he has a limited understanding of social ‘niceties’ he says what he is thinking without consequence (both good and bad!) – you definitely need a sense of humour living with him! He can be loving and giving and kind but then because of his frustrations/barriers with communication he can tend to be quite aggressive and lash out at people. He has got better as he’s got older – we can reason with him more. ” – 9 years*

*“ He does enjoy being around other people and kids but he does not engage in co-operative play very much. He’d rather watch or do his own thing. He is very laid-back, loving and gentle. ” – 10 years*

*“ She is a sweet child. ” – 11 years*

*“ She is normally happy. She is loving and likes lots of kisses and cuddles. She is very single-minded. ” – 12 years*

*“ She is usually happy but very sleepy. ” – 14 years*

*“ She likes music and going out shopping and for meals. She is very people-friendly. She is always happy and smiley and easy to look after. ” – 25 years*

## Sleep

The majority of children go to bed easily at bedtime and sleep well. However, sleep problems or disturbances affect a small minority of children. Night-time seizures or sleep apnoea can disturb some children's sleep. Sleep medication has been necessary for one Unique child (Unique).

## Puberty and Fertility

There is limited information available on puberty in both males and females with 1q4 deletions. However, the published medical literature describes a 19-year-old man with a 1q44 deletion who had delayed puberty and Sertoli-cell-only syndrome (a condition where there is an absence of living sperm in the semen resulting in sterility) (Hathout 1998).

One Unique girl showed signs of puberty at 12 years with pubic hair and breast development, but has not yet started menstruation at the age of 25 years. Another Unique girl started puberty at 7 years (Unique).

To date there are only two individuals known to have passed on a 1q4 deletion.

There are two reports in the medical literature of mothers who have passed small interstitial deletions of 1q42 on to their children (Sanford Hanna 2001; Puthuran 2005).

## Adults with a 1q4 deletion

Unique has four adult members between the ages of 18 and 31 years. One young woman

needs 24 hour care and attends a day rehabilitation centre where she has occupational, speech and physiotherapy. She also belongs to a religious group that fosters inclusion in the community which enables her to take part in many activities. She loves chocolate milk and ice cream!

Another young woman lives in a residential home which is a great success and her family visit often. She needs a wheelchair to get around and enjoys swimming and horse-riding. She also requires 24 hour care but is always happy and smiling. She is non-verbal but uses some signs and gestures to communicate (Unique).

The adults reported in the published medical literature include an 18-year-old girl with a learning disability and developmental delay. She had a few simple words and was

learning to sign. She had microcephaly, suffered from seizures and walked with a walker. Another young woman (24 years) had microcephaly, normal growth, learning difficulties and a mild scoliosis that required physiotherapy. Her facial appearance was said to be characteristic of 1q4 deletions in babyhood but in adulthood the features had disappeared. Another 24-year-old woman had severe learning difficulties, short stature, microcephaly and epileptic seizures. A 19-year-old man had developmental delay and seizures.



24 years

A 40-year-old woman left school at 16 years and was employed as a childcare assistant and hospital worker. She passed the 1q42 deletion on to two sons. Her deletion was only detected after the birth and detection of the 1q42 deletion in her sons. She had a complete absence of the corpus callosum and is short. Another mother, aged 41, also only discovered that she had a 1q42.1q42.3 deletion after the deletion was detected in her son. She had fine, thin hair and wore an upper dental plate and had a bifid uvula (the uvula, the little V-shaped fleshy mass hanging from the back of the soft palate, is cleft or split) with nasal speech. She receives assisted living services (Hathout 1998; Sanford Hanna 2001; Gentile 2003; Puthuran 2005; Hill 2007; van Bon 2008).

## Ongoing research involving 1q4

The features of a 1q4 deletion are likely to be a result of the loss of a number of different genes found in this region. The size of the deleted region found in those with 1q4 deletions varies widely, ranging from a very small deletion of 400 kilobases to much larger ones of more than 20 megabases.

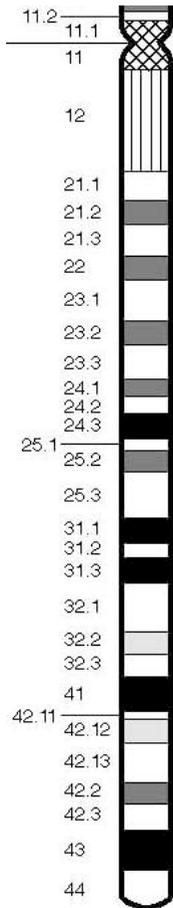
Since people with both submicroscopic deletions (or microdeletions) and larger terminal deletions all show similar features (albeit often less severe), it is likely that the features of 1q4 deletions are mainly caused by genes located at the end of the chromosome which is compatible with the fact that the ends of chromosomes are relatively gene-rich.

The increasing use of molecular techniques such as array-CGH and FISH in the research laboratory has enabled more accurate definition of the breakpoints. This, in turn, enables researchers to study which parts of the chromosome correlate with the different clinical features of the condition. Indeed, a number of recent studies have attempted to correlate the clinical features in people with a 1q4 deletion with the part of the chromosome they have missing in order to define a critical region of 1q that is responsible for the features of 1q4 deletions, and to help to narrow down the genes responsible.

A team of scientists in the UK studied the breakpoints and the region of 1q4 deleted in a number of people with microcephaly and ACC. They defined a 3.5Mb critical region in 1q44 containing one or more genes leading to microcephaly and corpus callosum abnormalities. They put forward the *AKT3* gene located in this region as the strongest candidate for the corpus callosum agenesis. *AKT3* codes for a protein that has been shown to control cell and organ size in flies, mice and humans. In mouse experiments, removing the *AKT3* gene leads to a significant reduction of brain and corpus callosum suggesting *AKT3* as a strong candidate for ACC (Verdu 1999; Shioi 2002; Easton 2005; Boland 2007).

However, there are reports of several patients who have corpus callosum abnormalities but who are not missing the *AKT3* gene. Additionally, a recent study involving 13 individuals with small submicroscopic deletions defined the 'critical region' for corpus for corpus callosum abnormalities to an extremely small region of 360 kb which contains only four possible candidate genes, but excludes the *AKT3* gene.

Furthermore, another study involved three related individuals with a 1q42 interstitial deletion and a complete absence of the corpus callosum, suggesting that a gene important for the development of the corpus callosum is situated at 1q42. The evidence at Unique backs this up: one Unique child with an interstitial deletion of 1q42 has agenesis of the corpus callosum. One possible explanation for these conflicting results is that multiple genes in different areas of 1q4 region interact or are otherwise involved in the corpus callosum abnormalities that affect those with 1q4 deletions (Puthuran 2005; van Bon 2008; Unique).



Research groups have also attempted to correlate other features with a particular region of 1q4. Hand anomalies are thought to be likely to be due to the loss of a more proximal region as several people with more distal breakpoints have hands and feet that are unaffected, whereas those with interstitial deletions of 1q42.1q42.3 have short hands. This is supported by the evidence at Unique (Sanford Hanna 2001; Gentile 2003; Hill 2007).

Hip dysplasia seems to be present only in patients with the largest deletions.

More studies are needed to determine if this points to a gene in the more proximal region that is necessary for normal hip development (Hill 2007).

It is also important to remember that while identifying the gene(s) responsible for certain features of 1q4 deletions is interesting and may help guide future studies, it does not lead directly to immediate improved treatment.

Additionally, even if the supposedly responsible gene is missing it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

Hand anomalies

AKT3

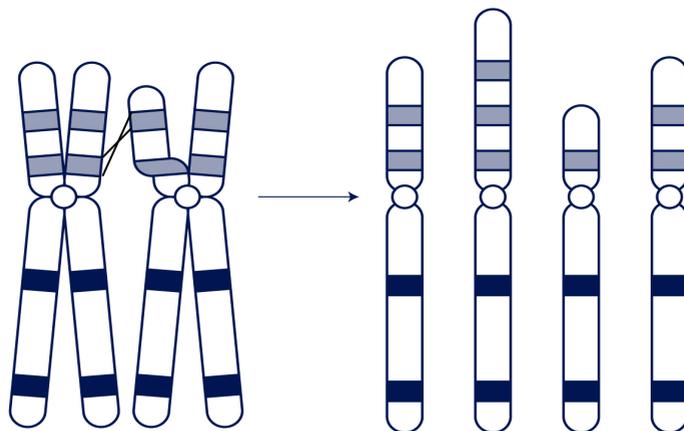
360 kb critical region for ACC

## Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 1q4 deletion occurred. In the majority of cases the 1q4 deletion occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 1q4 deletions are caused by a change that occurred when the parents' sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined. Some 1q4 deletions are accompanied by a gain of material from another chromosome and are often the result of a rearrangement in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers.

Whether the deletion is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 1q4 deletion and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

*De novo* 1q4 deletions are caused by a sporadic change that is thought to occur when the parents' sperm or egg cells are formed.



One way that a deletion and a duplication could theoretically arise during the formation of egg or sperm cells. On the left are two matching chromosomes, each split to the centromere and ready to pair and exchange segments. The shaded bars show similar sequences of DNA in the chromosome that enable correct pairing. But just above the centromere mispairing has occurred. When the chromosomes separate (right), the mispairing has given rise to two normal and two abnormal chromosomes, one with a deletion and one with a duplication.

## Can it happen again?

The possibility of having another pregnancy with a 1q4 deletion depends on the parents' chromosomes. If both parents have normal chromosomes when their blood cells are tested, the deletion is very unlikely to happen again. However, there is a very small theoretical possibility that the deletion occurred during the formation of the egg or sperm cells in a parent. When this occurs there is a tiny chance that parents with apparently normal chromosomes could have another affected pregnancy. On the other hand, if either parent has a chromosome rearrangement or deletion involving 1q4, the possibility is greatly increased of having other affected pregnancies. Parents should have the opportunity to meet a genetic counsellor to discuss the specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

# Notes

# Inform Network Support



Understanding Chromosome & Gene Disorders

## Rare Chromosome Disorder Support Group,

The Stables, Station Rd West, Oxted, Surrey. RH8 9EE. UK.

Tel: +44(0)1883 723356

[info@rarechromo.org](mailto:info@rarechromo.org) | [www.rarechromo.org](http://www.rarechromo.org)

## 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/donate](http://www.rarechromo.org/donate) Please help us to help you!

There is a Facebook group for families affected by 1q4 deletions at [www.facebook.com](http://www.facebook.com):

[www.facebook.com/groups/133964299961835](http://www.facebook.com/groups/133964299961835)

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their 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. It was compiled by Unique and reviewed by Brenda Barry, Genetic Counsellor and Research Co-ordinator, Walsh Laboratory, Children's Hospital, Boston, USA and by Professor Maj Hulten BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, UK.

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