

# Ring 15

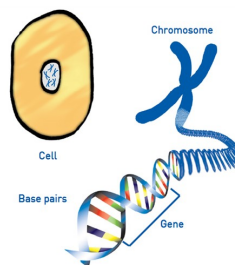


## Ring 15

Ring 15 is a very rare genetic condition caused by having an unusual chromosome. There are fewer than 50 reported cases in the medical literature (Eid 2013).

## Background on chromosomes

The human body is made up of billions of cells. These cells are important for carrying out different functions in the body, as well as housing the vital “instructions” that enable our body to work properly, which are contained within the DNA that make up our genes. Genes are grouped along thread-like structures called chromosomes that are packaged to fit inside our cells. Chromosomes cannot be seen by the naked eye but they are large enough to be studied under a microscope and come in different sizes, each with a short (p) and a long (q) arm. A normal cell in the body has 46 chromosomes, 23 received from the mother and 23 received from the father. The chromosome pairs 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 girl will have two X chromosomes (with a chromosome constitution represented as 46,XX) and a boy will have one X chromosome and one Y (with a chromosome constitution represented as 46,XY). Both will have two chromosomes 15, one received from each parent.



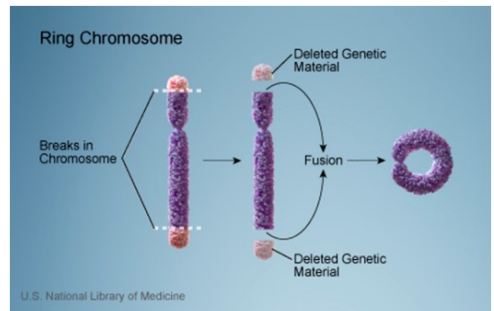
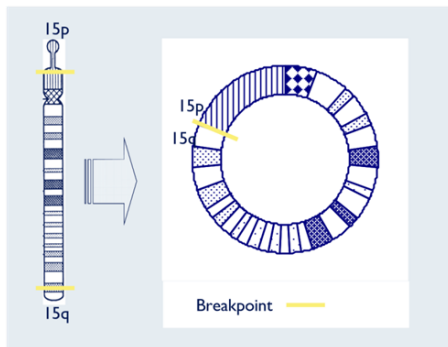
In those with a ring chromosome 15 (r(15)), there are two breaks in one of the chromosomes 15. One break occurs in each chromosome arm and the ends are joined to form a circle, like a ring. The genetic material in the extremities of the breakpoint is lost (deleted). Thus, some genes are often lost when this happens and these missing genes cause many of the features of ring 15 syndrome (See [Genes, pages 21 - 23](#)).

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

The information in this booklet is drawn from published medical literature and information from Unique members. The first-named author and publication date from articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>). If you wish, you can obtain most articles from Unique. Unique member surveys were carried out in 2004 and 2017. Unique is very grateful to the families who took part in these surveys.

The following diagrams show how a chromosome 15 can form a ring with loss of genetic material from either side of the chromosome. The breakpoints in the chromosome 15 may occur in different positions and different people will therefore have different breakpoints and consequently different amounts of lost genetic material. Thus, individuals with ring chromosome 15 may present with different features. More details about some of the important genes that may be lost when a chromosome 15 forms a ring can be found on pages 21 - 23.



## Different ring 15 chromosomes

The effects of ring 15 depend on:

- **Different breakpoints.** The amount of chromosome material lost from the long (q) arm of chromosome 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 different chromosome constitution due to the instability of cells with ring chromosomes, such as:
  - a single ring 15 and a normal chromosome 15 (usually present in the majority of cells).
  - a double ring 15 and a normal chromosome 15.
- **Imprinting.** The medical literature shows that a person with mosaicism may present with Prader-Willi syndrome (PWS) when two cell lines with different constitutions are present: one with two normal chromosomes 15 inherited from the mother and the other with a supernumerary r(15) originated from one of the father's chromosomes 15. When both normal chromosomes 15 are inherited from the father, the person may present with Angelman syndrome (AS). The presence of two chromosomes from the same parent is called uniparental disomy (UPD). Thus, UPD together with supernumerary ring chromosomes seems to be the cause a range of highly variable features similar to PWS or AS in some patients. In fact, the association between marker chromosomes and PWS has been documented in the past as a rare condition. This phenomenon

where the effects differ depending on which parent the normal chromosome 15 came from is a process called imprinting, where genes have different effects depending on the parent of origin (Robinson 1993; Bettio 1997; Kozot 2000; Dawson 2002; Roberts 2002; Werner 2004).

“ To know that there is a wide variety of ways that this diagnosis may or may not impact your child can be difficult and overwhelming. Reach out and ask for help when needed. Listen and respect the experts on various issues, but you are the only one that can see the big picture. Don't be afraid to advocate when you have to. Have patience with your child and yourself and don't forget to care for the others who are also supporting you and your child ” - mosaic ring 15, age 19

## Why did this happen?

Ring 15 usually occurs out of the blue (*de novo* (dn)) for no apparent reason and tests show that the parents have normal chromosomes. The ring chromosome may be formed as an error during the formation of gametes, or more rarely during development of the embryo. 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). Parents should feel reassured that no lifestyle change would have prevented this from occurring.

## Could it happen again?

If the parents' chromosomes are normal, the possibility of having another child with ring 15 is no higher than anyone else's. The extremely unusual events that have led to a baby with ring 15 is very unlikely to occur again.

However, in the rare cases of inherited ring 15, the chances are greater of having another child with the chromosomal abnormality. There is also a small chance that even though a blood test taken from parents shows normal chromosomes, a few of their egg or sperm cells could carry a ring 15. This is called germline (in the egg or sperm) mosaicism and could result in another baby with ring 15.

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.

## Diagnosis

In most cases, diagnosis of ring 15 happens after the baby is born but there have been a small number of reports of pre-natal diagnosis (PND). PND tests, including chorionic villus sampling (CVS) and amniocentesis to test the baby's

chromosomes, are usually undertaken following abnormal ultrasound features being picked up, for instance delayed growth. The features are often related but not definitely linked to ring 15 (Tan 2012), although with advances in ultrasound technology it is becoming easier to pick up features that could be linked to ring 15.

Within the *Unique* series there were only a few instances of PND with most diagnoses happening between 1 month and 2.5 years. Two cases of pre-natally diagnosed ring 15 identified congenital diaphragmatic hernia (CDH) in the foetus. This is an extremely rare condition where the diaphragm does not develop properly and can lead to poor lung function, which can affect a baby's breathing. Several genes that are important for normal diaphragm development are found on chromosome 15 at positions 15q26.1-26.2 (See Genes, Pages 21 - 23) (Britto 2014). In the *Unique* series there is no mention of CDH being a problem during pregnancy (Unique).

## Main features

Not all children with ring 15 will show all the features listed below. Most children show the first four 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.
- A 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 or low-positioned ears.
- Short fingers and sometimes small hands. The little (fifth) fingers may be bent.
- Patches of different coloured skin, reported on various places on the body and in a variety of sizes.

## 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 when the ring was formed 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 usually due to ring instability ([See Different ring 15 chromosomes, page 3](#)).

“ He has very good powers of observation and often accomplishes things unexpectedly that I thought he was incapable of. ” - ring 15, 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. ” - ring 15, 10 months

## 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 eleven *Unique* families for whom we have information relating to pregnancy, four mothers had problem-free pregnancies. In the other pregnancies, three had unusually small amounts of amniotic fluid (oligohydramnios) and in six cases the baby was small for dates during pregnancy. One mother had to have multiple scans due to concerns regarding the baby's heart and kidneys but both turned out to be fine. Another mother had excess amniotic fluid (polyhydramnios). Three babies were born prematurely, all at around seven months (Butler 1988; Liu 2001; Unique).

“ Perfect, a wonderful pregnancy. ”

“ Spotting, low amniotic fluid, little movement, growth delay. She was born prematurely at 32 weeks . ” - mosaic ring 15

## Birth and Newborn babies with ring 15

All newborn *Unique* babies had birth weights below the average for babies without chromosome anomalies, which is 3.4 kg (7 lb 8 oz). The range of birth weights among 12 *Unique* babies was from 1.1 kg (2 lb 7 oz) to 2.8 kg (6 lb 4 oz) with an average birth weight of 2.1 kg (4 lb 10 oz), although this does include three premature babies ([See How is growth affected?, pg 8](#)).

The picture in terms of health is variable and babies may be entirely healthy as newborns. Among ten *Unique* babies with ring 15, three had no health problems and this has also been recorded in the medical literature.

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 to 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 up their feeds frequently and forcefully and are at risk of inhaling milk as it flushes up their food pipe. This is called gastro oesophageal reflux disease (GERD) 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; *Unique*).

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. Another *Unique* baby born at term had severe colic but successfully breast- and bottle-fed for 11 months. He also developed complications due to a cow's milk allergy, but these were overcome with steroids and the replacement of cow's milk by soy milk. Another baby had trouble keeping food down as a newborn, which was later found to be due to delayed gastric emptying (slowing of food moving from the stomach to the small intestine). One baby born at term needed six days in neonatal care due to feeding difficulties and concerns about low blood sugar levels and kidney failure.

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 directly into the stomach (gastrostomy) or passed down through the nose (Butler 1988; *Unique*).

All *Unique* children grew out of their feeding problems, including a boy who had problems starting on solids due to a lack of the instinct to chew solid food. His feeding greatly improved once at school and "he no longer has to think to chew".

A follow up study of a 27-year-old patient, who when born weighed 2.05 kg, found that she had developed a problem



with compulsive overeating leading to her being overweight. Importantly, this is the only reported case of over-eating and could be due to extra deletions that have occurred from her chromosome 15 over time (Guilherme 2012) or could be completely unrelated to her chromosomal abnormality.

“ No problems in the newborn period. ” - ring 15

“ He couldn’t breastfeed. He also had projectile vomiting, diarrhoea, sleeplessness, failure to thrive and a wailing cry. ” - ring 15

## 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 (See Genes, pages 21 - 23).

Babies are typically born small and with a low birth weight and remain short, although this pattern is not universal: one *Unique* baby weighed 1.9 kg (4 lb 4 oz) when born prematurely at seven months but by the age of seven was taller than average. Most *Unique* members with ring 15 measured around 18 inches long (48cm) at birth and are expected 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).

While small in size, children’s bodies are described as proportionate, although children’s hands and fingers may be especially tiny.

Some children have responded well to treatment with injections of growth hormone. One four-year-old child’s predicted adult height rose by 1.6 inches (4 cm) after two years of growth hormone treatment (Fryns 1979; Ledbetter 1980; Butler 1988; Peoples 1995; Nuutinen 1995; Rogan 1996; Unique). Another four and a half year old girl who had a similar treatment for four months increased in height by 3cm, and importantly there were no obvious side effects reported with this treatment (Xu 2011). In four instances of *Unique* members being administered growth hormone treatment, they all responded well (Unique).





“ Severely growth-retarded, had growth hormone for two years and then stopped treatment for six months, during which growth almost stopped. Restarted growth hormone and have had a very positive growth increase. ” - ring 15, age 15

“ Growth hormone deficiency, low calcium and carnitine levels. He does daily injections of growth hormone and takes a calcium and carnitine supplement. He was diagnosed as growth hormone deficient at age four and has been on treatment since then, doing daily shots...his body is in proportion. He is short and of average build . ” - ring 15 (15q26.3 deletion), age 7

## Appearance

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-shaped face with wide-set eyes and a small head (microcephaly) 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 or low-set ears and a small lower jaw. One researcher has commented that children may appear older than their actual age (Fryns 1979; Butler 1988) but no *Unique* families mentioned this and one even commented on their child appearing younger than his age.

Children with mosaic chromosome disorders sometimes have areas of lighter skin. Both light skin and darker café au lait patches have been described in some children with ring 15. These patches have historically been observed on the upper legs and stomach, but more recent cases describe patches on the genital region, feet and front of the lower legs (Boente 2011, Eid 2013). A girl has been described with pigment changes, including light brown patches of skin 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 *Unique* members, four 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).

“ 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. ” - ring 15

## 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 and some form of developmental delay, but some are only slightly affected or appear not to be affected at all. Generally, children's memory is reported as good, but abstract thinking and mathematical skills may be less well-developed (Fryns 1979; Meinecke 1980; Butler 1988).

In the *Unique* series, the level of learning difficulty was generally described as mild to moderate, although two children had a severe learning difficulty. On average children began to read at around five years of age, with writing skills emerging over a wider age range of five to 14 years. 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 8-year-olds had different levels of achievement. One started to read and write at the age of five 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.

In the small *Unique* series, most children attended mainstream school with support, but three children attended a special school. Some children learned better with visual support, and the parent of one noted that 'repetition and bribery' help (Unique). In the medical literature, it was indicated that a 27-year-old woman was unable to read or write (Guilherme 2012).

“ Classroom modifications have been made (modified seating for size and hearing impairment, special keyboards for small hands, large font for visual processing issues). She just completed high school and reads at first grade level with basic math and time-telling skills. She picks up subjects and skills that she has an interest in and has an extensive Individual Education Plan with a network of specialists who work with her. She goes to a mainstream school, but attends a special day class. Her reading and math progress has been slowed by processing and focusing issues. She has taken well to new technologies and she can navigate her iPad and computer pretty well. She has also developed skills to work around her challenges. She is reading more and continues to develop in areas of interest. She understands more complex ideas, but cannot always express what she is thinking which has led to a lot of frustration. ” - mosaic ring 15, 19 years

“ She writes names in capitals and writes some words and sentences as homework. Has no problem with a standard PC keyboard. Very good at remembering what she is to do days and weeks ahead but has problems with remembering what she did yesterday or what she did at school. She is at a

special school and has a statement of special educational needs.” - ring 15, 15 years

“ He has a modified curriculum and expectations at school that are documented in an Individualized Education Plan (IEP). In general, it takes him much longer to master things, so I notice he will avoid those things or gives up very early. He is easily frustrated watching his friends catch on to something so quickly. All learning is difficult. We did not have any issues obtaining the plan. We used the medical diagnosis and documented research studies to prove that he needs help and support through special education. He attends a public school and participates in a special education project that includes speech, physical and occupational therapy. He has learned his alphabet and can count to 50.” - ring 15 (15q26.3), 7 years.

“ Her memory is good once things have sunk in but this can take a while. She is very musical.” - ring 15, 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.” - ring 15, age 6.

## Speech and Communication

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 using 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 the scientific literature. All families indicated some form of speech and language difficulties. These 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 six years); difficulty in using longer or more complex sentences; difficulty processing more than one instruction in one sentence.

Six children old enough to talk had speech delay and some difficulties verbally communicating but appeared to understand more than they could communicate verbally. The difference between speaking and understanding was less obvious in an 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 five to 7 word sentences and had some understanding

of the meaning of tenses but tended to be repetitive.

A cleft or high arched palate can affect a child's speech quality and is common in children with chromosome disorders (Unique).

An assessment by a speech therapist should be able to identify your child's specific difficulties allowing regular therapy sessions tailored to your child's specific areas of need. Speech therapy has proved beneficial to many *Unique* families.

“ He has always had a speech delay and continues to struggle with it. He was completely non- verbal until he was 2.5 years old. The sounds associated with 'm', 'n', 'g', 'b', 'd' and others are a big struggle for him. At the age of 7, he uses basic four to five word statements. He struggles with using the right words and getting them into the right order. I believe he understands when I speak to him, but he can't get the words back out to answer me. ” ring 15 (15q26.3 deletion), age 7

“ At six years he is non-verbal but makes his wants & needs known. Learning some self-modified signs at 7 years. Uses gestures, makes vocalisations and has some spoken words. ” ring 15 mosaic, age 7

“ Says five to seven word sentences and has some understanding of tenses and their use. He understands a little more than he can express. ” ring 15, age 45

“ Uses shorter sentences and gets muddled sometimes. Has difficulty in expressing her thoughts at times but understands pretty well. ” ring 15 (15q26.2-q26.3 deletion), age 8

“ Quite often her sentences are not grammatically correct but are understandable. If people don't understand what she is saying, she has difficulty putting it into other words. ” - ring 15, age 15

## Medical concerns

Most people with ring 15 do not have serious medical conditions and there are many reports in the medical literature of children and adults with this chromosome disorder who 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 a minority of babies, around one in three or five, are born with a heart condition but many of these are not serious. Some heart conditions resolve naturally with time. Others need to be corrected with surgery (Butler 1988; Schinzel 2001).

Among *Unique* members, the majority had no reported heart problems. But there is some evidence, consistent with reports in the literature, of some *Unique* members suffering heart conditions. 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 had abnormal blood flow occurring between two of the major arteries connected to the heart (PDA). She needed surgery when she was one-year-old, which was successful; this has also been reported in the literature, in the case of a two-year-old girl, who also had an irregular heartbeat (Eid 2013). An adult with a slow and irregular heartbeat was otherwise healthy.

“She was diagnosed immediately with an Atrial Septal Defect and PDA. While in the NICU, they discovered that she had a rare form of arrhythmia (JET) which took some time to diagnose and determine how to medicate. The JET arrhythmia resolved after heart repair. She has a low heart rate and blood pressure and is still being monitored by a Cardiologist.” - mosaic ring 15, age19

## ■ Brain

An unusually small head (microcephaly) is very common in people with ring 15, and one *Unique* member had trigonocephaly, where when seen from on top the head looks pointed or triangular. There is a report in the literature of a two-year-old girl with ring 15, who had an underdeveloped “corpus callosum”; this is the middle region of the brain that connects the right to the left side of the brain (Eid 2013). This part of the brain will still be developing at this age and therefore the implications of this observation are unclear. The underdevelopment in this region of the brain could be explained by the deletion of the *SLC12A6* gene, which is found on chromosome 15 at position 15q14 (Eid 2013) (See Genes, pages 21–23). 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; Unique).

## ■ Spine

Among the small *Unique* dataset, three have a mildly curved spine (scoliosis). Researchers have also noted this (Butler 1988; Unique).

## ■ Genitals

A review of ten boys with ring 15 showed that one in three were 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). Two *Unique* members needed surgery (orchidopexy) to bring down the testicles into the scrotum (sac) and one also had hypospadias. The majority of families did not mention any problems with genitals or sexual organs (Unique).

## ■ 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 (Unique).

## ■ Kidneys

It is highly likely that a child with ring 15 will undergo tests on their kidneys. This is because evidence shows that as many as one fifth of children may have a kidney condition (Schinzel 2001). Among *Unique* members, one child had a mildly enlarged left kidney (hydronephrosis), while another child had a small but functional kidney. The majority of *Unique* families do not mention kidney problems.

## ■ Seizures

Among *Unique* members, two have had seizures and in a third (an adult) they are suspected. One child who experienced focal (partial) seizures was treated with Phenobarbital but was seizure-free after the age of two years and stopped needing medicines. Another child had absence (petit mal) seizures where there is a brief loss of awareness (Unique).

## ■ Joints

In three *Unique* members, joints were affected with several reports of joint hypermobility/hyperextension. This means they can move their limbs into positions others find impossible. While this may cause no problems, hypermobility is sometimes associated with pain and stiffness in the joints and muscles, joints that dislocate (come out of position) easily and injuries including sprains.

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 (Unique).

## ■ 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, curved/overlapping toes (clinodactyly) and toes joined by a bridge of skin (syndactyly). 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). *Unique* data reflects published data including the frequency of clubfoot (Unique).

## 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 involves coordination of the small muscles in the hands and fingers and hand-eye coordination that allows us to carry out activities such as holding cutlery or a pencil and bouncing and catching a ball.

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 data presented in the scientific review. Babies sat and walked a little later than presented in the review, on average they sat at 10 months (the range was from 5 to 18 months) and walked on average at 23 months (from 10 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 six-year-old child and an adult had taut muscles (hypertonia, high muscle tone), which 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 in the case of one older child 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; *Unique*).

“Fine motor skills are good (but still unable to tie shoes or work buttons and zippers). Elbow does not twist normally, which means she has difficulty making her hand go flat to receive change, for example.” - mosaic ring 15, age 19

“He still struggles with fine motor skills. Things like holding a pencil, colouring, applying pressure, and gripping... He can run, jump, skip, and ride a bicycle with training wheels.” - ring 15 (15q26.3 deletion), age 7

## What about hearing?

Among the limited *Unique* series, a third mentioned some form of hearing impairment. Four members 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.

Hearing problems are associated with speech delay and language problems in some cases. Other members indicate normal hearing (Unique).

“When she doesn't hear well, her speech becomes worse” - mosaic ring 15, 19 years.

“She has learned overtime that she doesn't like loud crowded areas (probably due to hearing challenges and over-stimulation)” - mosaic ring 15, 19 years.

## What about vision?

Some children with ring 15 in the *Unique* series have good eyesight but three quarters of the *Unique* members noted a visual impairment. The most common impairment reported was a 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 (Unique).

## Teeth

Dental problems are common in children with rare chromosome disorders. Two *Unique* families mentioned that first teeth emerged later than usual. Weak enamel, overcrowding and grinding of the teeth were also noted in a select few cases (Unique).

“She had oral surgery and extensive orthodontic treatment to address abnormal tooth placement (several teeth grew in roof of mouth). We originally thought she was going to need surgery but her problems were effectively treated through orthodontic treatment.” - mosaic ring 15, 19 years.

## 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, although found it “confusing” (Matsuishi 1996; Unique). Puberty also progressed normally in two young girls in the *Unique* series where both menstruated at roughly 12 years (Unique). This is supported by reports in the medical literature of at least two young women entering puberty normally (~14 yr) and having regular periods (Guilherme 2012).

“Her puberty was pretty normal. Menstruation began at age 12, but her cycle remains sporadic. She has had quite a bit a hormonal fluctuation, which may have contributed to her behavioural challenges over the past several years.” - mosaic ring 15, age 19

“He does not seem to be attracted to either sex, and if anything seems confused about sexual relationships – so he says he wants to marry his mother



or a male or female friend. He can be fun-loving and sweet but is usually negative and petulant. He complains constantly of ill health. ” - ring 15, age 32

## 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, good humour and overall happiness, although sociability has been a concern for a couple of families due to over friendliness with strangers. One girl has high energy levels and has been diagnosed with ADHD; another girl is said to be shy. An adult in his thirties became more withdrawn due to suffering with depression and OCD. Tantrums and stubbornness were also mentioned among *Unique* members. In a follow up report of a lady at 27, her mother mentions aggressive behaviour (Guilherme 2012). Just like any group of individuals, behaviour is variable and not all behaviour will be related to the chromosomal abnormality. While 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.

“ We had some behavioural issues from age 10 on. We worked with a behaviourist, which helped...has settled down over the past few years. ” - mosaic ring 15, age 19

“ Some aspects of his behaviour are not good but he loves to help anyone and is very sociable. Still unaware of stranger danger and how to behave socially. Has temper tantrums and if told no, will stamp his feet, cross his arms and turn away. Will sometimes throw things and back chat. ” - ring 15, age 16

“ Very sociable, loves the attention for being small, strong personality. Very sociable and chatty child. Very caring and loving. ” - ring 15 (15q26.2-q26.3 deletion), age 8

“ She has a very high energy level and is very persistent about going after what she wants. She is clever with a terrific memory - we can't keep up with her! ” - mosaic ring 15, age 6.

## Sleep

The majority of *Unique* members remarked that at some point sleep has been a problem. Mild sleep apnoea and problems staying asleep were the most common difficulties. There is an indication in some cases that sleep problems improved with age. Nevertheless, one adult suffers insomnia but this could be related to other psychological difficulties.

“ She has always gone straight to sleep on going to bed and awakes quite early in the morning. Has been afraid of sleeping alone but by five years is fine. ” - ring 15, age 15

“ Was two-years-old before slept through the night but at 8 yrs is now a good sleeper, although can take a while to settle. ” - ring 15 (15q26.2-q26.3 deletion), age 8

“ When she was younger, she had a difficult time staying asleep. She was an early riser and would often get really busy while we were still asleep. As she has gotten older, she sleeps much more, but fatigues easily. Was recently diagnosed with mild sleep apnoea (snores and mouth breathing throughout the night). ” - mosaic ring 15, age 19

## 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 and have a variety of hobbies, from painting, cooking and dancing to swimming, tennis and gymnastics, just to name a few.



“ Although he is still very short, he is generally able to keep up with his peers. He can run, jump, skip, and ride a bicycle with training wheels. ” - ring 15 (15q26.3 deletion), age 7

“ Loves company and is good at painting and drawing. Loves her dolls...Likes ballet, tap, jazz, swimming. Started tennis and gymnastics at 8 yrs. ” - ring 15 (15q26.2-q26.3 deletion) age 8

“ At 32-years-old he plays golf and bowling and cooks. ” - ring 15, age 32

“ She loves socializing, little field trips, cooking, Youtube, shopping trips, walking the dog, going to the park, practicing sports, spending time with her favourite people. She doesn't like loud sporting events, crowds, unpredictability (animals that move to quickly, scary movies, being alone). ” - mosaic ring 15, age 19

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

“ 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. ” - ring 15, age 7

## 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. Although some members are still in nappies at night due to having the odd accident. 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 (Unique).

“He can get dressed alone but occasionally forgets that tags go in the back so sometimes things are on backwards.” - ring 15 (15q26.3 deletion), age 7

“Can dress herself at 8 years but can't tie shoes herself... still unable to tie shoes or work buttons and zippers (at 19 years).” - mosaic ring 15 age19

“Brushes own teeth, can wash in the bath, dresses herself but needs help with laces and buckles etc.” - ring 15 (15q26.2-q26.3 deletion), age 8

## What therapies may be needed?

All *Unique* members who have given information on therapies have received physiotherapy, and most have had occupational therapy and speech/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. Families noticed improvement and progress with various therapies.

“Speech therapy from just over three years and is progressing very well.” - ring 15 (15q26 deletion), age 4

“Some hypotonia in early years helped by physio and OT.” - ring 15 mosaic, age19

“At six years receiving aggressive physio on a great programme called Europeds, rides horses once a week at a programme called Oats.” - ring 15 mosaic, age 7



A good ear and a lovely singing voice - age 8.

## 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 evidence from research reports and from *Unique* is that some people with ring 15 may become independent enough to live in a sheltered setting.

“ He attended regular schools with support for academic subjects and undertook a three year special college programme, travelling to and from college on the subway independently and working under supervision in Starbucks. In his early twenties he was working three days a week with the help of social services but health problems disrupted this. As a 45-year-old he lives in a house with five residents. There are eight houses altogether and each house is self-sufficient. Residents have their own bedrooms, with communal dining room, living room and kitchen. The house is staffed from 7am to 9.30 pm. At night, night-staff check every few hours. ” - ring 15, age 45

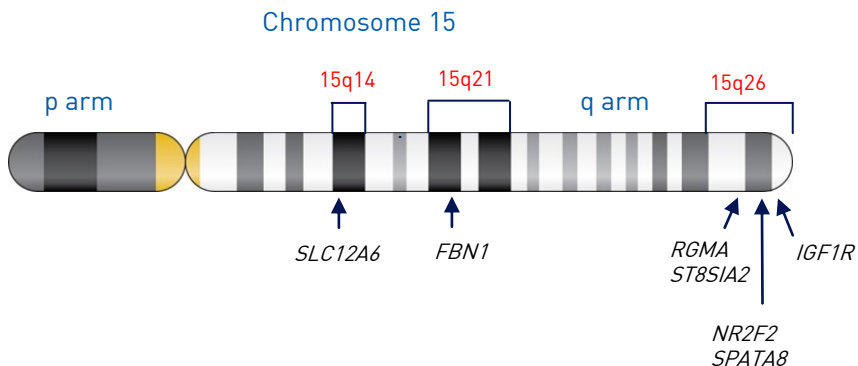
“ She recently completed high school and will be attending a transition program to work on daily living skills over the next three years. She is very outgoing, curious and social. She loves meeting people and going on new adventures. She has many friends and a wide network of community support but not necessarily close relationships. She seems to bond better with adults than with her peers. She is very close to her aides and specific family members. She loves belonging to and contributing to her sports teams. She worked at a veterinary clinic for one year. She will focus on job training in the next three years. She lives at home. ”  
- mosaic ring 15, age 19

## 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 had either 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).

## Genes



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 (p) arm of chromosome 15 that could cause illness or defect, so losing a bit of this short arm does not apparently matter.

However, losing genes from the long (q) arm is much more significant. Some of these genes that exist on the long arm of chromosome 15 have been outlined below. Most commonly genes are lost from the 15q26 region.

While identifying the gene(s) responsible for certain features of ring 15 is valuable and may help guide future studies, it does not lead directly to immediate improved treatment. Also, even if the supposedly responsible gene is missing, it does not always mean that the associated feature(s) will be present; other genetic and environmental factors play a role.

■ **SLC12A6** A gene called *SLC12A6* found at **15q14** has been reported to be involved in development of the “corpus callosum”; this is the middle region of the brain that connects the right to the left side of the brain. It has also been reported to affect the peripheral nervous system (the part of the nervous system that is outside the brain and spinal cord) and therefore may affect the development of nerves in the body’s extremities, for instance the hands and feet (Eid 2013).

Two genes in the **15q26.1** band have been suggested as ‘candidate genes’ for epilepsy:

■ **RGMA** *RGMA* plays an important role in the development of the nervous system and is therefore a candidate for both learning disabilities and seizures (epilepsy) (Li 2008; Capelli 2012).

■ **ST8SIA2** The gene *ST8SIA2* may also be involved in epilepsy, although some individuals with epilepsy have not lost this gene, so clearly more remains to be discovered (Dhamija 2011; Capelli 2012).

The 15q26 region also contains a cluster of genes expressed in the developing diaphragm:

■ **NR2F2** A gene *NR2F2* (also known as *Coup-TFII*) located in band 15q26.2 is believed to be essential for normal diaphragm development (Slavotinek 2005; Klaassens 2007; Clugston 2008; Poot 2013). However, losing the *NR2F2* gene does not always cause abnormal diaphragm development, so other factors must be involved. *NR2F2* is also known to be involved in heart development and its absence may cause the heart defects reported in 15q26 deletions, although it hasn’t been shown to give rise to a specific heart defect. Other genes are therefore likely to be involved in the development of heart conditions (Slavotinek 2005; Poot 2007; Dateki 2011; Rudaks 2011; Poot 2013).

■ **SPATA8** Currently little is known about the function of the *SPATA8* gene, which is located in band 15q26.2, but it has been suggested that it may have a role in determining how severely people are affected by deletions of 15q (Rudaks 2011).

■ **IGF1R** The insulin-like growth factor 1 receptor gene, is situated within the 15q26.3 band. This gene is probably the most significant gene as it is commonly lost in ring 15 and is vital for proper growth. When it is disrupted or deleted during chromosome 15 ring formation, people are typically, although not always, unusually short (Ester 2009; Choi 2011; Rudaks 2011).

We don’t yet know the full role of *IGF1R* and different research teams have suggested other possible features that it may contribute to including unusual facial and skeletal features; mild early developmental delay (Veenma 2010; Dateki 2011); the development of the eye and lens (Walenkamp 2008; Veenma 2010); brain development and carbohydrate metabolism (Rudaks 2011); hearing (Ester 2009). There is uncertainty as to whether it plays a role in heart

development (Dateki 2011). One research group has suggested that *IGF1R* may act with *FBN1*, a gene outside the 15q26 region in 15q21, to produce joint hypermobility and growth failure (Ester 2009). Apart from being short and having some speech delay, some people who have lost the *IGF1R* gene have developed normally (Walenkamp 2008; Rudaks 2011).

“ There are good days and bad days, but this child can bring so much joy and meaning not only to your life, but all of the lives he or she touches. ”

## Notes

# Inform Network Support



## Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at

[www.rarechromo.org](http://www.rarechromo.org) Please help us to help you!

<http://www.rarechromo.org/html/DonateNow.asp>

Unique mentions other organisations' message boards and websites to help families looking for information. 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 Eva Morava, Department of Pediatrics, University Medical Center, Nijmegen, The Netherlands and Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK in 2004. Revised by Unique (CA) and Katherine Fletcher, The Babraham Institute, Cambridge and reviewed by Dr Maria Isabel Melaragno, Department of Morphology and Genetics, Universidade Federal de São Paulo, Brazil in 2018 (V2) (CA).

Rare Chromosome Disorder Support Group Charity Number 1110661

Registered in England and Wales Company Number 5460413