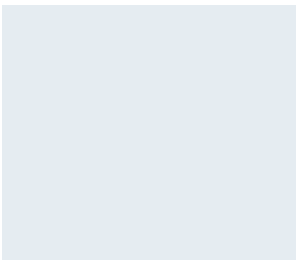
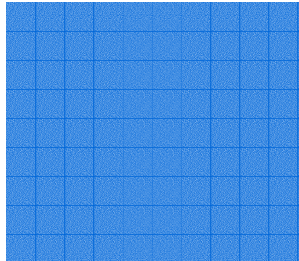


*Unique*

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# Ring 21



## Sources

The information in this leaflet comes from the medical literature and from Unique's members with Ring 21 (referenced U), who were surveyed in 2004. Unique is very grateful to the families who took part in the survey.

## References

The text contains references to articles published in the medical press. The first-named author and publication date are given to allow you to search for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain abstracts and key articles from Unique.

## Ring 21

Ring 21 is a rare genetic condition caused by having a ring-shaped chromosome.

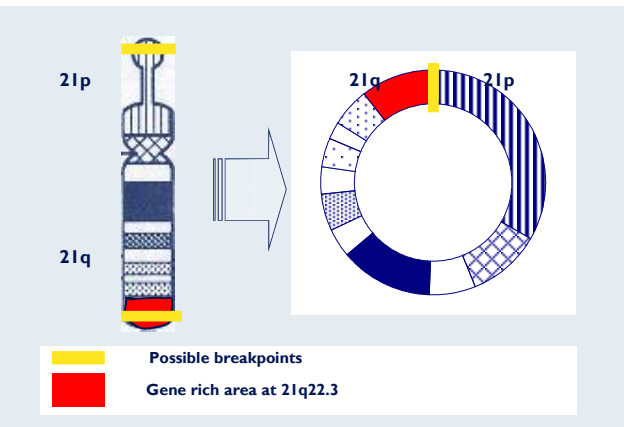
Almost half of the people with ring 21 chromosomes described in the medical literature are healthy and develop normally. Their unusual chromosomes are discovered by chance, during tests for infertility or after repeated miscarriages or after having an affected baby.

In other people the ring 21 chromosome affects development and learning and can also cause medical problems. In most of these people these effects are slight but in some people they can be severe. The effects can even vary between different members of the same family. The reason for these differences is not yet fully understood.

### What is a chromosome?

The human body is made up of cells. Inside most cells is a nucleus where genetic information is stored in genes which are grouped along chromosomes. Chromosomes are large enough to be studied under a microscope and come in different sizes, each with a short (p) and a long (q) arm. They are numbered from largest to smallest according to their size, from number 1 to number 22, in addition to the sex chromosomes, X and Y. A normal, healthy cell in the body has 46 chromosomes, 23 from the mother and 23 from the father, including one chromosome 21 from each parent.

In people with Ring 21, the ends of one of the chromosome 21s have joined to form a circle.



## Main features

There are three different types of Ring 21. Types 1 and 2 are associated with a loss of material from chromosome 21. Type 3 is associated with extra material from chromosome 21. The paediatrician or geneticist should assess which type best fits your child.

### Ring 21: Type 1

- Normal development.
- No effects on health.
- Possibly short stature.
- Discovered by chance, *or* during infertility tests *or* investigations for repeated miscarriages *or* after a baby with abnormalities *or* Down's syndrome is born.
- In boys and men, puberty may possibly be slightly delayed.

This type of Ring 21 makes no difference until people want to have children.

It is believed that people who show no effects of their ring chromosome have a single ring with a break at the very end of the long arm of chromosome 21. The site of the break in the short arm is not important as the short arm carries no genes of clinical importance. In one child, the end of 21p was found attached to chromosome 1 (Schmid 1983; Howell 1984; Kleczkowska 1984; Rhomberg 1984; Huret 1985; Gardner 1986; Hertz 1987; Ikeuchi 1990; Falik-Borenstein 1992; Melnyk 1995; Ki 2003).

### Ring 21: Type 2

People with this type of Ring 21 have a wide variety of different effects, which can range from being slight to severe. Some of the more common ones are:

- Short stature.
- Small head circumference (microcephaly).
- Seizures.
- Learning disabilities, ranging from mild to severe.
- Underdeveloped sex organs (both boys and girls).
- Vulnerability to infection.

Other more common effects described in the medical literature include heart defects; hypospadias (where the hole normally at the end of the penis is on the

## Different forms of Ring 21

Many people with Ring 21 syndrome have a mixture of cells, some with a single chromosome 21, some with a ring 21 and some with double or even larger rings. This is known as mosaicism.

## Families say ...

*“ He has very good powers of observation and often accomplishes things unexpectedly that I thought he was incapable of - adult.*

underside); cleft lip and palate or a high palate (roof of the mouth); eye defects (see list under Eyes, page 10); defects in the development of the brain or skull, with the plates of the skull fusing early (craniosynostosis); defects in the immune system; torticollis (twisting of the neck); thrombocytopenia (a low level of platelets in the blood).

The band at the tip of 21q, known as 21q22.3, is unusually rich in genes and many of the clinical problems are believed to be caused by the loss of genes in this band or by an imbalance in other genes.

### Other features

Many other features have been described in babies and children with Ring 21 or 21q- (loss of chromosome material from the long arm of chromosome 21). They do not occur commonly and it is not known whether they are specifically linked with chromosome 21 or not. These include: inguinal hernias (in the groin); choanal stenosis (blocking of passage from nostrils to throat); missing auditory canal; kidney anomalies; rib abnormalities, missing bones (fibula, in lower leg); abnormal site of the anus; hydrocephalus (abnormal increase in cerebrospinal fluid in the ventricles of the brain); underdeveloped lungs; a delicate, dry skin; ‘sandal gap’ between the big and second toes; short neck; congenital deafness; missing fifth finger (Stetten 1984; Cibis 1985; Aronson 1987; Meire 1994; Melkild 1994; Ohga 1997; Valero 1999; Ki 2003).

### Ring 21: Type 3

A few people with Ring 21 have:

- Features similar to Down’s syndrome.

Down’s syndrome is caused by having three copies of chromosome 21 and specifically three copies of the ‘Down’s critical region’ that appears on the long arm of chromosome 21 at 21q22.3. In people with Ring 21, it is believed that Down’s syndrome is caused by having a double-sized or multi-sized ring in many cells, so that the ‘Down’s critical region’ appears at least three times in most of the child’s cells. Having three copies of the critical region does not appear to always cause Down’s syndrome, however. One child has been described in the medical literature with a double (dicentric) ring and

three copies of the Down's critical region in most cells who nonetheless had no signs of Down's syndrome (Ieshima 1980; Howell 1983; Schmid 1983; Stetten 1984; Melkild 1994).

## Will the pregnancy be different?

The information from *Unique* is that pregnancy is usually normal. The rate of premature birth is slightly raised but no babies were born extremely prematurely and the neonatal period was generally straightforward apart from feeding difficulties.

## Diagnosis

Ring 21 syndrome can usually be diagnosed from a small blood sample. The chromosomes from the white blood cells are examined and the ring is normally obvious under a microscope. Additional molecular genetic tests from the same blood sample will show more precisely where the ends of the chromosome have broken and how much chromosomal material, if any, is missing. A small sample of skin may also be taken to check the proportion of cells with the ring chromosome.

Results typically show a mixture of cells: some with a single ring, some with a single chromosome 21 and no ring and some with a double-sized or larger ring or even with two rings. This is the mixture of cell types called mosaicism.

## Appearance

Most children and adults with Ring 21 will not look obviously different from other people. There are some subtle signs that may help doctors look for the correct diagnosis and may be obvious to others but every child does not have them. Among these signs are down-slanting and sometimes deep set eyes, a small jaw or chin, low set ears, a high, prominent forehead with a high hairline. Other



## How common is Ring 21?

Around 60 people have been described in the medical literature but there are certainly many more.

Generally speaking, ring chromosomes occur in around one in every 25,000 recognised conceptions (when you make a baby). At the time of writing, *Unique* had 25 member families affected by Ring 21, making a small community of affected families. Families who wish for contact can be put in touch with each other.

## Families say ...

*“ Luke only weighed 6 pounds 6 ounces (2891g) at birth while his sister who doesn't have Ring 21 weighed 9 pounds 10 ounces (4365g). His parents were warned he would be small, but in fact he is average. Both his parents are tall.*

*“ Amie measured 19 inches (48 cm) at birth and weighed 5 pounds 5 ounces (2409g). Now she is 6 and is tall for her age. Amie has features of Down's syndrome.*

features that have occasionally been noticed include a large sagittal suture (on the crown of the head), epicanthic folds (skin folds across the inner corner of the eye) and a broad, flat or prominent nasal bridge (Dagleish 1988; Kennerknecht 1990; Schinzel 2001).

## What about growth?

Many people with a ring chromosome are unusually short and while short stature is observed among some people with Ring 21, this does not affect everyone. Among *Unique* members, ten birth weights are recorded. They vary between 3 lb (1360 grams) and 8 lb 11 ounces (3840 grams), with an average of 6 lb 9 ounces (2986 grams). Although babies born small tend to grow into short children, this is not always the case.

## How can Ring 21 affect learning?

The medical literature reports that half of all people described in published studies are unaffected

## Families say ...

*“ He has mild to moderate learning difficulties. He is very determined and his memory is reasonable. His computer skills are confident and rapid and his reports show that he can match and identify colours, do an alphabet jigsaw and know that number names are used in counting. He has difficulty concentrating without 1:1 support and an adapted TEACCH approach involving a menu made up of photographs or symbols is to be introduced to help him structure his own day without relying on an adult for direction - age 4.*

*“ She can read words singly and has been writing letters and numbers since she was 5 - age 6.*

*“ He has difficulty writing because he cannot hold a pencil correctly. He understands how to count to 10 but does not grasp the concept of number. He finds it hard to focus and tends to forget what was learned yesterday - age 8.*

*“ In mathematics, she can multiply and subtract double digits. She can spell simple words and names and do word problems and read from school readers - age 20.*

- TEEACH is a programme for people with autism and similar developmental disorders. [www.teeach.com](http://www.teeach.com)

intellectually by Ring 21 and the level of learning difficulty among the others is usually mild (Gardner 1986; Falik-Borenstein 1992; Schinzel 2001).

This is generally true of *Unique* members, although two children, one with the Down's presentation, are described as having severe learning difficulties.

## How can Ring 21 affect a child's ability to speak?

There is very little published information on speech and language development in children with Ring 21. One child is described with mild features of Ring 21 and a marked delay in verbal skills attributed to severe speech dyspraxia (Dagleish 1988).

In *Unique*'s experience, speech and language problems reflect children's learning ability. Among those children whose learning ability is affected, speech development is delayed and these children have generally benefited from learning a sign language and other forms of assisted communication (using images, symbols) until their speech has developed. Generally, understanding has been better than speech. A small number of children with severe learning disability do not use words.

### Families say ...

- “ Some words, mainly using sign language - age 3.*
- “ When younger, he tried to communicate using gestures and eye pointing but got frustrated if he wasn't understood. Now he uses some signing and pictures and is saying many more words, in 2 to 3-word sentences, but some are very difficult to understand. His speech is very nasal because of a cleft in his soft palate. He almost certainly understands more than he can express and can follow simple, direct instructions within routines but has difficulty with conversations and more abstract language - age 4.*
- “ She has talked from 18 months and now uses 4 to 7-word sentences or even more sometimes. She understands an instruction but sometimes forgets what she has heard. Some sounds are difficult to understand now because she is losing her baby teeth - age 6.*
- “ He has severe speech delay but is improving and now has a 40 word vocabulary. He cannot pronounce the K sound - age 6.*
- “ He has no speech but seems to have a good understanding of things around him. Using facilitated communication, he is able to make people understand his needs - age 20.*

## Families say ...

*“ At the age of 4, he enjoys running, football or riding, any outdoor activity. He would live outside. He can ride a bike in a straight line backwards!*

## How can Ring 21 affect a child’s mobility and the way they use their hands?

There is little specific information on the development of gross or fine motor skills (large body movements and hand control) in the published medical literature.

In *Unique*’s experience, the overall picture is very varied and does not necessarily reflect cognitive development. Some babies are slow to reach their milestones of rolling, sitting and walking but go on to become as mobile and independent as other children of their age. Others become mobile with help, while a few remain wheelchair-dependent.

Hand control is also often delayed, and children may be late to establish whether they are right or left handed. None of these features is specific to Ring 21 and they are common among other children who are slow to develop.

Many babies with chromosome disorders show an unusual degree of floppiness (hypotonia) in their early months and may need intensive physiotherapy to improve this. This is also seen in children with Ring 21 syndrome, as is the opposite condition, hypertonia, where the muscles are unusually taut. In some children both hypotonia and hypertonia co-exist (Richer 1981; U).

## What medical problems can Ring 21 be linked with?

### ■ High rate of infections

Children with Ring 21 are vulnerable to infection. A significant number – possibly as many as two children in three - will have an unusual number of infections originating in the respiratory or sinus systems. They may also have a large number of bacterial infections and have delayed wound healing, including late separation of the umbilical cord and infection of the site. When baby teeth erupt, the gums may become inflamed and infected. Bacterial infections such as pneumonia and deep abscesses are more common in childhood. A blood test may reveal immune deficiency (a low level of the immunoglobulins IgA and IgG - antibodies), which can be treated with regular injections of

gammaglobulin to reduce the number of infections (and their severity). Some children who are prone to repeated bacterial infections are treated with regular antibiotic infusions.

Genes linked with hypogammaglobulinaemia (low levels of antibodies in the body) may reside near the end of the long arm of chromosome 21 at q22.2 or q22.3 and have been lost when the ring formed (Dagleish 1988; Ohga 1997).

### ■ Thrombocytopenia

Some children also have thrombocytopenia, a low level of platelets in the blood, causing prolonged bleeding and spontaneous bruising (Ohga 1997; Dagleish 1988).

### ■ Heart

Various heart conditions have been described as part of 21q- syndrome and some children with Ring 21 are also affected. Persistent ductus arteriosus (PDA, a persisting fetal circulation after birth) has been described and among *Unique's* members, one has a small hole between the left and right sides of the heart that is expected to close on its own, while another has more complex cardiac problems involving two of the heart valves (the pulmonary and mitral valves), the left ventricle and the aorta (the main artery taking blood from the heart to the body). As a baby, he required surgery to the pulmonary valve (U) .

### ■ Brain

Your child is likely to have a scan to ensure that the structure of the brain is intact. Holoprosencephaly, the incomplete development of the forebrain into two separate hemispheres, can occur in Ring 21 (see *Glossary*). When this occurs, the *HPE1* gene at 21q22.3 may have been deleted. In classic holoprosencephaly there are often signs of disrupted development in the mid-line of the child's face such as a cleft palate or lip, a single eye or central front tooth. In holoprosencephaly in Ring 21, these signs are often not seen and the child's face and mouth may develop entirely normally (Aronson 1987; Estabrooks 1990; Muenke 1995).

## ■ Head

A small head is typical of children with ring 21, but as many children have a petite build, it may be in proportion to the rest of their body. Some babies have a prominent occiput (back of the head) and in others the sutures between the plates of the skull fuse too early (craniosynostosis), not allowing the brain enough room to expand. In babies with Ring 21, this is most typical of the suture line on the top of the head (sagittal suture) and may be linked with early closure of the front fontanelle (soft spot) (Richer 1981).

## ■ Eyes

Many vision defects have been described in the medical literature, including cloudy or opaque corneas (the invisible, transparent front of the eyeball), colobomas (a gap in part of the structure of the eye (for more information, see [www.rnib.org.uk](http://www.rnib.org.uk)), cataracts, glaucoma (a rise in pressure inside the eye), Peters' anomaly of the eye (thinning of the back of the cornea and opaque areas at or near the centre), lens dislocation, small, underdeveloped optic nerves, microphthalmia (very small eyes) and detachment of the retina (Cibis 1985; Meire 1994).

*Unique's* experience is that none of its 25 families has reported severe visual problems, although one child has a divergent squint (the eyes do not work together and look outwards).

## ■ Mouth

Some children with Ring 21 may have a high arched or cleft palate (roof of the mouth).

## ■ Spine

Malformations of the vertebrae may cause a spinal curve to develop (scoliosis, kyphosis). This may be evident at birth and affects at least one child in five in *Unique's* experience. Treatment may require special seating, bracing, and if these measures do not work a surgical operation to straighten the spine.

## ■ Hands and feet

The fourth and third fingers have been noted to overlap. The nails may be underdeveloped (Richer 1981; Stella 1984).

## ■ Joints

Cervical dystonia, causing torticollis, a twisting of the neck to one side, has been attributed to Ring 21 and specifically, in one medical description, to the loss of genetic material beyond 21q22.3. The child was successfully treated with botulinum injections (Hou 2003). *Unique* has no experience of this effect.

## ■ Increased risk of leukaemia

The risk of developing leukaemia appears to be slightly raised, as it is in children with Down's syndrome (Falchi 1986; Palmer 1995; Song 1999; Streubel 2001; Massey, personal communication).

## ■ Seizures

Although a small number of people with ring 21 syndrome develop seizures, *Unique's* records suggest that there is no typical pattern.

## Can Ring 21 affect a child's behaviour?

The information in the medical literature about behaviour in children with Ring 21 is sparse. From *Unique's* experience, a common feature is a very high level of activity.

## Will a child ever be able to live independently?

Children who have difficulties with muscle tone and hand control are likely to be delayed in acquiring personal care skills such as washing, dressing and feeding themselves. The evidence from *Unique* is that the majority of children do acquire these skills in early to mid childhood and are also successfully toilet trained.

Some people will be able to go on to live semi-independently or in a sheltered setting. One adult member of *Unique* developed schizophrenia in her early twenties. This is now well controlled with medication and she leads a full life working in the family business, and at the local hospital. It is not known whether the mental illness is linked with her Ring 21.

For more information, read [One family's story](#) on page 15.

## Families say ...

*“ At 11 months, he loved opening and shutting doors, and was very active, by four he is never still and has a short attention span. He will try new experiences and activities and is a sociable, pleasant child.*

*“ He enjoys singing & dancing to music, and plays alongside his peers.*

*“ He is not good with change and likes things to be the same. Although he is not autistic, he may have ‘a small trace’ of autism.*

*He can get very frustrated and then he hits and cries a lot, bangs doors and walls and seems to enjoy the noise and movement as well as doing it to get attention.*

*“ He also likes us all to be together as a family. We tend to think he was a sheep dog in a past life.*

## What about food and eating?

There is no typical pattern of feeding disorders among children with Ring 21. Among *Unique*'s members, very few succeed in breastfeeding because low muscle tone usually undermines a new baby's ability to suck. It may be necessary to use soft teats or to tube feed babies until they gain the strength and coordination to allow them to drink enough milk to nourish themselves. On moving to solid foods, low muscle tone may lessen their ability to chew and babies with a very tiny lower jaw may not have gums or teeth that make contact with the upper jaw. After a slow start, however, most children eventually eat a wide range of foods. Only one *Unique* member with Ring 21 is known to be fed by gastrostomy (a tube direct into the stomach).

## Causes and mechanisms

A ring chromosome can arise in different ways. It may be inherited from a parent, almost always the mother. When it is passed down in this way it may stay unchanged (stable) or it can change.

The ring can also form for the first time (*de novo*) while the egg or sperm cells are being created or it can be formed after conception (when a baby is made). In this case, both parents have normal chromosomes and their chance of it happening again is very low.

## How does a single ring 21 form?

- For reasons that are not understood, the ends of the chromosome may simply join up, without any loss of chromosome material. This is known as telomere to telomere fusion.
- More often, the ends of the chromosome break off and the broken ends stick together.
- The ring can also be caused by a section of the long arm of chromosome 21 forming a loop, joining up and breaking off.

## How do double or multiple rings form?

When extra copies of 21q are generated, the child can have features of Down's syndrome. Some of the ways in which this can occur include:

- The ring can copy itself to form a double-sized ring.
- The ring can copy itself and form more than one ring.

- The ring may have formed from a Robertsonian translocation chromosome 21 in one of the parents. This type of chromosome consists of two long arms fused together without any material from the short arms. The ring will therefore contain material from the two long arms.
- During cell division, the chromosome may split horizontally instead of vertically, so that it contains two long arms which then join to form a ring.
- The ring can combine with the remaining normal chromosome 21 and form a new chromosome with duplicated material arranged end-to-end along its length. This is termed *tandem duplication* (Howell 1984; Miller 1987; Falik-Borenstein 1992; McGinniss 1992; Palmer 1995; Conte 1995; Muroya 2002).

## Passing it on

Parents with Ring 21 can pass it on to their children although this has almost always occurred with mothers. Men with Ring 21 are generally believed to be infertile but there is at least one report of a father transmitting the ring to his son. A parent with Ring 21 can also have children with a Robertsonian 21/21 translocation (Crusi and Engel 1986; Fryns 1987; Hertz 1987; Kennerknecht 1990; Falik-Borenstein 1992; Melnyk 1995).

## Will a child with Ring 21 passed on by an unaffected parent also be unaffected?

This is very difficult to answer. In some families, the ring is extremely stable and does not duplicate or delete itself. It can then pass down without causing symptoms. In one family four generations are known to have had a ring 21 chromosome.

It is very difficult to be certain about the outcomes of a pregnancy where a ring 21 has been found. These notes may provide some guidance.

A good outcome is more likely if:

- The ring appears to be the same as in the mother who is herself normal.
- Ultrasound shows that the growth rate and anatomy of the baby appear to be normal.
- Chromosome analysis shows that the ring 21 appears to be stable.

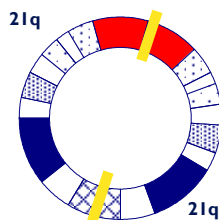
## Chromosome 21



## Robertsonian translocation chromosome 21



## Double ring formed from a Robertsonian chromosome 21



Breakpoint area

Indicators that the ring is stable include:

- Ring stability in the parent.
- Ring stability in other members of the same family who are also unaffected.

The natural instability of ring chromosomes means that the ring seen in placental cells or amniotic fluid may not reflect the ring found in the baby and interpreting the result becomes more difficult if there is mosaicism. This may reflect genuine mosaicism in the baby or just mosaicism in the placenta or amniotic tissues. It may also be an artificial result created by the way the cells are cultured.

These difficulties mean that it is very important for couples to have every opportunity to discuss their individual situation with a well-informed geneticist or genetic counsellor (Howell 1983; Huret 1985; Melnyk 1995; Muroya 2002).

The ring can also pass down apparently unaltered and still cause symptoms. One family has been described in which the mother had no symptoms other than a small head, while her daughter with the same ring 21 chromosome also developed normally but was very small for her age and was hyperactive.

The ring can also create rearrangements that give rise to Down's syndrome in the baby. One study of 17 children of mothers with Ring 21 showed that five babies had Down's syndrome. This can happen if:

- The ring does not separate.
- The ring miscombines with the other chromosome 21, causing tandem duplication (see page 13).
- One end of the ring comes unstuck and it then gives rise to a Robertsonian translocation chromosome made up of two long arms of 21.

(Howell 1983; Kleczkowska 1984; Dallapiccola 1986; Fryns 1987; Ikeuchi 1990; Kennerknecht 1990; Falik-Borenstein 1992; Melnyk 1995; Valero 1999).



## One family's story

When Wendy was born in the 1970s in Singapore, there was no sign or suspicion that she might have a rare chromosome disorder. She was not a large baby, but at five pounds ten ounces (2551g) at birth neither was she remarkably small, although she did show a worrying failure to gain weight in her first two months. But once on solids, Wendy had no more major health problems and made steady progress.

Home in England, Wendy's speech was slow to develop and hard to understand and when speech therapy started at

primary school, a high arch to her palate was pinpointed as the cause of her articulation difficulties.

At school, Wendy made slow progress, repeated some classes and had remedial support but continued in mainstream education through to upper school. Tests revealed an IQ score of between 55 and 74. The educational psychologist commented how sensible, mature and self possessed Wendy was at the age of 12, when she received a statement of special educational needs. She left school able to read and write well and went on to college.

As an adult, Wendy came into her own. She passed her driving test, held down a full time job in a factory, married and had two children. By her own description, she became a 'happy, friendly, helpful, bubbly' person.

When her son Jason was born, a healthy seven pounds four ounces, he showed the same inability to gain weight as Wendy. He had the same high arch to his palate and a hernia in the groin. From birth, Jason also experienced seizures, although by the age of three the frequency dropped from two or three a day to around once a week, usually triggered by stress.

The doctors investigated and found in both Jason and Wendy the same ring 21. Like his mother, Jason has made steady progress, sitting at a year, walking at two and a half and using single words from the age of three. It is too early to know how Jason will develop, but so far he is 'a happy little chap'.



## Support 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 is believed to be the best available at the time of publication and has been verified by Dr Nicky Foulds, consultant clinical geneticist, Wessex Clinical Genetics Service 2004 and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, Unique's chief medical advisor 2005.*

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