

## Support and Information



**Rare Chromosome Disorder Support Group,**  
G1, The Stables, Station Rd West, Oxted, Surrey RH8 9EE, United Kingdom  
Tel/Fax: +44(0)1883 723356  
info@rarechromo.org | www.rarechromo.org

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Ring20uk@outlook.com | [www.ring20researchsupport.co.uk](http://www.ring20researchsupport.co.uk) |  
[www.facebook.com/Ring20ResearchandSupportUK](https://www.facebook.com/Ring20ResearchandSupportUK)  
26 Headley Chase, Warley, Brentwood, Essex CM14 5BN United Kingdom  
+44 (0) 1708 403620

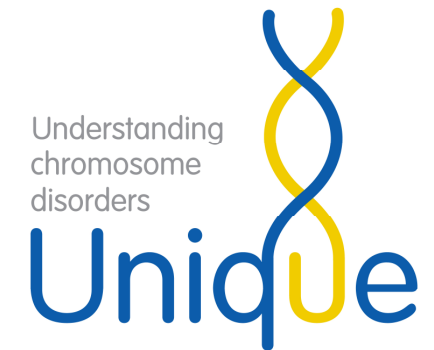
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This updated guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field 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.

This guide was compiled by Unique and reviewed by Professor Nancy Spinner, Professor of Pathology and Chief, Division of Genomic Diagnostics, The Children's Hospital of Philadelphia, USA; by Professor Lieven Lagae, professor of paediatric neurology, University Hospitals, Leuven, Belgium; by Dr Daniela Giardino, Laboratorio Citogenetica Medica, IRCCS Istituto Auxologico Italiano Milan, Italy; and by Dr Sophia Varadkar, consultant paediatric neurologist and honorary senior lecturer, Great Ormond St Hospital for Children and UCL Institute of Child Health, United Kingdom.

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# Ring 20



[rarechromo.org](http://rarechromo.org)

## Sources

We know about ring 20 syndrome from more than 100 people who have been reported in the medical literature, ranging in age from newborn to 66 years, as well as people in support groups for ring 20, and at Unique. When this guide was revised, Unique had eight families with a child with ring 20 syndrome. Three families completed a survey. For articles from the published medical literature you can use the first-named author and publication date to look for abstracts or original articles on the internet in PubMed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)) (Brandt 1993; Yamadera 1998; Garcia 2001; Chawla 2002; Alpman 2005; Parr 2006; Ville 2006; Zou 2006; Elghezal 2007; Herrgård 2007; Rossi 2008; Kurahashi 2009; Vignoli 2009; Conlin 2010; Giardino 2010; Traylor 2010; Daber 2012; Elens 2012; Walleigh 2013).

## Ring 20 syndrome

Ring 20 syndrome is a very rare condition in which one of the two copies of chromosome 20 has formed a ring rather than the typical linear chromosome structure. Ring chromosome 20 is associated with epilepsy. In some people, the ring chromosome 20 is found in every cell in the body, whereas in others, it is only seen in a percentage of cells, with the remaining cells having two normal chromosome 20s.

The syndrome has these key features:

- Abnormal brain function, showing as seizures and frequently learning and behaviour difficulties. Imaging shows that the structure of the brain is usually normal.
- First signs usually develop in childhood or adolescence, but have also been found in young adults. The first sign is usually the onset of seizures. Before the first signs develop, the child or adult has usually been healthy, does not look in any way unusual and has typically developed at a normal rate.
- Learning difficulties of varying degree, from very mild to severe. In a few people the difficulties are apparent before seizures develop but in most they become more obvious with the onset of epilepsy.
- Behaviour problems, starting before the onset of seizures or soon afterwards.
- People with ring 20 are usually otherwise healthy.

### How common is Ring 20?

All human chromosomes can form a ring chromosome, although they are all very rare, with a combined incidence of only one in 30-60,000 births. Ring 20 is one of the more common ring chromosomes, but we do not know yet exactly how common ring 20 syndrome is.

### Ring chromosomes

Our bodies are made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; the genetic information they carry in the form of DNA tells the body how to develop, grow and function. Genes are carried on structures called chromosomes, and there are usually 46 chromosomes in every cell. Of these 46 chromosomes, two are a pair of sex chromosomes: two Xs for a girl, and an X and a Y for a boy. The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from largest to smallest. This means that chromosome 20 is one of the smallest chromosomes.

A chromosome is usually a long, fairly straight structure with a constriction in the middle, called the **centromere**, and two arms that are called the **p** (short) and **q** (long) arms. Ring chromosomes generally form when ends that have become unstable fuse, or when there is a break in both p and q arms and the broken ends join together.

*CHRNA4*: this is a neurotransmitter receptor that has a role in passing signals between brain cells. Changes (mutations) in this gene are associated with epilepsy.

The exact role these genes play is still not fully understood, and research is continuing. It is possible that the combined loss of both genes could contribute to the problems experienced by people with ring 20 syndrome. However most people with ring 20 syndrome have not lost these genes. What is more, people who have lost these genes but do not have a chromosome 20 that has formed a ring do not have ring 20 syndrome. This is puzzling. One possible explanation is that the change in chromosome structure when the ring is formed, particularly within the telomeres, may have a wider ranging effect on nearby genes and this could lead to the abnormal brain activity that underlies the seizures. Another idea is that the ring itself may affect genes that control the way cells divide and grow (Daber 2012; Conlin 2010; Giardino 2010; Traylor 2010; Kurahashi 2009; Elghezal 2007; Zou 2006).

### How did this happen?

In the great majority of people studied so far, the ring 20 chromosome has occurred out of the blue for no obvious reason. The genetic term for this is *de novo* (dn) and a blood test shows that neither parent has a relevant chromosome change.

In a small number of families – to date, just three have been reported – the ring 20 has been inherited directly from the mother or the father (Giardino 2010; Herrgård 2007; Canevini 1998; Back 1989).

What is certain is that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary or lifestyle factors are known to cause a ring 20 chromosome. There is nothing that either parent did before or during pregnancy that caused the ends of the chromosome to fuse.

### Can this happen again?

In the most likely situation where both parents have normal chromosomes, it is unlikely that another child will be born with ring 20.

Where one parent has the same ring 20 as the child, the possibility of having another child with the ring chromosome is 50 per cent in each future pregnancy.

If they wish, parents should have the opportunity to meet a geneticist or genetic counsellor to discuss their specific recurrence risks, reproductive choices, and options for prenatal/preimplantation diagnosis.

"During periods where J suffers increased seizures his behaviour becomes more problematic, he has very little patience and can be aggressive. More recently since a reduction in seizures, J' behaviour has improved, but patience is still an issue at times." 5 years

Behaviour problems can include:

- Difficulty paying attention
- Apathy
- Hyperactivity
- Irritability
- Loss of social skills
- Obsessive behaviour
- Autistic features

"D shows traits of ADHD such as hyperactivity, frustration, and aggression - probably due to his epilepsy. His seizures often make him angry and confused either just before or just after, and he shouts and can lash out during these outbursts. They pass quickly as it is not in his normal nature to behave in this way." 17 years

"R has seizures when she is coming out of sleep, and is then awake all night on a 5-6 day basis. She has many autistic tendencies and can get upset and angry." 17 years

## Long term outlook

There are people in their 50s and 60s with ring 20, and apart from epilepsy, most people are completely healthy, so there would seem no reason why they should not look forward to a normal lifespan. However, the epilepsy typically remains hard to control, and puts them at risk of developing status epilepticus, which is life threatening, although there are no cases recorded in the medical literature of people with ring 20 dying in status epilepticus. In most people, although not all, there does seem to be a noticeable decline in mental abilities over the years (Daber 2012; Elens 2012).

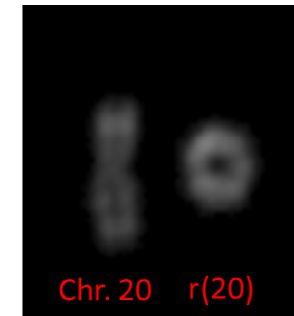
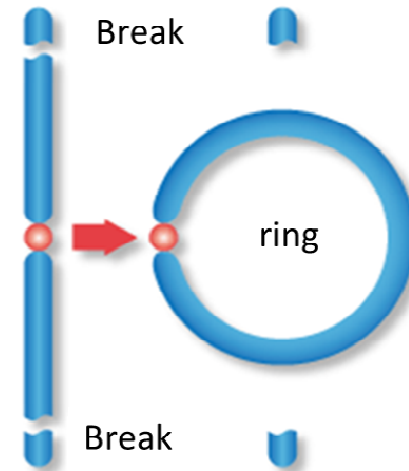
## Ring chromosomes: more information

### How does the ring chromosome cause problems?

We do not yet understand how ring chromosomes cause the problems seen clinically, although there are several theories. Due to their structure ring chromosomes can get tangled up when a cell is trying to divide, and this may lead to general problems within the cell. During cell division, the ring chromosome may break, become duplicated, or get lost, which may affect the viability of the cell. For many years it was thought that losing cells in this way would cause a child to be small. However most children with ring 20 are not short, and the short height associated with other ring chromosomes has recently been shown to be due to the loss of specific genes, and not only the presence of a ring chromosome. The main effects of ring 20 are therefore likely to be specific to chromosome 20 and not just the fact that it has formed a ring (Rossi 2008).

The clinical effects of having a ring chromosome 20 may also be related to specific genes on chromosome 20. There are two genes near the tip of the long q arm of chromosome 20 that have been associated with epilepsy. These are:

*KCNQ2*: this produces a protein that sits in the membrane of brain cells and plays a role in allowing the cell to recover once it has fired. Changes (mutations) in this gene have been associated with a particular type of seizure known as benign neonatal familial seizures.



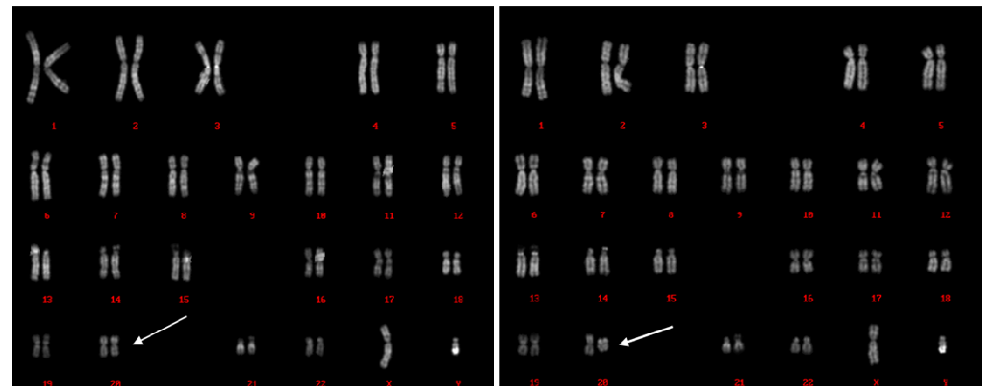
Left: Breaks near the ends of both chromosome arms leading to ring formation.

Right: A standard chromosome 20 (left) and a ring chromosome 20.

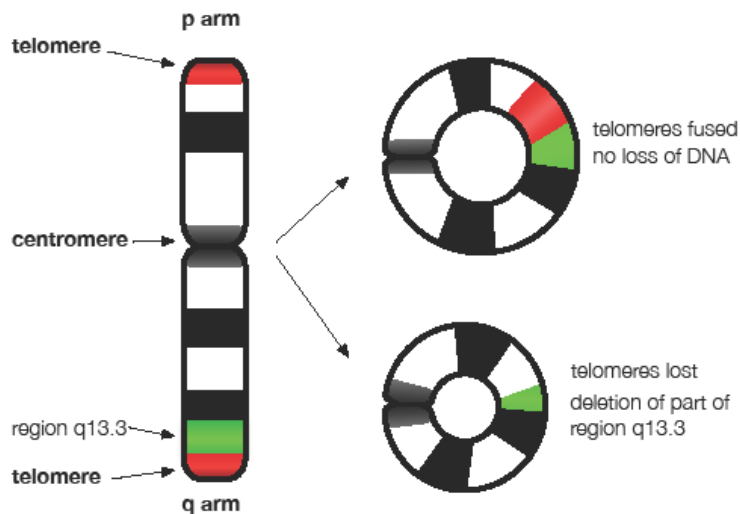
## How do rings form?

There are two main ways in which ring chromosomes are assumed to form and both can happen in ring 20.

At each end of the chromosome there is a cap called the **telomere** that protects the ends of the chromosomes from damage. A telomere is a region of highly repetitive DNA bound to special proteins. Rings can form when the telomeres at each end fuse together. If this is the case, there is no loss of genetic material. This event usually occurs very early in the life of an embryo and means that the embryo has two different cell lines, one with a standard chromosome 20, and one with the ring 20. This condition is named chromosomal **mosaicism**. Around two out of three people with ring 20 syndrome have this type of chromosome disorder.



Ring 20 mosaicism where two cell lines coexist in the same person. Left: the normal cell line, with the chromosome 20 pairs shown by an arrow. Right: the cell line with a ring 20, with one chromosome 20 substituted by a ring 20 [shown by an arrow].



Ring 20 chromosomes can also form from two breaks, one in the short (p) arm, usually in the region known as 20p13, and one in the long (q) arm, usually in the region known as 20q13.3. When this occurs, the chromosome ends can stabilise themselves by fusing to produce a ring. A ring formed in this way will usually lose the final segments of the p or q arms, including any genes. This type of ring usually arises during the formation of the egg or sperm before fertilisation (when a baby is made), so that the ring chromosome is present in every cell of the embryo. This kind of ring 20 is less common, affecting around one in three people with ring 20 syndrome (Daber 2012; Conlin 2010; Giardino 2010).

*For more information on ring formation, see pages 10-11*

### How is ring 20 diagnosed?

Ring 20 is usually diagnosed by cytogenetic (chromosome) analysis from a small blood sample. The chromosomes from the cells in the blood are examined and the ring is usually obvious under a microscope. The diagnosis can also be made from skin cells.

Newer DNA tests such as sequencing will miss rings, and even chromosomal microarray analysis will miss rings where no DNA has been lost. For a diagnosis, it remains necessary to look at chromosomes through a microscope to see their shape. However, additional molecular genetic tests such as FISH and microarrays from the same blood sample will show more precisely where the ends of the chromosome have broken and how much chromosome material, if any, is missing. The ring 20 may also be analysed from skin cells, but this is rare because the test is invasive.

responds best to prompts to remind him of tasks as organisation skills are poor – he doesn't have a good sense of time or urgency." 17 years

"R has no energy. She doesn't participate. She goes to school at 10 o'clock; it is just too much for her to get upon time. Earlier, she used to be bouncy between seizures, but now she isn't. Now and again just for 10 minutes." 17 years

Many families and some doctors agree that poorly controlled seizures affect an individual's ability to learn. It does seem that once seizures are better controlled, it is possible to regain some skills that may have been lost, but this is not true for everyone. What has been documented more clearly is a link between episodes of abnormal EEG activity (non-convulsive status epilepticus) and a decline in the ability to learn. This means that most neurologists would recommend that all children with ring 20 should have an EEG to monitor for unnoticed seizure activity (Daber 2012; Elens 2012; Giardino 2010; Vignoli 2009; Kobayashi 1998; Holopainen 1994; Zuberi, personal communication).

"D currently attends college. D enjoys lots of activities outside of college namely, Explorer Scouts, young leader for Beaver Scouts, karate (brown belt), electric guitar (working towards grade III) and is near to completing his Silver Duke of Edinburgh Award. This summer he is partaking in National Citizen Service (NCS). Handwriting is scruffy, but legible for his age. He still has issues with spelling: English is his weakest skill and he is trying to retake his English GCSE (national examination taken at 16 years) to obtain a pass. D reads well and enjoys reading much more than writing. He likes to read young teen fiction or science fiction/fantasy eg Eragon." 17 years

### Behaviour

Behaviour and attention problems have been reported in a number of people and have sometimes been the first sign that anything was wrong. Problems can vary from minor difficulties with concentration and restlessness to aggression and more serious difficulties. In several cases, the periods of difficult behaviour have coincided with spells when seizure control has been poor or when there have been long or frequent episodes of NCSE. Behaviour problems do vary with time and may improve as seizures are better controlled. The extent to which the anti-epilepsy drugs themselves contribute is not yet clear, but they are very rarely the only cause of behaviour problems.

Encouragingly, a number of children had behaviour problems during their school years that resolved during adolescence (Elens 2012; Giardino 2010; Vignoli 2009; Herrgård 2007; Yamadera 1998).

Unique families have been prescribed a variety of medications to help with their child's behaviour including methylphenidate (Ritalin) and Vallergran, but overall do not report finding them very helpful.



16 years

## What are pregnancy and birth usually like?

Pregnancy and birth are usually uneventful. Growth delay in the womb has been recorded, but most babies with ring 20 are born a normal weight and size (Garcia 2001; Brandt 1993).

## Appearance and growth

Most children with ring 20 look no different to other children, and are not noticeably short. The minority who do have an unusual appearance are more likely to have the non-mosaic form of the syndrome (Elens 2012; Conlin 2010; Giardino 2010).

Unusual physical features in this minority can include:

- Growth delay and being short
- A relatively small head
- Subtle facial features such as downslanting eyes, low placed ears and a small mouth and jaw
- Low muscle tone, so a baby or child feels floppy to hold

## Intellect and ability to learn

Ring 20 syndrome can affect learning ability and development but the extent to which it does is extremely variable. Some adults with a diagnosis of ring 20 have a level of learning disability while others have no more than specific memory problems. There are university students with ring 20 and others who are working independently, but this is not possible for others. The reason for these differences is not fully understood.

It is often stated that development usually appears to be normal until the onset of seizures. However, some children have a mild to moderate delay before epilepsy occurs and in others a decline in learning ability clearly sets in before any recognized seizures start, while in others it is true that the learning decline and obvious seizures coincide. It seems possible either that the epilepsy and the decline in ability to learn are each caused by separate effects of ring 20 on the brain or that the unnoticed NCSE causes a decline in learning ability. In yet others, there is no apparent decline in learning ability despite erratic seizure control.

[“D’s seizures have never been controlled, though his learning has improved with age. He achieves well despite his seizures and with a good support network in place.” 17 years](#)

When seizures begin early, it seems that learning abilities are more severely affected. However the level of ring 20 mosaicism does not necessarily affect learning ability, and this may relate to the fact that chromosomes are usually checked in white blood cells which does not tell you about the proportion of ring 20 cells in other organs such as the brain. The extent and speed of loss of learning capacity is extremely variable, ranging from relatively mild to profound, although the most typical level of ability is mild to moderate.

Families report that even with reasonable seizure control, school-age children miss out on education through frequent medical appointments, and time out for seizures and recovery.

[“J did not miss much school due to his seizures but was often tired. J is currently attending full time school without additional support, teachers are fully aware of the condition and we are working towards a support plan.” 5 years](#)

[“Seizures affect D’s education – he has 1:1 support at college as he misses learning input through frequent seizures and inability to process information easily at all times. He](#)

## Genetic test results

The results of chromosome analysis of someone with ring 20 syndrome are likely to look like one of these two examples:

**46,XX,r(20)[11]/46,XX[9]**

This shows that the expected number of chromosomes [46] were found, and that there were two X chromosomes [XX], so this is a girl or woman. **r(20)** shows that a ring chromosome 20 was seen. [11] shows that the ring was seen in 11 cells in the tissue examined, which is usually white blood cells. **46,XX[9]** shows that nine of the cells examined in the same tissue looked different, having just the 46 expected chromosome including two Xs for a female, and no ring. This is therefore someone with the mosaic form of ring 20.

**46,XY,r(20)(p13q13.32)**

This shows that the expected number of chromosomes [46] were found, and that there was an X and a Y chromosome [XY], so this is a boy or man. **r(20)** shows that a ring chromosome 20 was seen. **(p13q13.32)** shows that the ring was composed of a chromosome 20 that had broken in the short p arm within the p13 band, and in the long q arm within the q13.32 band. This means that the ring contains the chromosome material between the two breakpoints and the final regions of both arms is missing.

## Does the percentage of cells with ring 20 matter?

This is still controversial. Studies to date have shown that in children with a ring 20 in every cell in their body seizures usually begin earlier, at an average age of 2½ years. In children with a mosaic ring 20 pattern, including some cells with normal chromosome 20s, seizures began later, typically between 4 and 14 years, but occasionally in young adults. Among the children, seizures began earlier in those with a higher percentage of ring 20 cells. In one family where a mother passed a ring 20 on to her two children, the mother had the ring chromosome in 10% of her cells and developed seizures as an adult at 24 years, while seizures in her children with 40% of ring cells started at 5 and 7 years.

Some studies have found that seizures in children with a higher percentage of ring 20 cells are harder to treat, and that children with higher percentages of ring 20 cells were more likely to have behaviour problems. The effects of seizures on mental activity appear to be greater in those with a higher percentage of ring 20 cells. However, this relationship is also controversial (Daber 2012; Conlin 2010; Giardino 2010; Kurahashi 2009; Herrgård 2007).

## Are there people with ring 20 who are healthy, without developmental delay?

Yes, there are, although we only know about very few people for the obvious reason that people who are entirely healthy would not usually have a genetic test. In three families, the ring 20 only came to light in one of the parents after one of their children was diagnosed. In all three cases, the ring 20 was the mosaic type. The three parents are all developmentally normal, and one, a woman of 38 years, had no seizures. The other two women had epilepsy, with seizures starting at 11 years and at 24 years (Giardino 2010; Herrgård 2007; Canevini 1998; Back 1989).

## Seizures

Ring 20 syndrome affects the development and function of the brain. Epilepsy is the main feature of the syndrome, but how the ring chromosome causes the epilepsy is not yet understood. Seizures are of a characteristic type, although they start at different ages and vary in severity from person to person. In children with the mosaic form of ring 20 seizures most commonly begin in childhood at an average age of 7-9 years, while in those who have the ring 20 in every cell seizures usually begin earlier, from an average of 2½ years. Although there is a large amount of variation, seizures in people with a higher proportion of ring 20 cells tend to begin earlier.

People with ring 20 usually have more than one type of seizure. These include:

**Focal dyscognitive seizures** (previously termed complex partial seizures) can present with different features including jerking of an arm or leg, turning the eyes or head, gasping, chewing, lip-smacking, stiffening, looking frightened and being unable to talk along with altered consciousness. Sometimes these seizures may come from the frontal lobe of the brain and may be called 'frontal lobe seizures' (see below regarding night-time seizures).

**Non-convulsive status epilepticus (NCSE)** Many children also have unnoticed seizures or a 'twilight' state of confusion or lessened awareness with staring and sometimes appearing to be frightened. These seizures are hard to recognize and can at first be mistaken for absences or atypical 'absence seizures'. In NCSE children may have specific visual hallucinations, may laugh in an unusual way and some may have a brief stiffening of their arms or legs. NCSE can usually be diagnosed on an electroencephalogram (EEG). The EEG may show a specific pattern, with trains of slow waves and sharp spikes over the frontal region of the brain. The abnormal EEG pattern can last for days or even weeks and as it can result in a lessening of learning ability and increased behaviour problems, children are usually given antiepileptic medicines to normalize the pattern. Children are sometimes misdiagnosed at first with Lennox-Gastaut syndrome or Landau-Kleffner syndrome, both of which have similar EEG patterns. Although NCSE is not in itself life threatening, rarely it can progress to status epilepticus which can be life threatening (Daber 2012; Elens 2012; Giardino 2010; Vignoli 2009; Herrgård 2007; Ville 2006; Inoue 1997).

**Night seizures/frontal lobe seizures** can be subtle and can happen many times in one night. Seizures can vary from a child suddenly waking, sitting up briefly, stretching, rubbing and turning before rapidly returning to sleep, to a seizure with jerking of all limbs. Because these may be subtle, they are easily missed. These seizures probably arise from the frontal lobes of the brain. When doctors talk about frontal lobe seizures, these are usually the type that they mean.

**Tonic seizures** The whole body or the limbs go stiff and the person affected may fall if they are standing or sitting. This seizure type is usually short, seconds rather than minutes.

**Generalised tonic clonic seizures** After sudden stiffness and a fall the muscles contract repeatedly and rhythmically. Seizures of this type usually last no longer than three minutes. If they do not stop spontaneously by five minutes, they need rescue (emergency) medication.

Seizure frequency can vary a lot ranging from many times a day to only a few in a year. Unlike other epilepsy syndromes, in people with ring 20 the seizures do not tend to

become less frequent with age. Individual families report that seizures became more frequent during puberty, but it is not known whether this link is causal or not. In those with mosaic ring 20 there does not appear to be any link between the percentage of ring 20 cells and seizure frequency. Generally, seizures become more severe with time (Daber 2012; Elens 2012; Giardino 2010; Vignoli 2009; Unique).

Triggers for seizures identified by families include physical exercise, bathing or showering, change of temperature, heat, eating, tiredness, and stress (Unique).

When the electrical brain wave patterns of someone with ring 20 syndrome are recorded on an electroencephalogram (EEG), they show a variety of patterns, including the specific pattern during NCSE described above. Bifrontal slow waves can be striking and when seen, may be the first clue to doctors to test for ring 20. When the brain is imaged using magnetic resonance imaging (MRI), it most typically appears normal (Daber 2012; Conlin 2010; Vignoli 2009).

"The day before his Christmas concert J had a terrible night, 10+ seizures." 5 years

"Often when she has a bad episode with her seizures she will stay awake for 48 hours, as if she is frightened to go to sleep." 9 years

"He appears in a dreamlike state, unable to verbalise, movements slowing or repetitive automatisms. Following a seizure D is often confused and angry and may require a short nap." 17 years

## Treating seizures in ring 20 syndrome

The seizures and NCSE associated with ring 20 do not generally respond well to drugs (drug-resistant), and epilepsy surgery is not possible. Several different anti-epileptic drugs (AEDs) may need to be tried, on their own or in combination. The treatment that is successful and acceptable varies from person to person. 'Broad spectrum' AEDs are usually tried first since they are active against different seizure types. These include valproate, levetiracetam, lamotrigine, topiramate and zonisamide. Success has been reported in some people with a combination of valproate and lamotrigine, but so far no single therapy has worked for everyone. More recently a child of 6 years was successfully treated for 8 months with retigabine (ezogabine), but the drug was withdrawn from the market after warnings about significant side effects of pigmentation of the skin and the eye. Conversely, no particular AED has been found that exacerbates seizures. Until the mechanisms underlying the way seizures are generated in Ring 20 are understood, neurologists cannot successfully prescribe specific drugs for the seizures (Walleigh 2013; Elens 2012; Vignoli 2009; Herrgård 2007).

"When his seizures are controlled J is a lot happier and interactive, for example will play by himself and enjoys tasks more."

Vagus nerve stimulation (VNS) has been tried and a reduction in seizures has been reported in some cases but not in others. This involves implanting a medical device under the skin, similar to a pacemaker that delivers a mild electrical current to the brain via the vagus nerve. The long-term effectiveness of VNS therapy is not yet known (Parr 2006; Zou 2006; Alpman 2005; Chawla 2002).

The ketogenic diet, which is high in fat and low in carbohydrate, has been shown to be helpful in other types of epilepsy. However there are no published reports about whether this is successful or not in ring 20 epilepsy.