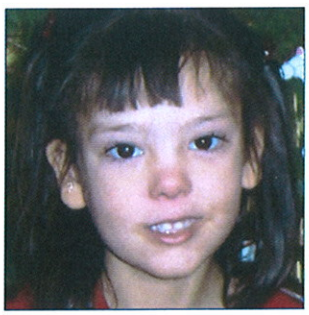
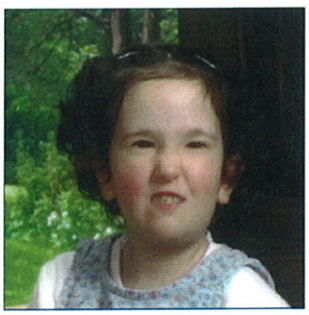
Unique

14q deletions from 14q32.2 & 14q32.3





Sources and references

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain abstracts and articles from *Unique*.

The leaflet also draws on *Unique*'s database. When this leaflet was written, *Unique* had 54 members with a 14q deletion, of whom 29 had a pure 14q deletion with no other chromosome involved.

Two chromosome 14s, stained and magnified

14q deletions

A chromosome 14 deletion means that part of one of the body's chromosomes has been lost or deleted. If the material that has been deleted contains important instructions for the body, some learning difficulties or disability, developmental delay and health problems may occur. How obvious 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. Genes act like a set of instructions, controlling our growth and development and how our bodies work.

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

Chromosomes come in different sizes and apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy) they are numbered 1 to 22, generally from largest to smallest. Each chromosome has a short (p) and a long (q) arm. In a 14q deletion, material has been lost from the long arm of one of the two chromosome 14s. The short arm of chromosome 14 contains no unique genes, so losing material from the short arm generally has no harmful effect.

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.

Chromosome deletions

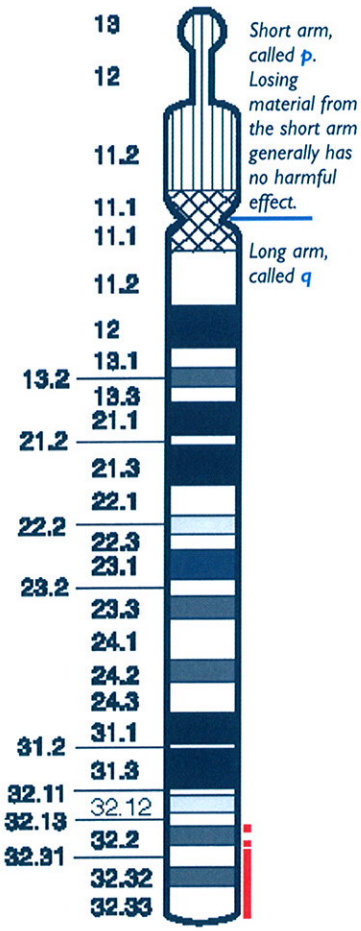
A small or a very large piece of the chromosome can be missing. If the piece is visibly missing when the chromosomes are magnified as much as 1250 times under a microscope, it is called a **deletion**. The missing piece may be so tiny that the magnified chromosome looks normal and it can only be found using more recently developed techniques, such as FISH or array-CGH. It is then called a **microdeletion**.

One type of deletion is called **terminal**. There is one breakpoint and a part of the chromosome from the breakpoint to the end of the arm is missing. Another type of deletion is called **interstitial**. There are two breakpoints on the same arm that have rejoined and the part between them is missing. The tip of the chromosome is called the telomere and a deletion from the area close to the tip is sometimes called a **subtelomeric** deletion.

This leaflet tells you what we know about **interstitial and terminal deletions from bands 14q32.2 and 14q32.3.**

Your genetic specialist can tell you more about what chromosome material has been lost. You will almost certainly be given a **karyotype**, a shorthand code that shows the bands where the chromosome has broken and rejoined. A band can contain many genes and depending on the technology used to find your child's chromosome deletion, the karyotype sometimes shows whether particular genes are present or not. But you will usually need to ask your genetic specialist for a full explanation.

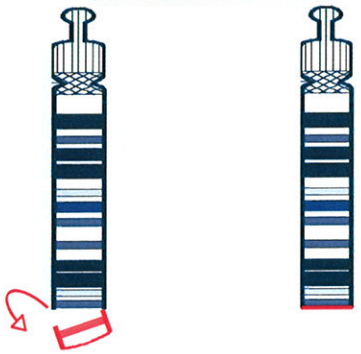
Your child's karyotype may look very like another person's, from *Unique* or in the medical literature, or it may look exactly the same. But even in people with the same karyotype, the chromosome may have broken at a different point within the same band. This is one important reason why people with apparently similar karyotypes do not all have the same problems or features. Individual differences can be quite marked and it is very important not to make direct comparisons between your child and others. After all, each of us is unique.



Twelve people, mostly babies and children, with a pure deletion of these bands are described in this leaflet, eight from the medical literature and four members of *Unique*. In addition, twelve members of *Unique* have been described with a terminal deletion of 14q as well as loss or gain of material from another chromosome (chromosomes 5, 7, 8, 9, 10, 12, 15, 19, 20). The oldest *Unique* member described was a teenager. An additional child with a slightly larger deletion starting at 14q32.2 is included.

(Maurin 2006; Schlade-Bartusiak 2005; Karnebeek 2002; Meschede 1998; Ortigas 1997; Wintle 1995/3; Miller 1992; Wang 1992; Telford 1990; *Unique*)

A terminal deletion



Chromosome 14 showing the end from 14q32.3 being lost.

Chromosome 14, without 32.3. The end is then 'sealed'.

Of seven cases where the **pregnancy** was described, it was uneventful in four cases, in two cases a decrease or little fetal movement was noted and in one case growth delay was observed before birth.

At birth

What was unusual?	How many babies affected?
■ Low muscle tone, known as hypotonia	9/11
■ Single palm crease, one or both hands	6/13
■ Feeding difficulties, including reflux	4/13
■ Premature birth	3/13

Range of birth weights at term: 4.16kg (9lb 3oz) to 1.76kg (3lb 14oz)

Most babies were born at or near term; three were born prematurely, in weeks 31 to 35. Birth weights in most of the term babies were in the normal range, and the mean birth weight was 2.98kg (6lb 9oz). The birth weight of the premature babies was also within the normal range. Known Apgar scores (rating of wellbeing at birth, scored on a scale of 0-10) were above 7 and most babies experienced no neonatal problems.

■ Hypotonia

An unusually low muscle tone, so that the baby or child feels floppy to handle. Babies with hypotonia tend to lie with their arms and legs loosely outstretched instead of bent at the knee or elbow. When held under the arms, their bodies easily slip through the hands. Babies and children with hypotonia benefit from early intervention with physiotherapy.

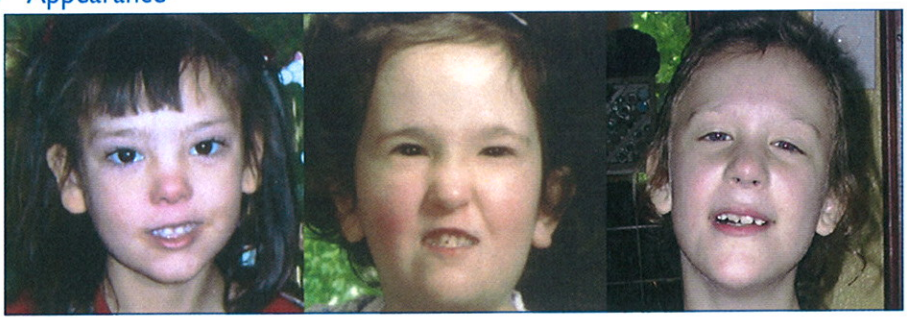
■ Feeding

Feeding histories are only available for three babies with a subtelomeric terminal 14q deletion. One baby had no feeding problems at all and breastfed successfully for eight months. The other babies had great difficulty establishing independent feeding and sucking on a bottle. One baby showed no hunger response, needing appetite stimulants and medication to assist gastric emptying and her low muscle tone caused difficulties with swallowing. She was initially fed through a Haberman feeder, which allows milk to flow even with a very weak suck. Both of these children showed continuing gastro oesophageal reflux, (GERD, GORD), needing medication to counteract its effects at the age of 5, and in one case developing laryngitis due to the reflux (Maurin 2006; *Unique*). In this condition, the stomach contents flush readily back up the food piassage and may cause two secondary problems, an inflammation of the food passage (oesophagitis) and aspiration, where the returned feed is inhaled into the lungs, with the risk of causing an infection. Reflux can be eased by careful semi-upright positioning during and after feeds, raising the head end of the baby's cot, giving thickened feeds and if necessary by prescribed medication that helps to keep the feed within the stomach. Babies who have continuing problems can have a surgical procedure called a fundoplication to improve the action of the valve at the junction between the food passage and stomach.

On weaning to solid foods, this baby continued to show swallowing difficulties (dysphagia) and needed to be fed bites of food followed by sips of liquid.

" She has always eaten far less than 'normal' but has made a slow gain in weight. We found increased calorie formula and a baby formula enriched with fatty acids found in breast milk very helpful. She can now eat all solids " - *14q32.3qter deletion, age 5*

Appearance



Three different girls: 3½ years (left), 4 years (centre), 7 years (right).

To a parent, there may be little sign in a baby's appearance of any underlying disorder although doctors may notice what are known as dysmorphic features. These features can mean that a baby or child looks more like others with the same disorder than like members of his or her own family.

The most typical features include: a small head, more obvious after birth than before; widely spaced and sometimes downslanting eyes, sometimes with a tiny skin fold across the inner corner (epicanthic fold); a short, possibly bulbous nose; a long groove between the upper lip and the nose; and an unusually small mouth with a thin upper lip. Other features may include a tall, broad forehead; the eyes sometimes have a hooded upper eyelid (ptosis) and sometimes have a narrow opening (blepharophimosis). The eyes may be almond-shaped and the outer aspect of the eyelids unusually full; low set ears, sometimes with an unusual shape or sticking out; a broad, flat bridge to the nose; a somewhat small chin and jaw (micrognathia). The skin may be singularly soft (Maurin 2006; Ortigas 1997). The palate is typically high and narrow and the teeth often crowded, so milk teeth may need surgical removal to allow adult teeth to emerge.

Hands and feet

Minor, non-functional anomalies of the hands are relatively common in children with chromosome disorders. In this group, a variety of hand anomalies was seen including most commonly a single palm crease; incurved fifth fingers; underdeveloped nails; short, chubby fingers; thumbs that start closer than normal to the wrist and somewhat resemble fingers and a large space between thumb and forefinger.

Foot anomalies were not seen in this small series, but two children had markedly flat feet. Two children, one with a 14q deletion and a duplication of the end of chromosome 7 from 7q36.1, the other with a duplication of chromosome 12 from 12q24.2, were born with talipes (club feet) needing casting or surgical correction.

Medical concerns

	How many children affected?
Frequent infections in early childhood	8/13
Heart conditions	3/13
Minor anomalies of the genital area	2/13

Frequent infections in early childhood

More than half the children in this series had repeated upper and lower respiratory infections from a very young age. Two children have needed their adenoids and tonsils removed; two have developed asthma; one child had repeated episodes of laryngitis (inflammation of the voice box) due to undertreated gastro oesophageal reflux (*see page 4*); and one has very high temperatures of 39.4-40°C/103-4°F associated with colds. The family understands that these are due to mitochondrial disease and have been told that their daughter probably is not able to regulate her body temperature well. As a result, they try to avoid extreme temperatures. Mitochondrial diseases are a group of conditions in which food and oxygen cannot be completely burned within the cells to generate energy. Treatment is individualised to the patient.

" No untoward events had arisen by the age of 5 years. Since the diagnosis of mitochondrial disease and getting through the first few months of pre-school, she has been very healthy, gaining weight, increasing skills developmentally and overall very well " - *14q32.3qter deletion*

Heart

Three children were born with a heart anomaly, in one unspecified and in two a relatively minor defect. One premature baby had a patent ductus arteriosus (PDA, a persisting structure from fetal circulation common in premature babies); the other had a bicuspid aortic valve, in which the valve that regulates blood flow into the aorta has two flaps instead of three, again common in the general population. At the age of five, she was well without surgery. Among babies with a 14q deletion and another chromosome deletion or duplication, holes were seen between the left and right heart chambers, in one needing surgical correction.

Genital area

Minor genital anomalies are quite common among babies with a chromosome disorder, especially boys. In this group, one boy with a 14q32.3qter deletion had hypospadias, where the urethra opens on the underside rather than the tip of the penis, and chordee, a downward curve of the penis. Among babies with a 14q deletion combined with another chromosome deletion or duplication, one boy had small genitals.

" The first genetic doctor said that her 'Genitalia examination revealed hypoplasia of clitoris and labia minora.' I cannot tell anything is different " - *14q32.3 deletion*

Other medical concerns

One baby with a mosaic constitution (cells with normal chromosomes as well as cells with the 14q deletion) had intestinal malrotation, a malformation of the intestinal tract. Among babies with a 14q deletion combined with another chromosome deletion or

duplication, one baby had a large hiatus hernia (protrusion of the stomach into the chest cavity through the hole for the oesophagus) and a child with a duplication of material from chromosome 20p (breakpoint at 20p11.2) had a complex malformation of the small and large bowel.

Outlook

Most babies in this series were not born with major defects. One baby died; he was the most severely affected in terms of birth defects although he had a mosaic constitution, with cells with the 14q deletion existing alongside cells with normal chromosomes. Two children from *Unique* died, each with a 14q deletion combined with another chromosome deletion or duplication.

Development

	How many affected children?
■ Slow growth rate in childhood	5/9
■ Disproportionately slow head growth	6/9
■ Mild to moderate developmental delay and difficulties with learning	9/9
■ Difficulties with eyesight	8/13
■ Difficulties with hearing	6/13

■ Growth

There appears to be no consistent pre- or postnatal growth pattern among children with a subtelomeric 14q deletion. While many babies and children have shown postnatal growth delay, the growth rate in other children was considered normal. One child showed diminished growth on the left side of the body, with left leg length 2cm (1") shorter than right at the age of 10. Two children with a duplication, of material from the end of chromosome 15 (from 15q26.3) and chromosome 19 (from 19q13.4), were tall.

■ Head and brain

In all children for whom information was given, the head was relatively small for body size with the growth rate dropping after birth. In one baby, the bony plates of the skull fused early (craniosynostosis). Despite this, in only two children with a pure 14q deletion was there information that brain structure was abnormal. One child had enlarged fluid-filled spaces (ventricles); the other child also had an increase in white matter around the ventricles. One child with a deletion of 14q and a duplication of the end of chromosome 9p with a breakpoint at 9p22 developed hydrocephalus (excessive fluid within the brain), requiring a shunt that was successful. A child with a duplication of the end of chromosome 19 had delayed maturation of the brain and was the only child in the series to develop seizures.

" Her brain was fully developed inside her small head " - *14q32.3qter deletion*

■ Eyesight

Four children had a visual defect: severe short sight; a developmental defect (coloboma) of the left optic nerve; a nuclear cataract of the left eye; and in the fourth case a visual

impairment causing double vision. Four other children had strabismus (squint) or amblyopia (lazy eye) requiring correction. Among children with a 14q deletion combined with another chromosome deletion or duplication, one was very long-sighted.

■ Hearing

Out of 13 children for whom information on hearing is available, one had normal hearing, three had fluid build-up in the middle ear causing a temporary hearing loss relieved by the insertion of aeration tubes into the eardrum; one has a cochlear defect and two have very narrow ear canals, in one case requiring hearing aids before age 5. Two further children need hearing aids, one with a mixed hearing loss (both conductive and permanent), the other child also with very narrow ear canals. Unusually narrow ear canals were also seen in two children with a 14q deletion combined with another chromosome deletion or duplication and a child with a duplication of chromosome 19q (breakpoint at 19q13.4) needs aids for a moderate hearing loss.

■ Sitting, moving: gross motor skills

Most babies and children with a subtelomeric 14q deletion do face delay in reaching their mobility milestones, but the picture is not consistent. At least one child sat, crawled and walked at the expected age; many showed a mild to moderate delay; and one showed a marked delay, walking by 4 years. No child in this series failed to walk. On average, babies learned to sit independently between six and 18 months; to crawl at 9 to18 months; and to walk at 13 months to two years.

The low muscle tone, flat feet and in-turned knees and ankles that affect some children means that they will need good supportive footwear or joint supports (such as ankle foot orthoses), but the evidence is that most children in this group did not need standers, walkers or special seating. Physiotherapy and additional therapies such as aquatic therapy were generally helpful in children achieving their milestones, but were not needed for all. By the age of 15, one boy was rollerblading, playing soccer, swimming, riding bike and horse, and playing baseball.

Among children with a 14q deletion combined with another chromosome deletion or duplication, the picture was more varied, with some children experiencing very marked delay in walking while others, such as a child with a duplication of chromosome 9p (breakpoint 9p22) showing no apparent mobility problems by the age of 3.

" She could not crawl backwards. When she was put into a walker she went forward, again she could not go backwards. Stairs are taken slowly and sitting is very floppy. Balancing on the flat is good – but could not balance for a two-wheeled bike " – *age 7*

" She is still tentative on uneven surfaces and usually needs to hold a hand when stepping off a kerb; needs help on stairs and has more problems with strength on the left side of her body " – *age 5*

■ Using their hands: fine motor and coordination skills

There is little specific evidence on this group of children, and a contrasting picture emerges, with some children achieving age-appropriate dexterity while others need

considerable support to master skills such as dressing and, later, writing.
Where occupational therapy has been provided, it has been beneficial and helped at least one child to achieve age-appropriate skills.

One teenager plays the piano; a seven-year-old is on target with fine motor skills and washes and dresses herself and cleans her own teeth with supervision; a five-year-old by contrast still has significant fine motor delays; she is able to use a fork and spoon, but not neatly, and to drink slowly from an open cup. She is able to help wash, brush her teeth and dress herself but needs assistance because of her motor delay.

■ Learning

Children can expect to need support during their academic career, but the amount of support needed and the eventual achievements appear to be very variable.
The terminal band of 14q contains few genes but many of them are involved in the development of the brain and nervous system and could play a role in the learning difficulties that children encounter. Within *Unique*'s membership are youngsters in mainstream (regular) education, achieving in line with their peers with minimal 1:1 classroom aid. At the other end of their spectrum are youngsters with a severe learning disability who require special education. Most come between these two opposites and until well on in their school career it may be neither possible nor helpful to predict eventual outcomes.

- A teenager with good grades and a good attitude started to read and write at 8 years.
- A seven-year-old loves to learn and has a 'pretty good memory'. She loves to read and started at 6 years and loves to write and draw but is still 3 years behind her peers. She is in mainstream school but is pulled out of class for 1:1 help.
- A five-year-old attends a special needs preschool. Her memory is sometimes good; at other times she needs prompting, possibly due to verbal skills. She is not yet reading but loves to look at books and be read to.

■ Speech and communication

Children typically experience a marked speech delay, possibly more than would be expected from the level of learning disability, although the evidence is not firm. Speech is typically the area of development that is most obviously affected. Most children appear to form words from age two to four onwards and benefit from early speech and language therapy, as well as music therapy where this is available.

" Music therapy enables her to articulate words in songs that she doesn't use in everyday speech; she loves to sing and carries a tune quite well "

Early communication problems can be helped by using sign language.

" At present she uses sign language, speech with babble and a device called an E-talk, a computer programmed with her needs. This feels like a world of difference. Without devices she can express 25 per cent of what she wants to and understands 95 per cent, if put in the right terms " – *7 years*

" She is still hard to understand and seems to have trouble with getting her tongue in the right position. She speaks in 2/3 word phrases to get something, longer sentences if

babbling. She used a few signs well until she could express herself verbally; is now able to talk and can mostly convey her needs well enough for her parents to understand; talks much more at home than anywhere else. She speaks only in declarative sentences; so far no questions unless prompted. She sounds somewhat nasal at times; has difficulty with ending and particularly beginning sounds of words "
– 5 years

Behaviour

No specific behaviour disorders have been identified in people with this chromosome deletion and individual children are usually described as happy and sociable. They may play more easily with children younger than themselves and with adults than with children of their own age.

" She has always had a very content, patient and happy personality. She loves to look at books; to sing; to colour in; she is very good at quickly learning different shapes of pieces and where they go in a puzzle; she is very sociable, especially with adults. She does still throw a good temper tantrum when she doesn't get what she wants. I just walk away – or carry her out of the store. "

" She loves to read, write, computers and music. She loves to play with her friends. Her three-wheel bike is also high on her list. "

Personal care and independence

Self care skills are rather late to develop and children are typically late to be toilet trained, although the small *Unique* series shows that day-time control is typically achieved from around three years and night-time control from around seven years. Until more children have grown into adulthood, it will not be possible to predict the likely levels of independence that they will achieve.

Ben

" He gives extraordinary amounts of love; cares about others, wants to help & share. "

Ben has a deletion from 14q (breakpoint at 14q32.3) and extra material from the long arm of chromosome 5 (breakpoint at 5q35.3).

At 10 years, Ben is soon to transfer from mainstream (regular) school to a special school. His progress has been pleasing: he reads common words and even cookery books and can write some familiar words and his name. He has basic keyboard skills and an excellent memory, especially for directions and past events. Ben responds well to praise and reward and is eager to please. His speech is quite good but he uses words literally, missing subtleties and hidden meanings. He uses long, if repetitive sentences.

Ben is sociable and, if anything, overfriendly. Sometimes he acts without thinking, he doesn't know how to avoid danger and when he gets upset he has difficulty calming down. Because he cannot think of two things at once, he easily forgets instructions. Ben enjoys riding his special bike, watching cars, rolling balls and marbles, blowing bubbles, watching familiar television and DVDs, being with people and watching others. Ben was not an early walker but with a rollator was on his feet by four and running by seven. At 10, he has been toilet trained since five, he can dress himself if his clothes are laid out and help is at hand. Ben has had few medical problems although he had many ear infections and is long-sighted.

Allie

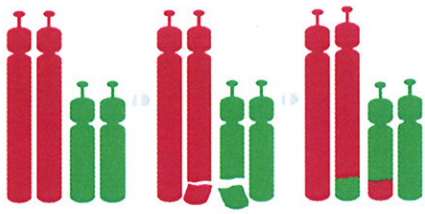
" She is very sweet and easy to love and we have learned to be very patient with her. We love to see her progress. "

Allie has a deletion from chromosome 14q (breakpoint at 14q32.3) and extra material from the long arm of chromosome 19 (breakpoint at 19q13.4).

At four years old, Allie has been making good progress at school. She loves books and being read to but is not reading yet. She has started to use some verbalisations alongside sign language and pictures and understands much more than she can say. She is in the early stages of starting to draw a circle and can feed herself. Feeding was no particular issue for Allie, who breastfed successfully for a year and now eats well, if messily. She is clean and dry both day and night and can brush her teeth and dress herself with pull-up shorts and T-shirts. She is very strong willed, loves playing with her brother, enjoys music, riding horseback, playing outside and swimming. As a baby, Allie made little eye contact but this is no longer an issue. Allie has no particular medical problems and is tall for her age.

How did this happen?

Some 14q deletions are the result of a rearrangement in one parent's chromosomes. This is usually a balanced translocation in which material has changed places between chromosomes but no material has been lost or gained and the parent usually has no difficulties with health or development. Other 14q deletions occur when both parents have normal chromosomes. The term that geneticists use for this is de novo (dn). De novo 14q deletions are usually caused by a change that 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 but this only occasionally leads to problems.



A balanced translocation

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 14q 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.

Can it happen again?

The possibility of having another pregnancy with a 14q deletion depends on the parents' chromosomes. If both parents have normal chromosomes, the 14q deletion is very unlikely to happen again. If a blood test shows that either parent has a chromosome change involving 14q, the possibility is increased of having other pregnancies with chromosome changes. Once a family chromosome change is known, a test in any future pregnancy can find out whether the baby's chromosomes are affected. A genetic specialist can give you more guidance for your family.

Unique

For support,
contact with other families and information

Rare Chromosome Disorder
Support Group
PO Box 2189, Caterham,
Surrey CR3 5GN, UK
Tel/Fax: +44 (0) 1883 330766
info@rarechromo.org

www.rarechromo.org

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 has been compiled by *Unique* and is believed to be the best available at the time of publication. It has been reviewed by Dr Kamilla Schlade-Bartusiak PhD, Department of Medical Genetics, University of Alberta, Canada and by Professor Maj Hulten BSc PhD MD FRCPath, Professor of Medical Genetics, University of Warwick, UK 2007.

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