Ring 15
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Ring 15 is a very rare genetic condition caused by having an unusual 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 15 from each parent.

In people with Ring 15, the ends of one of the chromosome 15s have joined to form a circle. Some genes are often lost when this happens and these missing genes cause many of the features of Ring 15 syndrome. No genes have yet been found on the short arm of chromosome 15 that could cause illness or defect, so losing a bit of it or all of it does not apparently matter. Losing genes from the long arm is important.

There is a less common type of Ring 15 that occurs when a third chromosome 15 is present as a ring. This is called supernumerary (extra) ring 15 and the features are different to those of the Ring 15 disorder described in this leaflet.

Sources
So far, no formal study of large numbers of people with Ring 15 has been carried out, but enough similarities have been noticed between people with Ring 15 for a ‘Ring 15 syndrome’ to be described. The information in this leaflet comes from the medical literature and from Unique’s members with Ring 15 (marked 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. You can search for the abstracts or original articles on the internet in PubMed or obtain abstracts and key articles from Unique.
Main signs
Not all children with Ring 15 will show all these features. Most children show the first three signs, but each of the other features is found in less than half of people with Ring 15. The spectrum of effect is extremely broad, from being scarcely noticeable to having a profound impact.

- Growth delay that starts before birth and continues through childhood, so that children are very short.
- Some degree of learning difficulty. This is quite variable.
- Small head (microcephaly).
- Speech delay.

Other features
- Heart defects.
- Floppiness (low muscle tone, hypotonia).
- In boys, unusual genital features such as undescended testes or hypospadias (where the hole is on the underside of the penis instead of at the end).
- Club foot (talipes).
- Typical facial features, including a pointed shape to the face, often with widely spaced eyes and possibly unusually shaped ears.
- Short fingers and sometimes small hands. The little (fifth) fingers may be bent.
- Patches of different coloured skin.

Why do children with Ring 15 differ from each other?
In some children more chromosome material and genes have been lost from the end of chromosome 15 than in others. The geneticist will tell you where the breakpoints are on your child’s ring chromosome 15. Generally, children with similar breakpoints will have more similarities than children with different breakpoints. Children with a mixture of cells with the ring chromosome and cells with normal chromosomes (mosaicism) are usually more mildly affected.

Some children have a type of mosaicism where the ring chromosome disappears, so that some of their cells contain only one chromosome 15. When there is only one chromosome 15 in a cell, there can be differences depending on which parent the chromosome came from.

See Different Ring 15 chromosomes, page 15.

Families say …

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

“She is such a sweet, happy baby. Her smile melts your heart. She has just learned to crawl and will squeal when she crawls over to a toy - 10 months.”
Does Ring 15 cause serious medical conditions?
Most people with Ring 15 do not have serious medical conditions and there are many reports in the medical literature of adults with this chromosome disorder. A minority of babies, around one in three or five, are born with a heart condition but many of these are not serious. Other heart problems may need to be corrected surgically (Fryns 1979; Butler 1988; Borgaonkar 2003).

How can Ring 15 affect pregnancy?
There has been no formal research into Ring 15 pregnancies. Features that may be apparent are the baby’s small size and slow growth rate in the womb and non-specific signs have been noted, such as an increased nuchal translucency (the skin fold at the back of the baby’s neck is unusually thick).

Among six Unique members, three mothers had problem-free pregnancies. Two had unusually small amounts of amniotic fluid (oligohydramnios) and the baby was small for dates during pregnancy. Another mother had excess amniotic fluid (polyhydramnios). Three babies were born prematurely, all around seven months (Butler 1988; Liu 2001; U).

Newborn babies with Ring 15
The picture is very variable. Babies may be entirely healthy as newborns. Among six Unique babies with Ring 15, two had no health problems and this has been recorded in the medical literature as well. One Unique baby who was born at term sucked weakly and fed slowly, taking an hour to drink an ounce or two of formula milk. The three Unique babies who were born prematurely spent many weeks in neonatal care and needed breathing support as well as feeding through a tube direct into the stomach (gastrostomy) or passed down through the nose (Butler 1988; U).
Will a child look different from other children?

The facial features that doctors look for when considering whether a child might have a chromosome disorder can be very subtle. To many parents, their child looks no different from other children although it is easier to see the similarities in a group of children with Ring 15. A triangular face with wide-set eyes and a small head are characteristic of children with Ring 15. Other typical features observed in one-fifth to one-third of children are a broad nasal bridge, a rounded forehead, unusually shaped ears and a small lower jaw. One researcher has commented that children may appear older than their actual age (Fryns 1979; Butler 1988).

Children with mosaic chromosome disorders sometimes have areas of lighter skin. Both light skin and darker café au lait patches have been described in a minority of children with Ring 15. Recently a girl has been described with skin pigment changes, light brown patches and premature hair greying whose breakpoint on the long arm of chromosome 15 was close to the telomere (tip), beyond any functional genes, suggesting that the skin colour changes are caused not by any gene loss on chromosome 15 but by the mosaicism often associated with a ring chromosome. Just how a mosaic pattern of chromosomes causes skin pigment changes is not yet understood. Among nine Unique members, three had patches of light or dark skin. One family commented that the café au lait patches on their daughter’s hips and stomach faded over the years (Morava 2003; U).

Families say …

“Apart from being short, she looks very like other children to me. What I would notice is her speed of reaction, which is a little slower than other children.”
How is growth affected?
Some growth delay is common in all ring conditions, whichever chromosome is involved. The reason is thought to be the ring changing size or disappearing when cells copy themselves. If this happens, the cells may die and this can cause growth delay both before birth and afterwards. Studies have shown that children with larger deletions are not necessarily smaller but in Ring 15 some children are extremely tiny and it is likely that losing a particular gene called the IGF1R gene near the end of the long arm of chromosome 15 intensifies the effect on height.

The small size is proportionate but children’s hands and fingers may be especially tiny. Babies are typically born small and with a low birth weight and remain short. Most Unique members with Ring 15 measured around 18 inches long (48cm) at birth and expect to reach around 5 foot (152cm) as adults. However, one girl who measured 14 inches (36cm) at birth was only expected to grow to 3 to 4 foot (91 to 122 cm) and another was only predicted to reach 4’6” (137 cm).

At birth, term babies in the Unique series weighed between 4lb12oz (2154g) and 5lb13oz (2650g). Babies born prematurely were lighter, one weighing 2lb 7oz (1105g) at 32 weeks.

However, although small size is very common, it is not universal. One Unique baby weighed 4lb 4oz (1927g) when born prematurely at seven months and at seven years old was taller than average.

Some children have responded well to treatment with injections of growth hormone. One four-year-old child’s predicted adult height rose by1.6 inches (4 cm) after two years of growth hormone treatment (Fryns 1979; Ledbetter 1980; Butler 1988; Peoples1995; Nuutinen 1995; Rogan 1996; U).

What about food and eating?
All newborn babies known to Unique and described in the medical literature have had initial feeding difficulties, although some babies have successfully breastfed. They may suck weakly and find it difficult co-ordinate sucking, swallowing and breathing. Around one baby in five has a high arched palate (roof of the mouth) which makes
sucking harder and others have difficulties in moving their tongue to allow a normal feeding action. Some babies also bring back their feeds frequently and forcefully and are at risk of inhaling milk as it flushes up their food pipe. This is called gastrooesophageal reflux and can be helped by holding a baby upright for feeds and letting them sit in a semi upright position afterwards. Your doctor can prescribe milks that are thickened and easier to keep down and medicines that help feeds to stay down and act against the acid effect of stomach contents on the food pipe. If these measures do not work, it is possible to strengthen the valve between the food pipe and the stomach with a surgical operation called a fundoplication. Occasionally babies need to be fed directly through a tube to the stomach (a gastrostomy) for some months or years. Finally, most children with Ring 15 have a tiny appetite (Butler 1988; U).

How can Ring 15 affect a child’s ability to learn?

A wide variation in children’s ability to learn has been noted. Most children are believed to have a moderate learning difficulty but some are only slightly affected and others may not be affected at all. Generally children’s memory is reported as good, but abstract thinking and mathematical skills have been reported to be less well developed (Fryns 1979; Meinecke 1980; Butler 1988). In the Unique series, the level of learning difficulty was mild to moderate, but one child had a severe learning difficulty. Parents reported that an adult in his 30s could read short stories, recipes and the Bible and could write short notes as well as copying print well. Two eight-year-olds had different levels of achievement. One started to read and write at the age of 5 and had basic computer skills. The other did not have any formal academic skills at that point. A six-year-old was reading simple words, writing some letters and starting to use a keyboard. A 15-year-old girl was writing and reading names and simple words. Some children were reported to have an excellent memory; one of the children had a precise forward-planning memory but poor recall of recent events. An adult had a better short term than long term memory.

Families say …

“She reads short sentences and can write family names with capitals as well as some words and short sentences. She has no problems remembering what to do days and weeks ahead but has a problem to remember what she did yesterday and what she has learned at school - age 15.

“Her memory is good once things have sunk in but this can take a while. She is very musical - age 8.

“She has an extremely good memory, she is good at grooming, doing chores in the house and packing her own backpack for school - age 6.”
In the small *Unique* series, most children attended a mainstream (regular) school with support, but three children attended a special school. Two children learned better with visual support, and the parent of one noted that ‘repetition and bribery’ help (U).

**How can Ring 15 affect speech?**

Children with Ring 15 usually speak late and there is some evidence that this may be caused by specific difficulties in co-ordinating and moving their tongue as well as by learning difficulties. When this is the case and when children understand much better than they speak, they may learn to communicate well by signing before their speech develops. When they do speak, they may have difficulties in making specific speech sounds. One review of six children with Ring 15 showed that they said their first words on average at 20 months (Butler 1988).

What *Unique* families said supported the evidence from research. Speech and language difficulties that families reported included: difficulties making the sounds of speech (articulation); problems putting sounds in the correct sequence (ts>st or sk>ks); difficulties saying longer words (*vegetable* as *vegeble* at 6 years); difficulty in using longer or more complex sentences; difficulty processing more than one instruction in one sentence.

Six children old enough to talk all had speech delay or difficulty and were reported to understand better than they spoke. The difference between speaking and understanding was less obvious in the adult with ring 15 and in one child who talked well from the age of 14 months. The one child who was initially taught to sign progressed to using speech instead. Another child with severe learning difficulties who had not learned a signing system was still able to communicate well through gestures. An adult with Ring 15 used 5 to 7 word sentences and had some understanding of the meaning of tenses but tends to be repetitive.

A cleft or high arched palate can affect a child’s speech quality and is common in children with chromosome disorders (U).
How can Ring 15 affect a child’s ability to move and to use their hands?

Gross motor development is the development of the large movements a child needs to move independently and reach traditional milestones, such as rolling, sitting, shuffling, crawling, walking and running. Fine motor development is using their hands.

A review of babies and children with Ring 15 showed that they were on average somewhat delayed in learning to move. They sat on average at 11 months and walked at 22 months. Around a quarter were unusually floppy (hypotonia, also called low muscle tone) (Butler 1988).

Unique families’ experience supported the research view. Babies sat a little later than expected (from 6 to 10 months) and walked late (from 20 months to 3 years). One child sat much later, at 18 to 24 months, with support. Most babies were floppy but with physiotherapy and occupational therapy outgrew this. One child of 6 and an adult had taut muscles (hypertonia, high muscle tone) and this can limit movement and cause pain. However, some older children and adults enjoyed a wide range of sports and activities: ballet, tap, jazz, swimming, gymnastics and tennis for one and baseball, bowling, swimming, cricket, soccer, golf and bowling for an adult.

Children with Ring 15 can have especially small hands and short fingers. This can affect how well they can hold a pen or use a keyboard, although Unique’s evidence on keyboard skills is that they are competent (Ledbetter 1980; U).
Medical concerns

Some children with Ring 15 are entirely healthy. However, these are the more common health problems that have been reported.

- **Heart**
  A child with Ring 15 can expect to have a series of tests on their heart. This is because there is evidence in published research that some children may have a heart condition. Some heart conditions resolve naturally with time. Others need to be corrected with surgery (Butler 1988; Schinzel 2001).
  Among nine *Unique* members, six had no reported heart problems. Two were born with a hole between the lower chambers of the heart (ventricular septal defect, VSD). One also had a hole between the upper chambers (atrial septal defect, ASD) and needed surgery. An adult with a slow and irregular heartbeat was otherwise healthy.

- **Brain**
  An unusually small head (microcephaly) is very common in people with Ring 15. Among *Unique* members, in one child the plates of bone that form the skull joined prematurely, putting pressure on the brain inside. This child has needed two operations (craniotomy), after each of which his development has apparently speeded up (Butler 1988; U).

- **Spine**
  Among six *Unique* members, three have a mildly curved spine (scoliosis). Researchers have also noted this (Butler 1988; U).

- **Genitals**
  A review of ten boys with Ring 15 showed that one in three was born with undescended testes and one in five with hypospadias, where the hole normally situated at the end of the penis is on the underside instead. (Butler 1988). Among three *Unique* members, one needed surgery to bring down the testicles into the scrotum (sac). Two other families reported no problems with genitals or sex organs (U).

- **Intestinal**
  Among *Unique* members, one had severe constipation caused by missing nerve cells from the intestines (Hirschsprung’s disease) and another child had chronic and severe constipation. Another initially developed constipation when she was put on solids (to accelerate her
growth) at the age of three months but the problem resolved (U).

■ Kidneys
A child with Ring 15 can expect to have tests on the kidneys. This is because evidence shows that as many as one fifth of children may have a kidney condition (Schinzel 2001). Among six Unique members, one had a mildly enlarged left kidney (hydronephrosis).

■ Seizures
Among Unique members, two have had seizures and in a third (an adult) they are suspected. One child experienced no more seizures after the age of two years and stopped needing medicines. Another child had absence (petit mal) seizures (U).

■ Joints
In three Unique members, joints were affected. One adult had fused elbows, limiting movement, and three children had incorrect development of the hip joint (hip dysplasia). To correct the hip joints, two children have needed bracing in a harness and one child needed surgery and plaster casts. At 19 years, one youngster also had a dislocated kneecap (U).

■ Hands and feet
A review of 27 people with Ring 15 showed that almost half had short fingers and a quarter had bent fifth fingers and very small hands. Other features that may occur include underdeveloped thumbs, clenched fingers, overlapping toes and toes joined by a bridge of skin. Feet are often very small as well and 15 per cent of children in one review of published research were born with clubfoot – talipes (Fryns 1979; Butler 1988; Schinzel 2001).

What about hearing?
Among nine Unique members, six had normal hearing and the other three had the type of hearing loss that is normally associated with multiple ear infections or structural changes in the middle ear (conductive hearing loss). Two children had grommets (tubes) placed in the ear drum to balance air pressure inside the ear and one adult with Ring 15 needed surgery to rebuild the eardrum and the bone structure in the middle ear (U).

What about vision?
Most children with Ring 15 in Unique have good eyesight. A quarter of parents reported squint (strabismus) needing
surgery, one child was extremely short sighted and two further children had an astigmatism, a common defect that distorts images and is usually caused by an unusual curve of the eyeball. One child has slight defects of the macula part of the retina at the back of the eye that may impact on her vision (U).

**Puberty**
The published research evidence suggests that puberty is normal in terms of sexual development. Unique’s evidence is limited, but among two adult men, one experienced incomplete puberty and the other apparently developed normally in terms of sexual activity (Matsuishi 1996; U). Puberty also progressed normally in one fourteen-year-old girl.

**How can Ring 15 affect a child’s behaviour?**
Research reports suggest that people with Ring 15 are pleasant, co-operative and sociable and mix well in social situations (Borghgraef 1988; Meinecke 1980). Family reports from Unique agreed with this. All families who have given information about their child’s behaviour have commented on their high levels of sociability and overall happiness. Although one family commented that their daughter is shy, others have noticed inappropriate friendliness and one family commented on inappropriate touching of women by a seven-year-old boy. Children can be extremely active; two families commented that repetition of the same phrase or question can become irritating. The generally problem-free behaviour of children with Ring 15 may mean that families are not offered behavioural or psychological support. They do, however, need parenting guidance to maintain their children’s good behaviour, teach clear limits and to support them if behaviour becomes negative.

**Personal care**
Unique families reported that their children became dry and clean in the early years of primary school if they had not achieved this earlier. Self care skills such as washing, tooth brushing and dressing depended mostly on how good their hand control was and most families
reported that their children gained independence in the early school years, apart from complex tasks such as tying laces and managing buckles. One adult with Ring 15 developed incontinence at the age of 28 after being clean and dry since childhood. An underlying cause remained uncertain (U).

What therapies may be needed?
All Unique members who have given information on therapies have received physiotherapy, and most have also had occupational therapy and speech and language therapy. All families whose child received physiotherapy (starting between birth and 12 months) found it helped them to achieve skills such as rolling, sitting and walking and all children except for one seven year old were walking independently. Speech therapy for most Unique members started around age one and continued into middle childhood, usually to make speech clearer or more fluent. Children received occupational therapy starting from four months to improve co-ordination and hand use and one baby was offered this therapy for oral (mouth) stimulation to encourage her to eat. One child was able to do without occupational therapy from the age of four; all other children were still receiving treatment in middle childhood.

Will a child ever be able to live independently?
This depends on individual development. There are probably some people living independently in the community who do not know that they have Ring 15, while others will remain dependent on others. The

Families say …

“He was working three days a week with the help of social services but recent health problems disrupted this. He was toilet trained until the age of 28 but has recently developed incontinence for which no cause has been found and has been depressed as a result - adult.”
Families say …

“She loves cooking, singing, dancing, making things with her hands, playing games and music - age 15.

“She loves company, is good at drawing and painting and loves her dolls - age 8.

“He loves riding the tractor with daddy after dinner, visiting family and friends, animals, riding horses, school and camp. He is very happy and social and loves ladies of any age - age 7.

“She especially loves to participate in cooking and cleaning. She is very social and has a great sense of humour - age 6.

Evidence from research reports and from Unique is that some people with Ring 15 may become independent enough to live in a sheltered setting.

Might he or she be able to have children?

Published research shows that it is likely that women with Ring 15 will be fertile, but will need high-risk care during pregnancy because of their own short height and the probability that they have a small uterus, as well as the likelihood of passing on the ring chromosome. Among three women, one had normal sexual development but no reported pregnancies, one had three pregnancies, including two pregnancies with Ring 15 and a miscarriage while another also had three pregnancies: one healthy son, a miscarriage and a baby with Ring 15 (Fujimaki 1987; Horigome 1992).

Men with Ring 15 are likely to be infertile. Among three men described in the medical literature with Ring 15, one had undescended testes and two either had no sperm or very small quantities of relatively inactive sperm. One man was only found to have a Ring 15 when investigated for infertility. Other men with Ring 15 may have a slightly feminine build and have small testes (Moreau 1982; Borgaonkar 2003).

What do children with Ring 15 enjoy?

There has been no formal study of this, but in Unique’s experience, children with Ring 15 particularly enjoy social activities.

A good ear and a lovely singing voice - age 8.
Why did this happen?

Ring 15 usually occurs out of the blue for no apparent reason and tests show that the parents have normal chromosomes. Occasionally, a ring can be passed from mother to child. Nothing that parents did or did not do during pregnancy caused this to happen and it is just as likely to affect the chromosome 15 that came from the father as the chromosome 15 that came from the mother (Horigome 1992; Matsuishi 1996).

Different Ring 15 chromosomes

The effects of Ring 15 depend on:

- Different breakpoints. The amount of chromosome material lost from the long arm of 15 differs between people. Material lost from the short arm (15p) has not yet been found to cause any illness or defects.

- Mosaicism. Different cells may contain:
  - a single ring 15 and a normal chromosome 15
  - a double ring 15 and a normal chromosome 15
  - no ring chromosome 15 at all, as the ring has been lost, leaving one normal chromosome 15.

- In people who have some cells containing only one normal chromosome 15, the effects differ depending on which parent the normal chromosome 15 came from. This is caused by a process called **imprinting**, where genes have different effects depending on the parent of origin.

  Some people with Ring 15 are similar to people with **Prader-Willi syndrome** (PWS). Some of the hallmarks of Prader-Willi syndrome, where the genes from the father are not present or are not active, include short stature, small hands, overweight, impairment of sexual development and a small chin. This would occur if the ring 15 that has disappeared came from the father, leaving a single chromosome 15 from the mother.

  Other people with Ring 15 are similar to people with **Angelman syndrome**. The hallmarks of Angelman syndrome, where the maternal genes are absent or not active, include seizures, an unsteady walk, a happy disposition and more severe learning difficulties including delayed or absent speech. This would occur if the ring 15 that has disappeared came from the mother, leaving a single chromosome 15 from the father (Ledbetter 1980; Rogan 1996).

Could this happen again?

If the parents’ chromosomes are normal, it is very unlikely to happen again. But parents may want reassurance in their next pregnancy that their baby’s chromosomes are normal. A ring chromosome can be seen in cells taken from amniotic fluid and parents who are considering amniocentesis should be offered the chance to discuss it at their genetics clinic.
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 Eva Morava, Department of Pediatrics, University Medical Center, Nijmegen, The Netherlands 2004 and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK 2005. (PM)