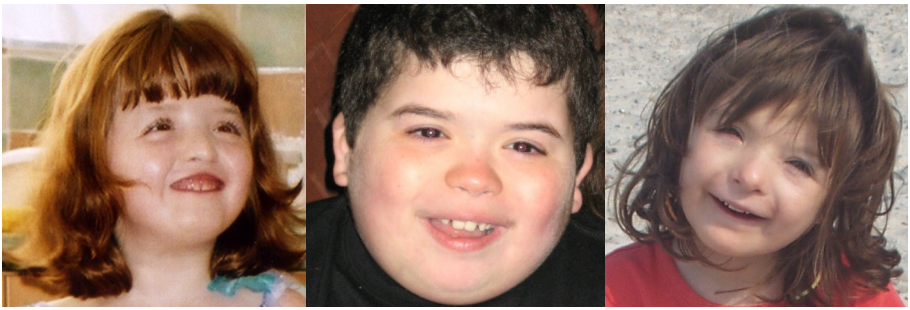
Understanding Chromosome & Gene Disorders

# 6q deletions
# 6q15 to 6q23



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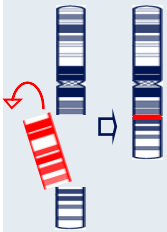
## Sources & references

The information in this leaflet is drawn partly from medical publications. The first-named author and publication date are given to allow you to look for articles on the internet in PubMed.

The leaflet also draws on *Unique*'s database. When this leaflet was written, *Unique* had 67 members with a 6q deletion, of whom 46 had a pure 6q deletion with no other chromosome involved.



**An interstitial deletion**

# Interstitial deletions of 6q: from 6q15 to 6q23

A chromosome 6q deletion means that part of one of the body's chromosomes has been lost or deleted. With an **interstitial** deletion, there are two breakpoints that have rejoined and the part between them is missing. If the material that has been deleted contains important instructions for the body, learning difficulties or disability, developmental delay and health problems may occur.
How serious these problems are depends on how much of the chromosome has been deleted and where the deletion is.

## Genes and chromosomes

Our bodies are made up of billions of cells. Most cells contain a complete set of genes. We have thousands of genes which act like a set of instructions, controlling our growth, development and how our bodies work.

Genes are carried on microscopically small, thread-like structures called chromosomes. We usually have 46 chromosomes, 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in 'pairs'. Chromosomes and genes are made up of a chemical substance called DNA.

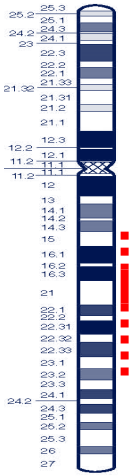
Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy), chromosomes are numbered 1 to 22, generally from largest to smallest. Each chromosome has a short (**p**) arm (at the top in the diagram on the facing page) and a long (**q**) arm (at the bottom). In a 6q deletion, material has been lost from the long arm of one chromosome 6.

You can't see chromosomes with the naked eye, but if you stain them and magnify their image under a microscope, you can see that each one has a distinctive pattern of light and dark bands.

A small or much larger piece of the chromosome can be missing.
If the piece is visibly missing when the chromosomes are magnified, it is called a **deletion**. The missing piece may be so tiny that it can only be found or characterised using more recently developed DNA-based techniques such as FISH or microarrays. It is then called a **microdeletion**.

Your geneticist or genetic counsellor can tell you more about the chromosome material that has been lost. You will almost certainly be given a **karyotype**, a shorthand code for the image of your child's chromosome make-up that shows the points where the chromosome has broken and re-joined. Comparing your child's karyotype with others can help to build up a general picture of what to expect.
But there will still be differences, sometimes quite marked, between your child and others with apparently similar deletions. It is very important to see your child as an individual and not to make direct comparisons with others with the same karyotype.
After all, each of us is unique.

Some thirty cases with a pure deletion in this area have been described, at least eighteen in the medical literature and twelve members of *Unique*.. The oldest member of *Unique* was 12 years old when this leaflet was written. The oldest child described in the medical literature was 13 years old.



**References** (Klein 2007; Le Caignec 2005; Gilhuis 2000; Hopkin 1997; Correa-Cerro 1996; Evers 1996; Pandya 1995; Villa 1995; Braverman 1993; Fryns 1991; Horigome 1991; Wakahama 1991; Chery 1989; Glover 1988; Schwartz 1984; Nakagome 1980; *Unique*)

Some children have a smaller deletion involving the bands between 6q21 and 6q23. *Unique* has briefing notes available for families on these smaller deletions.

In most cases where **pregnancy** was described, the baby's rate of growth gave concern and this was reflected in the weight and size at birth. However, three pregnancies were considered normal. Three mothers became aware that their baby was moving very little towards the end of the pregnancy.

## At birth

| What was unusual? | How many affected? |
|---|---|
| Small or very small-for-dates baby | 16/25 |
| Birth by Caesarean section | 6/13 |
| Reluctant or unable to feed | 16/20 |
| Abnormal muscle tone (floppiness or tightness) | Most |
| Needed special care | Most |
| Heart problem | 13/30 |
| Minor foot anomalies | 11/29 |
| Minor hand anomalies | 10/29 |
| Minor anomalies of genitals | 4/18 boys; 1/11 girls |
| Complex split hand defect | 5/29 |

**Range of birthweights at or near term: 3lb 15oz/1.79 kg to 7lb 5oz/3.32 kg.**

### Small or very small-for-dates baby; Caesarean section; special care

Delivery was normal in a few cases, but almost half the babies were delivered by Caesarean section, usually planned because of their slow growth rate in pregnancy and expected vulnerability at birth.

Babies were generally born at or near their due date and, as expected from the pregnancy measurements, turned out on average to be small or very small. There was a very vulnerable group of four babies who weighed less than 4lb 7oz / 2kg at or near their due date. Two babies are known to have experienced respiratory distress during delivery and in general Apgar scores (a 0-10 rating scale of the baby's general wellbeing at birth) were low although some babies were well enough to rate 9 or 10 five or 10 minutes after delivery.

Some babies needed resuscitation and immediate care, but not all babies needed support at birth: two *Unique* babies were born a healthy weight, fed well and a chromosome problem was only identified later when they showed developmental delay.

## ■ Reluctant or unable to feed

Most babies had difficulty establishing feeding either because they showed no interest, showed no sucking reflex, were too weak to suck effectively – possibly due in part to immaturity or a heart problem - or could not coordinate the actions of sucking with swallowing. In some babies the problems were mild and temporary and it was possible to breast or bottle feed for some months, sometimes using a teat designed for babies with a cleft palate (Haberman teat). Other babies needed support and were fed for a while either through a nasogastric tube or a gastrostomy tube (PEG, button) direct into the stomach. Some children have retained their gastrostomy tube for years, feeding both orally and direct through the gastrostomy.

Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food passage, affected some babies. Reflux raises a baby's risk of inhaling food contents and setting up an infection in the lungs known as aspiration pneumonia. Reflux can be eased by careful semi-upright positioning during and after feeds, sleeping in a prescribed sleep chair rather than a bed, raising the head end of the baby's cot and if necessary by prescribed medication that helps to keep the feed within the stomach and counteract any acidity. 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 food pipe and stomach. Where feeding and reflux problems are persistent, a gastrostomy tube can be inserted.

Feeding proved to be an ongoing challenge for almost all families, as children usually moved on to solids late and needed foods pureed to prevent choking (gagging) well into mid-childhood. Once they learn to move a filled spoon from the bowl to their mouth, life becomes easier but at least one child was still unable to take any solid foods at the age of nine. Other children were taking drinks and feeding themselves by school age. Babies were rarely able to meet their own nutritional needs and enriched formula and food supplements were often required to ensure weight gain. Nonetheless, a child's pace of growth cannot be hurried by extra feeding. One family who declined to have a feeding tube inserted when their child – who had no problems feeding - failed to gain weight, found that he grew and gained weight steadily, at a pace that was slower than typically growing children. One child became very overweight by the age of four despite having a small appetite (Klein 2007; Gilhuis 2000; *Unique*).

**Overweight despite a normal appetite**
*- 11 years old, 6q16q21 deletion*

## ■ Abnormal muscle tone (floppiness or tightness)

Most babies with abnormal muscle tone had low tone (hypotonia). Babies with hypotonia feel floppy to handle and tend to lie with their arms and legs loosely outstretched. When held under the arms, their bodies easily slip through the hands. Low tone may improve with maturity but babies generally benefit from physiotherapy to help them reach their developmental milestones.

A few babies showed increased tone (hypertonia), also sometimes called cerebral palsy. This causes the muscles to contract and stiffen and babies are helped by physiotherapy.

## ■ Heart problem

Defects in the structure of the heart ranged from minor anomalies requiring observation to complex defects needing surgical correction. Problems included:

- Persistent ductus arteriosus/PDA - an open channel linking two major blood vessels leaving the heart that normally closes after birth. In one case this eventually closed naturally. One child with a PDA also had a hole linking the upper storage chambers of the heart (atrial septal defect/ASD), and a narrowing of the main blood vessel leaving the heart. In another child with a PDA there was a hole linking the two lower (pumping) chambers of the heart (ventricular septal defect/ VSD). Treatment for holes between the chambers of the heart depends on the individual case and whether the defect is causing breathlessness or difficulties feeding or gaining weight.
- Large holes between the storage and pumping chambers.
- Truncus arteriosus - a defect in the blood vessels leaving the heart, with a single vessel supplying both the lungs and the body and a large VSD.
- Compression of the airways by malposition of the heart and its major vessels.
- Tetralogy of Fallot - a complex of heart defects that results in oxygen-poor blood being pumped to the body.

The complex heart conditions that needed surgery occurred in the group described in the medical literature while *Unique* members mostly had simpler heart anomalies that either resolved naturally in time or with a simple surgical intervention. *Unique*'s usual experience is that children thrive well after their heart defects have been corrected. In this group one child with a complex heart defect died after surgery.

## ■ Minor foot anomalies

Minor anomalies of the feet include webbed toes (usually toes 2 and 3), unusually long and broad big toes, overlapping toes, a 'sandal gap' between the first and second toes and very flat arches or a curved sole (known as rocker bottom feet). One child had a second big toe on each foot, surgically removed; another had big toes that were bent upwards towards the foot, which were managed without surgery.

Many foot anomalies do not need treatment although suitable footwear may be needed, with referral to a physiotherapist, podiatrist or orthopaedic surgeon as appropriate.

## ■ Minor hand anomalies

Minor anomalies of the hands may just be cosmetic or may make it harder for the child to use their hands. Among the anomalies seen in this group are very small hands and feet, long, tapered fingers, incurved fifth fingers and one child had finger-like thumbs with an extra joint. One child with a 6q16q22 deletion was born with bent fingers that have been progressively but not completely straightened by wearing splints.

### ■ Missing or extra fingers, with hand/ arm defect

A group of babies has been reported in the medical literature with a deletion between 6q16.2 and 6q23 who have a serious hand defect and there are further cases, as yet unpublished, with a deletion between 6q16.2 and 6q21; however, no *Unique* children are affected in this way so it is uncertain how commonly this occurs. The defect usually involves missing or, more rarely, extra fingers and missing nails. Depending on the extent of the defect, the bones in the hand that correspond with the missing fingers may also not be formed and the bones of the forearm may also be short or missing. Other fingers may be webbed and one or more fingers may be stiff and unable to be used. No child's hands have been affected in exactly the same way but if this affects your child s/he will have access to orthopaedic and cosmetic surgery and therapy to achieve the best possible outcomes.

Some of these babies also had more minor anomalies of their feet, including very small fourth toes, underdeveloped nails and short toes.

### ■ Minor anomalies of genitals

Problems included undescended testicles, very small genitalia and hypospadias. The testes descend during fetal life from just below the kidneys at the back of the abdomen to reach the scrotum, usually before birth. If one or both testicles remain undescended, a decision will be taken on the need for treatment with hormones or surgery.
In hypospadias, the hole that is usually at the end of the penis is on the underside. Hypospadias can be repaired by surgery usually carried out in early childhood. One girl had minor genital anomalies and the hole for her bottom was positioned unusually far forward. This does not usually cause problems although it is important to be careful with cleanliness at nappy/diaper changes.

## Appearance

There may be little sign in your baby's facial appearance of an underlying disorder but you and the doctors may notice that your baby has a slightly unusual head or face. He or she may have features that make him look more like other children in this leaflet than like his own family. These features do not usually affect health.

Features typical of many chromosome disorders include ears that are set below the usual level (in line with the eye) that may be small, floppy or oddly formed, a somewhat small and receding lower jaw and chin (micro/retrognathia), eyes that slant slightly upwards or downwards, tiny skinfolds across the inner corner of the eye (epicanthic folds), a short neck, eyes set wide apart (hypertelorism) and a flat bridge but a prominent nose. Features more specific to this 6q deletion include narrowing of the head at the temples, a bulbous nose tip and a thin upper lip. Some features are seen in babies with other 6q deletions, such as a tiny hole in front of one or both ears.

Many babies have an unusually small head that may have an unexpected shape, most typically broad (brachycephaly). In one child with a very small lower jaw, insufficient room for the tongue to flatten out caused the airways to block, so she was fitted with a tracheostomy to allow direct inflow of air and oxygen until her mouth grew large enough to accommodate the tongue.

### Growing

Most babies and children with an interstitial 6q deletion are short, in some cases - but certainly not all - in lowest three per cent of the child population for height and weight. Children who are persistently very short may be referred to a growth clinic and treatment with growth hormone considered. In some children who have severe feeding problems, the growth rate can drop off very sharply; the length of one baby with a 6q15q21 deletion dropped from close to the top of his growth charts to the lowest ten per cent. Some children with this interstitial 6q deletion undoubtedly develop a tendency to plumpness around their abdomen and in some cases an increased weight: height ratio and a tendency to general overweight despite not overeating.

We do not yet know how tall these children will be as adults but it is already clear that birth weight is not always directly related to childhood height. Small-for-dates babies and long, heavy babies can both grow into tall children, while the heaviest baby at birth in this group became a short six-year-old.

## Medical concerns

| | How many affected children? |
|---|---|
| Heart problem (see page 5) | 13/30 |
| Brain anomaly on scan | 9/16 |
| Respiratory infections | 7/16 |
| Seizures | 3/24 |
| Eyesight problem | 14/26 |
| Hearing problem | 7/24 |

### Head and brain

Head size may be unusually small (microcephaly), normal or large (macrocephaly). Some children also have an unusually shaped head but this is not usually important. Where there is any concern, the brain may be imaged to assess its structure and growth and in a few babies and children the fluid filled spaces (ventricles) within the brain have appeared enlarged. Scans in two children showed delayed myelination, where the process of insulating several types of nerves in the body is immature. Another child showed periventricular leucomalacia, evidence of softened white areas around the ventricles within the brain. A baby in an unpublished case had part-formation of the corpus callosum, the broad band of nerve fibres that usually joins the two hemispheres of the brain. One child had an Arnold-Chiari abnormality, an abnormality of the base of the skull that allows part of the brain to intrude into the spinal canal. What these findings might mean for an individual child is not always clear but your child's doctors will explain them for your child.

### Respiratory infections

Respiratory infections were very common in the early years of children's lives, affecting more than half the *Unique* series. Some children had lasting symptoms of asthma that were relieved with inhaled or nebulised preventer and reliever therapies. Half the children in the *Unique* series had their tonsils and adenoids removed; in one child this helped breathing while feeding. These children by and large outgrew their tendency to respiratory infections by the age of eight or nine and in some cases much earlier.

## Seizures

Three children experienced seizures, and in each there was evidence of abnormal configuration of the brain. One child was thriving at the age of six with her seizures fairly well controlled with anti-epileptic medication. Another child died while asleep.

## Eyesight

Various vision or eye defects were seen so it will be important for a child with a deletion from this region of 6q to have an eye examination and assessment of vision. The defects included strabismus (squint), affecting one eye or both, directed inward or outward. Severity varied, with the squint resolving naturally in some babies, but requiring monitoring and surgical correction in others. Nystagmus, making the eyes jerk or wobble, was also seen, particularly in a child under stress. Nystagmus can be related to vision or caused by an imbalance in the muscles controlling eye movement. Your child will have an eye examination to find the cause and start any treatment needed.

Three children were short sighted, four had long sight and one had a developmental defect of the pupil in each eye (coloboma). One child had cortical visual impairment, a condition in which the visual systems in the brain do not understand or interpret what the eyes see and another had delayed visual maturity. The tear ducts fairly frequently got obstructed in this group.

## Hearing

A fluid build-up within the ear leading to the temporary hearing impairment known as glue ear is fairly common in young children. It can be relieved by inserting aeration tubes (grommets) in the eardrums. Two children reported in the medical literature with a deletion between 6q16.2 and 6q22/3 and one *Unique* member had a permanent hearing loss requiring hearing aids.

## Other concerns

One boy had diabetes insipidus (caused by insufficient anti diuretic hormone, leading to passage of large quantities of dilute urine). One child had small but well-functioning kidneys; another had horseshoe kidneys (the bottom points of the two usually separate kidneys are joined, creating a U (horseshoe) shape. This is not usually in itself harmful but it can increase the risk of urinary tract infections. Another had a duplicate drainage system from the kidneys. This usually causes no problems but may lead to repeated urinary tract infections.

A split in the voicebox (laryngeal cleft) was found in one child and a split in the soft part of the roof of the mouth in another (submucous cleft). In another the first part of the intestines was partly blocked. One child had an umbilical hernia. This shows as a soft, skin-covered bulge at the umbilicus (navel, belly button) that can look bigger when a baby strains or cries. The bulge contains a small piece of abdominal lining and sometimes a part of the abdominal organs. Most umbilical hernias close naturally in time but if one persists it can be closed in an operation usually performed as day surgery. An unpublished case was born with a meningomyelocele (a defect in the spine allowing a section of the spinal cord and membranes to protrude through it).

## Skin

Two children developed a skin condition known as keratosis pilaris, in which the skin on the upper arms, cheeks and thighs is rough and like gooseflesh. This usually resolves in time but meanwhile creams with salicylic acid, lactic acid and urea may be helpful.

### Teeth

Dental problems are common in children with chromosome disorders. The underlying facial structures may be abnormal, affecting tooth development; feeding and mouthing experiences also have an effect. Some children fed entirely by tube can become mouth-averse, making tooth brushing and visits to the dentist challenging. These children may need to have their teeth cleaned and treated under a general anaesthetic.
Children in this group have experienced very early emergence of the teeth, poorly positioned teeth and failure of the first set of milk teeth to fall out when the adult teeth came in.

### General wellbeing

*Unique*'s experience is that once children have overcome initial problems and a vulnerability to coughs, colds and common respiratory infections in early childhood, they are generally as healthy as other children. However, the outlook for any child is determined largely by their clinical problems. Three children in this group are known to have died as babies or very young children, two as a result of a heart problem and one child, affected by sleep apnoea, while asleep.

## Development

### Sitting, moving: gross motor skills

Children typically appear to face delay in reaching their mobility milestones but the extent of the delay is varied and cannot be predicted from the karyotype. All children known to *Unique* have walked although one child has been reported in the medical literature who was unable to sit at six years. In general rolling over was achieved at 4-12 months and crawling at 8-24 months. Babies learned to sit between 6-21 months and could walk with support between 15 months and six years. Walking independently came soon afterwards, between two and three years for some, although walking has not been achievable for all. Some children learned to climb stairs, starting as young children between two and five years, and at least one child was running by the age of six.
Most children have considerable hypotonia (low muscle tone, so they feel floppy) and loose, very mobile joints and need support (splints, braces, walkers) in the early stages of mobility as well as regular physiotherapy. Two teenage boys had a degree of spinal curvature.

**Age 4 years 8 months**

**Age 7 years**

These descriptions are of children with the same karyotype involving a deletion of 6q16q22. Both children are six years old but their levels of mobility are quite different.

> "She sits very well alone, crawls indoors and out, walks with her hands held and lies and rolls when playing. She has a wheelchair, stander and walker."

> "He is walking well with some running; can climb stairs and manage play and obstacle courses."

### Using their hands: fine motor and coordination skills

Hand and eye coordination skills such as holding a bottle and playing with small toys may not develop in line with gross motor skills. Overall, there appears to be fairly consistent delay in hand use and fine motor skills, so that children learn to hold a cup and cutlery and to dress and undress themselves later than typically developing children. These snapshots give an idea of what children are capable of at different ages.:

- At 10 to 11 months, reaches for toys and can hold his bottle with a firm grip.
- At 2 years, holding and transferring toys. He can hold a bottle but this is a struggle; he has no saving mechanisms.
- At 6 years, we are working on using cutlery. He can take his clothes off but not put them on; has to be restrained to have his teeth brushed.
- At 6 years - she holds and transfers toys very well but can hold only handled cups. This is not her preferred area of development.
- At 9 years – she knows how to brush her hair and teeth but lacks coordination; she cooperates fully un/dressing and can put on her own coat but not fasten it.

Toilet training tends to be achieved late. In *Unique*'s experience, the earliest age at which children are trained to be dry and clean in the daytime is four years.

### Speech and communication

Some delay in speech and language is to be expected but how much delay varies and probably reflects the child's learning ability. Some children communicate best using alternatives to speech, including gestures, expression, vocal noises and signing, picture boards and picture exchange systems. Some understanding of speech is evident even in children who do not develop the ability to use it. Among eight children over the age of five, three are using speech and one other is using a consistent sign language.

- " She does not speak but babbles and can hum a perfect tune " – *age 4*
- " He is 'talking up a storm'; not everything is intelligible, but it's enough to get his needs and wishes met. He has used single words and then phrases since he was 5 and now uses 3-4 word phrases " – *age 6*
- " She had a fairly quiet cry as a baby. She makes more sounds than words but uses and understands many signs " – *age 6*
- " She communicates by speech and signing and understands a lot more than she lets on. She uses 3-word phrases but speaks very quietly and her words are not always clear " – *age 9*

### Learning

Some learning difficulties or disabilities can be expected to have but it is not possible to predict the severity from the karyotype. It appears that most children have a moderate to severe learning disability. Some children learn to read; *Unique*'s experience is that this has been possible for children who use speech to communicate. Some children have a good memory and pleasure and interest motivate them to learn.

### Behaviour

The evidence from *Unique* is that most children have an easy-going, calm nature. Some are quiet, others like to interact. Children show individual stress reactions, with apnoeas, fever, crying and hitting or becoming withdrawn. Among favourite toys and activities are jingling bells; toys that play songs; light and music toys; crumpling

newspapers; videos and DVDs; pets; music especially if it can be danced to; swimming; horse riding; fast spinning rides.
There is almost no information from the medical literature on behaviour, but one boy with a 6q15q21 deletion had attention deficit/ hyperactivity and a mild obsessive compulsive disorder, treated with medication, at 13 years.

“ Very cheery, determined, brave little girl. ”
“ She can be very stubborn and at nine is getting quite cheeky. ”

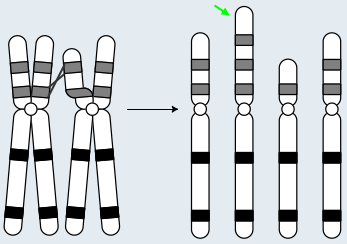
## Why did the deletion occur?

Most 6q interstitial deletions occur when both parents have normal chromosomes. The term that geneticists use for this is **de novo** (**dn**). A blood test to check the parents' chromosomes will show if this is the case.

De novo 6q deletions are caused by a change that has usually occurred when the parents' sperm or egg cells were formed. We know that chromosomes must break and rejoin when egg and sperm cells are formed. This only occasionally leads to problems.

Here is one possible scenario: during the formation of the egg and sperm cells the two members of each pair of chromosomes normally line up together and then break and rejoin to create new chromosomes. These new chromosomes contain different combinations of the genes passed down by the grandparents to the parents of the child. We believe that after the chromosomes break, the rejoining can take place between the wrong broken ends, leaving some chromosome material out and this can lead to a 6q deletion. However, nobody has ever seen this happen.

The breaking and rejoining is part of a natural process and as a parent you cannot change or control it. Children from all parts of the world and from all types of background have 6q deletions. No environmental, dietary or lifestyle factors are known to cause them. There is nothing that either parent did before or during pregnancy that can be shown to have caused the deletion to occur and equally nothing could have been done to prevent it.



**One possible way a deletion can occur. This picture shows how one chromosome is created with a short arm deletion (red arrow) and one with a duplication (green arrow).**

## Can it happen again?

The possibility of having another pregnancy with a 6q deletion depends on the parents' chromosomes. If both parents have normal chromosomes, the 6q deletion is very unlikely to happen again. If a blood test shows that either parent has a chromosome change involving 6q, the possibility is increased of having other pregnancies with chromosome changes.

Once a family chromosome change is known, a test can be done in any future pregnancy to find out whether the baby's chromosomes are affected.

Discussing any chromosome change with other family members also gives them the opportunity to have a blood test to see if they too carry it.

A genetic specialist can give you more guidance for your family.

## Support and Information

**Rare Chromosome Disorder Support Group,**
The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
Tel: +44(0)1883 723356
info@rarechromo.org | 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 Please help us to help you!

### Chromosome 6 research project

The C6 project works with families to collect detailed information with the aim of linking specific disease characteristics with specific regions of chromosome 6.
https://www.chromosome6.org/

### Facebook page for chromosome 6:

www.facebook.com/groups/chromosome6

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 Professor Robert Hopkin, Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA and by Professor Maj Hulten BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, UK. 2007. Version 2.

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