

Unique

Ring 22



Ring 22

Ring chromosome 22 is a rare condition caused by having an abnormal chromosome 22 that forms a ring.

What is a chromosome?

All our genetic information is contained in the cells of our body. The genetic material that contains this information is the DNA, tightly coiled and forming a number of rod-like structures called chromosomes. Genes are fragments of the DNA strand and there are about 20-25,000 genes located on 46 chromosomes. The chromosomes occur as 23 pairs and we get one of each pair from our mother in the egg, and one of each pair from our father in the sperm. The first 22 pairs are numbered 1 to 22, approximately from longest to shortest, although in fact chromosome 22 is longer than chromosome 21. The remaining pair are the sex chromosomes. Girls and women usually have two X chromosomes (XX) and boys and men usually have an X and a Y chromosome (XY). Each chromosome has a short arm (p for French *petit*) and a long arm (q), separated by a pinched area known as the **centromere**.

Chromosome 22, along with chromosomes 13, 14, 15 and 21, has a distinct shape with a very small short arm that does not contain genes that are relevant to development. This group of chromosomes is known as **acrocentric** chromosomes, meaning that the centromere is near one end.

Development works with clockwork precision and the right amount of genetic material is needed for normal growth and development. If there is any substantial amount of missing or extra genetic material, then it is likely to result in problems in growth and development and most often also in the functioning of the body systems.

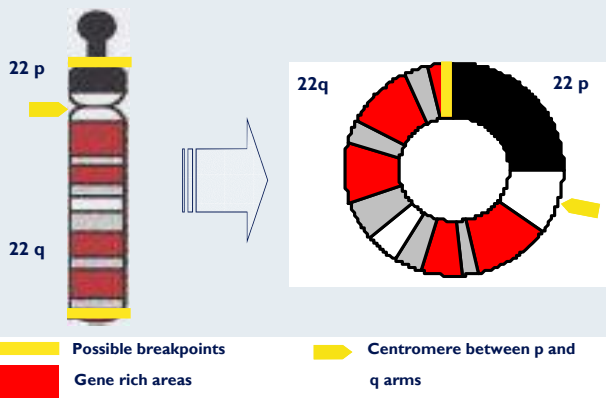
What happens when a ring chromosome forms?

In most people with Ring 22, one chromosome 22 is usually intact but the other has formed a ring. When a ring forms, both arms of a chromosome break and the broken 'sticky' ends fuse at the breakage points, known as breakpoints. The broken fragments

Sources

The information in this leaflet comes from the medical literature and from Unique's members with Ring 22, who were surveyed in 2003. Unique is very grateful to the families who took part in the survey.

Formation of a ring chromosome 22

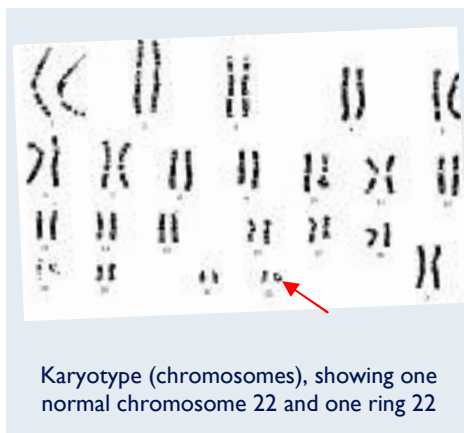


are lost and with them any genes they may contain. In the case of a ring chromosome 22, only the genes in the long arm matter. A study of 35 people with Ring 22 has shown that the amount of material lost can vary between 0.15% and 21% of the total length of the long arm but in virtually every case a gene known as *SHANK3*, (also called *PROSAP2*) situated close to the end of the long arm in the band known as 22q13.3, has been lost. This gene spells out the message for a structural protein that is associated with signalling pathways in the brain and two copies of the gene are needed for proper development. When one copy is lost, the effects of Ring 22 will be very like the effects of 22q13 deletions seen in people with Phelan-McDermid syndrome. But a child's other genes and personality, their home environment and the opportunities and experiences offered them also have an impact on their future development, needs and achievements.

For more information on Phelan-McDermid syndrome, please read *Unique's* 22q13 deletions leaflet.

Does it help to know the breakpoints in the ring?

Knowing the breakpoint in the short arm is unlikely to be helpful, but knowing the breakpoint in the long arm is helpful especially if this shows whether *SHANK3* is missing or not. In one case, a woman whose ring 22 had not lost the *SHANK3* gene was only very mildly affected. There are a number of other genes near the end of the long arm of chromosome 22 that may play an important role in neurological development, but at the time of writing (2005), their influence was less clear.



Karyotype (chromosomes), showing one normal chromosome 22 and one ring 22

Why did this happen?

The great majority - 99% - of ring chromosomes are sporadic. They happen out of the blue and the actual cause is not known but should be regarded as an accident during cell division in the process of making sperm or egg cells. These accidents are not uncommon. 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 to form.

Very occasionally, a ring chromosome may be inherited from a parent who passes it on to his child. Passing on a ring 22 is very rare. Only four cases have been reported. In one family an unaffected father passed the ring to his daughter who had a slight learning disability. She passed it on to her twin daughters who were also unaffected.

Can it happen again?

So long as tests show that parents' chromosomes are normal, they are very unlikely to have another affected child. All the same, you should have a chance to discuss prenatal diagnosis if you would like it for reassurance.

Ring chromosome syndrome

Ring chromosomes can have particular effects on cell growth. During development, cells naturally divide, but the ring chromosome may occasionally disrupt this process by becoming entangled, breaking or doubling in size when replicated. This results in what is known as **ring chromosome syndrome**, with similar effects regardless which chromosome is involved. Effects include growing slowly and eventually being unusually short and having streaky or patchy light or dark skin colouring on a part of the body. This only happens occasionally with ring 22 because it is almost the smallest chromosome and so less likely to get entangled and cause disruptions than larger chromosomes.

Mosaicism

People with a mosaic form of a chromosome disorder have a mix of cells with different chromosome arrangements. This happens quite often with ring chromosomes and lessens or intensifies the effects of the ring chromosome, depending on how much extra or missing chromosome material there is. Some people have some cells with 46 normal chromosomes instead of the ring 22 and this may lessen the impact.



Supernumerary ring 22

A few people have two normal chromosome 22s and an extra 22 in the form of a ring. This results in a condition that is different to the Ring 22 disorder described in this leaflet and has more in common with a chromosome disorder known as Cat Eye syndrome where there is an extra copy of part of the long arm at 22q11.2.

Main features of Ring 22

- Delayed development
- A degree of learning difficulty or disability, generally described as moderate to profound
- Specific delay in developing speech and language. In some cases, absence of speech
- Unusual degree of floppiness of the skeletal muscles (hypotonia)
- In most cases children are healthy, without striking birth defects
- Behaviour typically involves features that are common in people with autistic spectrum disorders
- Growth is usually normal and height is normal to tall, although a minority of youngsters are short.

How common is Ring 22?

This is a relatively rare chromosome disorder. Over 100 people with Ring 22 have been mentioned in published reports or on the internet. At the time of writing, *Unique* had 64 members; if families wish, they can be put in touch with each other.



Will a child with Ring 22 look different from other children?

Children with Ring 22 often share facial similarities and paediatricians and geneticists may notice specific features that are common in this chromosome disorder. However, these features can be subtle and this, together with the typical absence of birth defects, major health problems and growth delay, means that a chromosome disorder may not be suspected at first during investigations.

Looking at the pictures in this leaflet of children with Ring 22 and comparing affected children with their brothers or sisters will show what some of the typical facial features are: large, beautiful almond-shaped eyes, sometimes with long lashes, a nose with a somewhat bulbous tip and a wide bridge and large ears. Occasionally the area around the eyes is puffy and the lower jaw is set back.

As regards other features, the most common appear to be a wide gap between the first and second toes (a so-called 'sandal gap'), a broad first toe, unusually large hands and sometimes feet and short end joints on the toes.

Children with Ring 22 are usually a similar height to their classmates or sometimes taller. However, a minority of children, possibly those demonstrating the effects of ring chromosome syndrome, are markedly shorter than their classmates.

How can Ring 22 affect the ability to learn?

Most children will need support with their learning and for some very considerable support will be needed. However, the range of ability is broad and a very few people with Ring 22 have no apparent learning difficulty or only mild difficulties. This means that it is not possible to predict precisely the effects on a child's intellectual capacities just from a chromosome analysis. It seems likely - although this is not yet certain - that the people with Ring 22 who are only mildly affected are those in whom the *SHANK3* gene has not been lost.

Among 18 *Unique* members surveyed in 2003, one had no apparent learning difficulties on entering reception class, three

“ If it is something he enjoys such as anything mechanical, he picks it up right away and responds very well to praise - age 3

“The doctors and teachers have felt that she is like a 3-4 year-old mentally but she has learned many skills far beyond those levels. She can put a new bag and try to put a new belt in a vacuum cleaner - age 32

had moderate learning difficulties and in 15 the difficulties were severe. Among those with severe learning difficulties were a 19-year-old college student who achieved UK Key Stage 2 in most subjects at school and was following a foundation course in essential life skills.

How can Ring 22 affect speech and communication?

“His four-phrase vocabulary was achieved through repetition. We talk to him constantly in a louder tone than normal and touch him when we talk to him - age 3

“I:1 language support for the past six years definitely helped - age 11

“Callum needs to see your face when he is speaking or being spoken to - age 11

“E considers that she can talk and others have the problem by not being able to understand her. I can understand most of what she says - E attended a specialist language boarding school from 7 to 18 years.

“A can make most of her needs known, but not all of her comments. She tends to lose old words when she learns new ones. Specialised speech therapy for apraxia works well with her - age 13

Typically, children with Ring 22 start to speak late, on average around age 3, and perhaps as many as fifty per cent only communicate non-verbally, using means such as touch, gesture, facial expressions, eye contact and vocal noises that may approximate to words. A very marked delay in expressive speech is typical and in general people with Ring 22 understand more than they can express. Some children learn to understand signing, but if they have low muscle tone active signing may be difficult for them. Among children with a 22q13 deletion, there is evidence that babbling and speech may emerge but then be lost and this is likely to be true of children with Ring 22. Speech therapy and communications skill training will help to retrieve some vocabulary but therapy usually needs to be intensive. Children often benefit from using alternative approaches to communication, including computer touch screens, voice based systems and picture exchange systems.

Among 28 people on the *Unique* database with information on language, 11 use words. The age at which children started to speak ranged from 2 to 8 years and command ranged from occasional isolated words to reasonable fluency and intelligibility.

Children like to have something to suck or chew



How can Ring 22 affect mobility?

Mobility is usually delayed in babies and children with Ring 22. Typically, babies reach their milestones somewhat late, sitting supported and then alone between 4 and 24 months, crawling between 7 and 36 months and walking in their third year (range 12 months to 8 years).

Hypotonia (floppy muscles) is estimated to affect at least half of all children with relative weakness in upper body muscles and poor balance contributing to the delay. The *Unique* experience showed no apparent difference between children with a ring 22 in all cells and children with a mosaic form of the condition, but the trend was to a slightly earlier age of reaching milestones among children with mosaic Ring 22. All children benefited from regular physiotherapy, occupational therapy, swimming and adapted sports.

The *Unique* experience showed that once children were mobile, they typically adopted a wide-legged gait to compensate for uncertain balance and might continue to trip and fall frequently. Typically, they also sat in a W-position. Many children showed a tendency to be active or overactive and would jump up and down on the spot. By age 5, some children had mastered skills such as cycling, dancing and kicking a ball as well as enjoying outdoor playground play. Some learned to swim by the age of 9 or 10 and by the teen years youngsters have reportedly skied, played football, trampolined, roller-skated and been horse riding and ten-pin bowling. Co-ordination may remain a problem and limit participation in team sports, but activities like walking and hiking were popular with some families.

“ Billy is an extremely active boy with an athletic build although lymphoedema in his left leg prevents him from being more able. He loves to kick a ball about and after a break for ear infections has recently just begun to enjoy swimming again - age 9



Medical concerns

Children with Ring 22 are usually healthy. The problems listed below generally only apply to a small number of children.

■ Upper respiratory tract infections

These are slightly more common than expected in young children. Middle ear infections are especially frequent, and may lead to repeated insertion of grommets/ventilation tubes into the ear drums. Chest infections and infant wheezing are common in early childhood but are outgrown typically by age 6 to 8, although some children remain asthmatic.

■ Lymphoedema

Puffy hands and feet may be apparent in babyhood and this tends to increase with age. In most children the swelling is not troublesome. In addition, many children have unusually large hands and feet. Some children have flat feet and benefit from supportive insoles or orthoses.

■ Seizures

A minority of children may have seizures. The *Unique* experience showed that seizures may start at any age, from early childhood to age 23. In all cases, seizures were successfully controlled with medication.

■ Heart problems

A few children have been found to have a heart condition at birth. Reported anomalies include persistent ductus arteriosus, where the ductus arteriosus (a channel between the aorta and the pulmonary artery that takes blood to the lungs) which usually closes shortly after birth stays open instead, so the lungs receive more blood than they should and the heart has to work too hard. Another anomaly that has been found is total anomalous pulmonary venous return, where the pulmonary veins that return oxygen-rich blood from the lungs drain to the right side of the heart instead of the left. Among *Unique* children one had a slow heart rhythm (diagnosed at age 12) and another left ventricular hypertrophy (an enlargement of the left pumping chamber of the heart) that was diagnosed at the age of 18.

■ Kidney and genitourinary problems

A recent survey showed that 17 per cent of children with Ring 22 had a kidney or genitourinary problem. The most common problem was vesicoureteric reflux (VUR), in which urine flows back towards the kidneys from the bladder. As untreated VUR can have long term effects on kidney function, a child will be carefully monitored and treated if necessary.

■ Squint (strabismus)

This common eye problem may occur and can be treated with patching, glasses or if necessary with surgery to realign the muscles controlling the eyeball.

■ Overheating

Many people with Ring 22 tend to overheat easily. Their skin turns red and they do not sweat enough. However, the sweat glands have not yet been studied to see whether they are abnormal.

“ *If the weather is cool she can be quite active but if it is hot, she just wants to sleep - age 11*

Behaviour

Children with Ring 22 are vulnerable to behaviour difficulties but this does not of course mean that every child will experience them. Typical areas of difficulty include low attention levels, outbursts of aggression and high levels of activity. With age, problems may lessen or, on occasions, families may need extra support and intervention in handling their child.

Overactivity amounting to hyperactivity affects some children, even toddlers for whom high levels of activity are natural. Occasionally children have extreme episodes of aggression when distressed or confused. Straightforward parenting approaches such as time out, or removal of everyone else if the child with Ring 22 cannot be moved, may be helpful and structured days with regular opportunities for activity also help. As communication matures, children may outgrow the frustrations that underlie some of their behaviour problems. Behaviour modification programmes using positive reinforcement have been successful for some children and although many parents are loath to use medication, it can be very helpful. Children who become hyperactive or who have repetitive self stimulatory behaviours can usually be helped with medication.

Autistic traits

Some children show autistic-like behaviour and in some cases the autistic traits are the first sign that anything is wrong and precede the diagnosis of Ring 22. It is believed that the *SHANK3* gene and genes from the same family may be important players in the development of autism. Avoidance of eye contact are often characteristic and some children dislike being touched, although this is not universal. In the *Unique* experience, autistic traits are especially noticeable in early childhood. By the pre-teen years, some children show a wish for social integration and are able to behave calmly in groups.

- “ When he gets frustrated and screams and bites, we hug him and calm him down - age 3*
- “ He went through a stage of hitting people and we had to hold him physically and show love, trying to ignore his bad behaviour. It worked, but he will regress now and then and need constant attention - age 5*
- “ Billy understands that some children are less able than himself and will voluntarily help them. He will take toys to children in class who are physically disabled or stroke them very gently - age 9*
- “ Joanne has difficulty sitting for a long time as she gets pins and needles in her legs and bottom - age 11*
- “ She is happy 99.9% of the time. She will never know hate or prejudice - age 13*



In the *Unique* experience, many children are characterised as both strong and stubborn. Families should not hesitate to seek help if their child shows any obsessive or compulsive behaviour or a high level of anxiety.

“ Rachel hates shops and having to stand in one place. Our solution was her love of music and her personal CD player goes everywhere with her. Rewarding her progress through a shop with her music stops her getting distressed and angry - age 13

“ I give her a place where it is OK to obsess - age 13

“ She is very aware of modern styles and likes to dress like other girls of her own age - age 13

“ Rhonda assembles plastic forks, knives and spoons rolled in a napkin and secured with a tie. She makes about 8000 of these annually, to be used for local church functions and other conferences - age 32

Will a child be able to live independently?

Independent living skills among children with Ring 22 are similar to those in children with 22q13 deletions. Most children are considerably delayed and although many have periods of successful toileting or structured toilet timing interspersed with periods of wetting and soiling, only a few are completely reliably toilet trained, particularly at night. Out of fourteen *Unique* members, four were consistently clean and dry and even they were liable to accidents, especially when ill. Children may be dry at night, but have difficulty saying what they need during the day and their increased tolerance to pain and discomfort may diminish their awareness of being wet or soiled. Overall, the problems with communication skills and reliance on others for personal care means that youngsters cannot be generally expected to live independently. Evidence suggests that children with a mosaic form of Ring 22 may achieve a higher level of personal care.

However, in a familiar environment, with supportive adults, individuals can learn to lead happy, contributory lives and the *Unique* records show adults with Ring 22 performing helpful tasks within the home.

Food and eating

Newborn babies tend to have difficulties with sucking and swallowing. The problems are not usually severe and most babies learn to drink milk successfully, if slowly, and need neither tube feeding nor a gastrostomy tube. However, it is often helpful to get the advice of a feeding specialist or a speech therapist. In *Unique*'s experience, by the late primary school years or early adolescence most children have put these feeding difficulties behind them.

Finger feeding usually starts late and because of difficulties with the fine motor skills that underpin handling cutlery, tends to persist well into school age. Many children continue to need their food cutting up small throughout childhood and a few do not achieve self-feeding.

Approximately one baby in three develops gastro oesophageal reflux (GO reflux, acid reflux, GORD).

In young babies, small feeds, adding thickener to formula milk and careful positioning to keep the baby sitting upright may be all that is needed. GO reflux may be more difficult to spot in older babies and young children because of their increased tolerance of pain and discomfort. Eating smaller meals, avoiding foods that cause irritation, raising the head of the child's cot or bed, sleeping on the left side and eating no food within two to three hours of bedtime may all help but if these measures are not enough, medication can be prescribed or surgery known as a fundoplication performed to improve the action of the valve between the stomach and the oesophagus (food pipe).

Sleep

There is no evidence from the medical literature that children with Ring 22 have particular sleep problems, but the *Unique* experience is that they can cause considerable disruption. Children are both hard to settle and wake frequently and for long periods during the night. Most parents prefer to rely on behavioural interventions at first and some children respond positively to a firm wind-down routine at the end of the day and minimal intervention at night. Positive reinforcement helps: the breakthrough came for one eleven-year-old when she understood that she would have to miss a sleep-over if she failed to settle properly.

Many *Unique* families used medication, frequently melatonin, a synthetic version of the natural hormone released by the body during darkness. However, the doses used in treatment are well above the natural levels in the body and until long-term trials have been set up, there is no hard information on the long-term use or safety of melatonin. Other medications used on an occasional basis include antihistamines with a sedative action such as Vallergran, and chloral hydrate.

One adult developed sleep disturbance after contracting Lyme disease and would wake regularly and be hyperactive at night. As she slept less, the night waking intensified but eventually the use of the prescribed medication zolpidem settled her sleep patterns.

Ways to encourage good sleep

- Make the bedroom safe and unstimulating
- Set regular bedtimes and waking times and stick to them
- Avoid late afternoon naps
- Keep activities low key in the hour before bedtime (quiet play, gentle music, soothing videos)
- Follow a pre-bedtime settling routine, using symbols and other cues. Keep this brief, manageable (for you), relaxing and consistent
- Once in the bedroom, settle your child rapidly in less than four minutes. Use the same good night phrase and gestures each night when you leave; leave the bedroom; turn off the lights; close the door
- Put your child to bed awake and teach them to fall asleep alone
- Be as unexciting as possible when dealing with your child at night.



For support,
contact with other families and information

**Rare Chromosome Disorder
Support Group**

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

www.rarechromo.org

Website with a copy of *Molecular and Phenotypic Characterization of Ring Chromosome 22*, published in 2005 in the American Journal of Medical Genetics 137A: 139-147.

The website is updated with new information on Ring 22

<http://sgdp.iop.kcl.ac.uk/r22/>

Email support group

<http://health.groups.yahoo.com/group/ring22>

French website

<http://www.anneau22.fr.st/>

At Chromosome 22 Central (www.c22c.org) you will find some information on Ring 22.

Other sites are listed to be helpful to families looking for information but a listing does not imply that *Unique* endorses its content.

This information sheet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication and the medical content has been verified by Aaron Jeffries, Institute of Psychiatry, London and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, UK.

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