Ring 14
**Ring 14**

Ring 14 syndrome is a rare genetic disorder. Typically, children with ring 14 have a delay in development, some level of learning difficulty, seizures and may have a high rate of respiratory infections.

Ring 14 is caused by a rearrangement of one of the chromosomes in the cells of the body. Chromosomes are the microscopically small structures within the nucleus of the cells that carry information in the form of genes that enables healthy, normal development. Chromosomes come in pairs of different sizes and apart from the sex chromosomes (two Xs for a girl and an X and a Y for a boy), they are numbered from largest to smallest approximately according to size from number 1 to number 22.

Chromosomes have a top (short) arm called p and a bottom (long) arm called q. In people with ring 14, both ends of one chromosome 14 have broken off and joined to form a circle, usually leaving out some chromosome material and genes. The p arm of chromosome 14 is very small and can usually be lost without apparent harm because similar genes are available on other chromosomes, so many of the effects of ring 14 are believed to be caused by losing genes from the q arm.

The long arm typically breaks at bands 14q32.2 or 32.3, although breaks at 14q31 and 14q24 are also known. Whatever the amount of chromosome material lost, the main features seem to be usually the same (Schmidt 1981; Fryns 1982; Wintle 1995).

**Mosaicism**

Most people with ring 14 have the ring chromosome in all their body cells. Some people have some cells with the ring chromosome and some with a different chromosome make-up. This is called mosaicism and your geneticist will tell you if this is what your child has.

Mosaicism appears to result in similar features to full ring 14 syndrome. Three people have been described in the medical literature, including a mother of average intellectual ability who suffered seizures during early childhood and was discovered to have ring 14 after the birth of a more severely affected daughter, also with ring 14. A Unique member who is mosaic for ring 14 is particularly severely affected (Gilgenkrantz 1984; Rethore 1984; Portoian-Shuhaiber 1986; Matalon 1990; U).
Main features

- Learning disability. The level is variable and depends to some extent on the frequency and severity of seizures. The ability to learn can be within the normal range
- Developmental delay
- Seizures. These are of variable types and are typically hard to control. Occasionally children outgrow seizures
- Repeated infections, especially respiratory (Zelante 1991; Morimoto 2003; Casas 2005).

Families say …

“She is extremely loving and affectionate. She also likes to tease us and play games. She has an adorable laugh and is quite bright and intelligent. She is also physically beautiful, somewhat exotic looking.

“Eli has terrific presence!”
How rare is ring 14?

It is not known how many people have ring 14 but they are certainly rare. More than 40 people have been described in the medical literature but these only represent a fraction of the total. When this leaflet was published, Unique had 28 members with a ring 14 chromosome (Ono 1999).

Other features

- Hypotonia (floppiness, low muscle tone), usually apparent soon after birth
- Slow growth during pregnancy, small to normal size at birth and sometimes slow postnatal growth
- Microcephaly (an unusually small head)
- White, yellow or grey spots on the retina and/or greyish colouring specifically of the macular area, a part of the retina. This does not affect vision. The retina, at the back of the eye, is the place where light signals entering the eye are converted into nerve signals to the brain
- Feeding difficulties and problems with weight gain
- Distinct facial features
- Puffy hands and/or feet. The feet may be flat
- Pale or coffee-coloured patches of skin

(Lippe 1981; Schmidt 1981; Fryns 1982; Zelante 1991)

Lifespan

Babies born with ring 14 typically have no major organ defects and neonatal respiratory difficulties are not usually severe. So most people with ring 14 are quite healthy.

However, seizures are an almost universal feature and can be serious. Parents can expect to be trained to manage a long-lasting seizure or one that occurs at night. Some parents have bought infrared video cameras to allow observation during sleep (Lippe 1981; Riley 1981; U).

Growth and appearance

A child with ring 14 will look much like other children, although she or he may well be short. In one series, 24/33 children were unusually short and in the Unique survey 7/11 children were short for their age. Mean birthweight is low at 2578g/ 5lb 11oz and intrauterine growth retardation may be the first prenatal marker of the syndrome. Postnatal growth patterns are variable and may be normal. Some children in the Unique survey grew at an uneven pace with periods of no growth interspersed with rapid catch-up (Riley 1981; de Blois 1990; Matalon 1990; Zelante 1991; U).

A disproportionately small head is typical and was noted in 28/32
children. In the *Unique* series at least 7/11 children had microcephaly. Five children whose overall size was recorded as small also had a proportionately small head (Zelante 1991; U).

The facial features that experienced doctors notice may not be obvious to parents. Although none of the parents surveyed by *Unique* mentioned their child’s appearance as being out of the ordinary, the following features have been noted as typical by doctors: epicanthic folds (skin folds across the inner corner of the eye) 26/26; high forehead 21/21; long, narrow palpebral fissures (openings for the eyes); oval face 20/22; broad nasal bridge 19/27; short neck (with extra skin, sometimes described as ‘buffalo hump’) 18/27; flat occiput (back of the head) 9/15; dolicocephaly (a long, narrow head shape) 9/16; micrognathia (a small lower jaw) 9/20; low set ears 10/24. A high palate is also common and was noted in 14/19 children. However, some children with ring 14 do not fit this facial stereotype (de Blois 1990; Zelante 1991; Morimoto 2003).

**Eli and his chromosomes**

[Image of chromosomal analysis with Ring 14 highlighted]

**Below**

**Age 4, with the dolphins**

[Image of Eli and a woman with a dolphin]
Seizures

All children with ring 14 syndrome known to Unique and reported in the medical literature have developed seizures. Combined data from the medical literature and the Unique survey show that most babies (18/29) had their first seizure at 6-9 months. Only six babies were affected at three months or less and in another five the first seizure occurred between 12 and 28 months. There is one child whose story is on a ring 14 website (see Sources of Support) who had not developed seizures at the age of 8 years (Zelante 1991; Morimoto 2003; U).

Seizures are of varying types and most children have more than one type. The type may vary in one child with age. Seizures may occur cyclically or be associated with sleep and with waking. Among the triggers noticed by parents are childhood infections, fevers and accidents. In around half of children MRI and CT scans have revealed underlying brain pathology. Although electroencephalogram (EEG) anomalies were found in 16/20 children, there was no single typical pattern (Sparkes 1977; de Blois 1990; Zelante 1991; Shirasaka 1992; Ono 1999; Morimoto 2003; U).

Despite the reputedly intractable nature of seizures in children with ring 14, the Unique survey shows that in many seizures are controlled or their frequency is markedly reduced by a dynamic policy of multi-drug therapy using newer antiepileptic medications. A small number of children become seizure-free and many have weeks or months of remission. In most other children medication markedly reduces the frequency of seizures, although they remain hard to control. One Unique member had a seizure-free spell of two years, another adult in Unique has been seizure-free without medication since the age of 3 and there is a research report of an adult with ring 14 who outgrew seizures at the age of 2½ (Riley 1981; Morimoto 2003; U).

Learning and education

Children with ring 14 syndrome typically face some degree of learning disability and children usually thrive best in a school equipped to teach children with moderate to profound learning difficulties. However, some people have no learning disability.

Research reports and the Unique survey agree that the level of disability is variable. Out of fifteen Unique members whose intellectual ability was scored, nine were rated severe, five moderate and one was too young for assessment.

Some children learn to read and write. Lisa, at 20, could write her name and one or two numbers, read letters and one or two words and could count to 20. More typically, Unique members do not learn to write. Many families and medical researchers report that seizures affect a child’s learning ability although the effect may be transient (Lippe 1981; Riley 1981; Schmidt 1981; Howard 1988; Matalon 1990; Zelante 1991; Morimoto 2003).
Speech and communication

Half of Unique’s members use at least some words. Typically, first words emerged in the third or fourth year and one girl speaks fluently. Lisa, who started to talk at nine months, could communicate needs, feelings and opinions and used complex sentences. Unless she was agitated from a seizure ‘her communication skills are excellent!’ her mother reported. Chris, at 8, asked simple questions like ‘Where’s my mum?’ or made appropriate remarks like ‘Yum! Yum!’

Other members used single words and supplemented speech with signing, gestures, eye pointing, picture exchange systems and vocal noises. In a pair of three-year-old twins, each with ring 14, one had a vocabulary of five to 10 words while the other had no speech but followed two to three-word instructions.

Some children show understanding in advance of expressive language. In his third year, Matteo was using a few words but understanding complex three-part commands and at 10 Joanne was able to follow instructions.

Most families noted that speech and language was more limited when seizures were frequent and five families specifically recorded deterioration over time in speech and language (Sparkes 1977; U).

Sitting, moving, walking

The evidence from the Unique survey is of a variable delay in motor development. In a few children the delay was minor but most started to sit and walk very late. One or two did not walk. Acquiring advanced mobility skills was also variable, with some children cycling, climbing and dancing while others depended on walking aids and support. The hypotonia that many people with ring 14 syndrome experience is a major factor and all children benefit from physiotherapy and occupational therapy.

These snapshot observations provide an insight into the range of mobility experience of Unique members.

- Chloe, at 2, walked, ran, climbed up and down stairs and was learning to kick a ball
- Eli started walking with support at 30 months. At 3, he could take a few steps but preferred to crawl or use a walker, in which he also liked to dance. He enjoyed swimming, swinging and bouncing
- Cameron walked for two months from 14 months. After a setback with seizures he learned to walk again at 20 months
- Anneliese walked at three and at eight walked well on her own but preferred a wheelchair for long distances
- Kenneth, at 13, could not walk or sit
- Lisa, at 20, loved to walk long distances for exercise

“Chris is good at remembering some things but cannot communicate back.”

“Matteo’s psychomotor development is not homogeneous. In some areas he’s absolutely in line with his age and in others, like language and concentration, he is delayed.”
Medical concerns

Typically, children have no major organ defects. There are three reports in the medical literature of children with heart murmurs. The Unique survey revealed no members with heart defects (Amarose 1980; Lippe 1981; U).

- **Respiratory infections**
  Vulnerability to infection, particularly respiratory infections, is fairly common, reported in 8/37 children in one series and 10/15 Unique members of all ages. In one child frequent respiratory infections were a reason for cytogenetic referral, in another they were reported as the only health problem. It is known that some children with ring 14 are immunodeficient and it has recently been shown that two children with low immunoglobulin (antibody) levels in their blood were missing one or more of a cluster of genes (known as IGH) in band 14q32.33 that are important for making immunoglobulins. All children with ring 14 who have lost any of the IGH genes and any children who catch repeated infections are recommended to have a blood test to check their immunoglobulin levels. If levels are low and the child has repeated infections, treatment with intravenous immunoglobulin should be considered.

  The research group that recently identified the loss of IGH genes as a possible cause of repeated infection also suspects that giving intravenous immunoglobulin may help with seizure control. In this context, the family of a 12-year-old reported to Unique that better seizure control and fewer respiratory infections went hand in hand (Schmidt 1981; de Blois 1990; Zelante 1991; Casas 2005; U).

- **Retinal anomalies**
  White, yellow or grey spots on the retina and/or greyish colouring of the macular area of the eye have been reported in 12/22 people. These spots do not affect vision and families are usually unaware of them. One Unique family reported abnormal retinal pigmentation (Schmidt 1981; Zelante 1991; U).

- **Genital anomalies**
  Undescended testes with or without hypospadias, where the hole usually at the end of the penis is on the underside instead, have been reported twice in medical literature and noted in one Unique member (Dzarlieva 1977; Lippe 1981; Matalon 1990; Kristensen 1992; U).

- **Lymphoedema of the hands and feet** (puffy hands and feet)
  This has been described in the medical literature but not by Unique members. The feet may also be flat (Iselius 1980; Zelante 1991).

  Other conditions have been described singly or in only one or two children and may not be typical of ring 14. They include intention tremor (movements directed at a goal produce shaking or trembling in the moving body parts, especially the hands); early childhood stroke (at 6 months);
Other concerns

Teeth

Unusual patterns of teething have been reported by two Unique families and in one research report. One child had late emergence of teeth, with none visible at age one; another had early teething; a third was born with two teeth. On removal, two ‘jelly-like’ teeth appeared in their place (Lippe 1981; U).

Skin

Unusual skin pigmentation is often described and may be a marker of mosaicism. Patterns include linear pigmentation, irregular vitiligo, linear café au lait spots on the abdomen and buttocks and dark & white streaks & whorls, as well as light spots on the trunk and coffee-coloured spots on the abdomen. Only two Unique members had abnormal pigmentation and in one child it was minimal (Schmidt 1981; de Blois 1990; Zelante 1991; U).

Behaviour

There has been no formal survey of the effects of ring 14 on behaviour. This information comes from the Unique survey. Most families did not report behaviour problems. A minority of families reported overactivity and hyperactivity. It is not known whether hyperactivity is a side effect of medication, a general characteristic or a part of ring 14 syndrome. These snapshot descriptions come from Unique families:

- At 2, unable to play other than fleetingly
- At 2, too hyperactive to complete psychological testing. Especially hyperactive during a seizure-prone phase. Spells of maturation are noted to alternate with regression during seizure crises
- At 3, hyperactivity had improved since vagal nerve stimulation in which a battery-powered device similar to a pacemaker was implanted under the skin delivering mild electrical stimulation to the brain via the vagus nerve. Therapy can reduce the severity and frequency of seizures in some patients
- At 20, had outgrown the hyperactivity and attention disorder she experienced as a youngster and preferred to spend her time quietly alone

"When she started lamotrigine (for seizures), she began to display aggressive behaviour (kicking, biting, pulling hair) when she didn’t get her own way. We now give her choices and warn her of an approaching change in her schedule. We also use a low-dose tranquilliser. She is much better now."
A small number of families reported **challenging behaviour**:
- At 4, could be restless, pull hair and throw objects
- At 8, resisted everything you ask him to do
- At 12, showed frustration by hitting and biting

**Independence**

Most children with ring 14 syndrome who have been studied have experienced considerable developmental delay. They have difficulty in communicating their needs and in co-ordinating the actions of daily living. For this reason, they are likely to need support throughout their lives.

The level of self care people reach is quite individual. *Unique’s* members include people who are able to dress and feed themselves and are fully continent as well as adults who need round the clock care.

**Food and eating**

Ring 14 syndrome does not appear to cause any specific feeding problems. However, people with chromosome disorders often have difficulties with feeding. For babies, these include difficulty coordinating swallowing with sucking, gastro oesophageal reflux, where feeds and stomach contents return into the gullet and are often vomited or may be inhaled, and poor weight gain.

Children may continue to accept a limited range of textures and quantities or on the other hand may overload their mouth and fail to chew. Antiepileptic medications may cause nausea and so suppress appetite but more commonly cause an increase in appetite, reported by some *Unique* families as voracious (Lippe 1981; Riley 1981; Matalon 1990; U)

**Will the pregnancy be different?**

Pregnancy is usually unremarkable, but by the second trimester slow growth may be apparent and may well be the only sign on the mid-pregnancy anomaly scan. Ring 14 can be detected during pregnancy by examining cells obtained by chorion villus sampling at around 11 weeks or by amniocentesis around 15 to 16 weeks.
Did this happen due to something I did wrong?
Rearrangements occur in chromosomes as part of evolution. They affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. So there is no reason to suggest that your lifestyle or anything that you did caused the ring chromosome to form.

Why did this happen?
- Has the child inherited the ring 14 from a parent?
  About 99 per cent of ring chromosomes occur out of the blue. Geneticists call this type of event de novo, which means that the child with the chromosome disorder is the only person in the family with the chromosome disorder. A blood test will then reveal that both parents have chromosomes without rearrangements that could have caused ring 14 and their chances of having another affected baby are usually no greater than for anyone else.
- What are the chances of a parent with ring 14 passing the ring on to their children?
  Very occasionally ring 14 may be passed from mother to child. Father-to-child transmission has not been recorded, perhaps because the ring chromosome in some way interferes with sperm creation. This suggests that boys with ring 14 may not be fertile as adults (Riley 1981; Matalon 1990).

A karyotype of a boy with ring 14. This would be written $46,XY,r(14)$
Ring 14 is a support group for families affected by ring 14 syndrome. The centre is in Italy but it operates worldwide and aims to disseminate information and to promote and fund research.

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There is a Facebook group for Ring 14 at www.facebook.com/groups/ring14

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 information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr Melanie Manning, clinical instructor, Divisions of Cytogenetics and Medical Genetics, Stanford University School of Medicine, California and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK 2004. (PM)