



Support and Information

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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 Dr Fowzan Alkuraya, Fellow, Genetics & Metabolism, Children's Hospital, Boston & Harvard Medical School, US and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, UK, 2005.

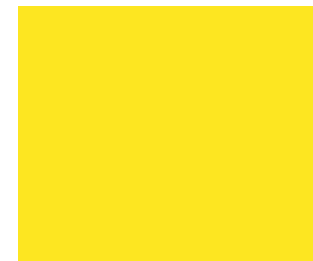
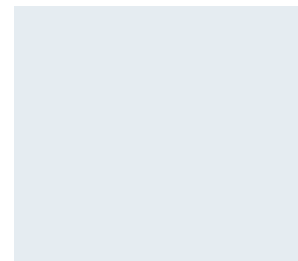
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Ring 2



Sources and References

The information in this leaflet is drawn partly from the published medical literature.

The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed. You can also obtain abstracts and articles from *Unique*.

The leaflet also draws on *Unique*'s database and a survey of members in 2005. References to statistical information held by *Unique* and to information from the questionnaire are marked U.

Ring 2 is an extremely rare chromosome disorder caused by the presence of a ring chromosome in the cells of the body. Chromosomes, the structures inside the nucleus of each cell that contain the genes that instruct the body to develop and work properly, are usually shaped like threads. Occasionally the ends of a chromosome join to form a ring. Any of the 22 different non-sex chromosomes can form a ring and so can either of the sex chromosomes X and Y. This seems to occur very rarely indeed to chromosome 2, which is almost the largest chromosome.

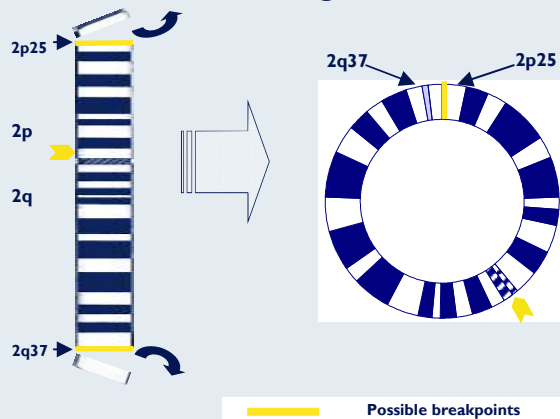
In 2005, only 11 children with this unusual chromosome disorder had been described in the medical literature and *Unique* had five affected members, one of them described in the medical literature. As finding a ring 2 chromosome is so very rare, there is some uncertainty over whether a ring 2 syndrome exists. What is certain is that everyone diagnosed with the disorder so far shares certain features, while other features differ between individuals.

Some people with ring 2 have some cells with the ring chromosome and some normal cells. This is called mosaicism and your geneticist will tell you if this is what your child has.

Frequent features

- All children known so far with ring 2 have been very short for their age. Their small size became evident during pregnancy and they were small for dates at birth. Their head was usually particularly small (microcephaly).
- Most children are healthy and do not have major birth defects.

Possible formation of a Ring 2 chromosome



Autism

Autism is reportedly common among children with a 2q37 deletion, although there is no information either way for ring 2. Nine people with a 2q37 deletion and autism have been fully described and autism or repetitive, hyperactive behaviour was noted in 35 per cent of children in a recent survey. Seventeen *Unique* families (46 per cent) said that their child had autistic features and leaving out pre-school children, the rate rose to 64 per cent. Familiar types of behaviour include limited eye and social contact, repetitive behaviour such as rocking, especially under stress, exclusive focus on certain toys or objects, extreme need for predictable routines, inability to express emotional thoughts or to interact emotionally with other people, fear and even panic at what appeared unpredictable and, finally, distress expressed as self injury. In some children, autistic features existed alongside a social, loving and contact-loving personality.

Families with a child with a 2q37 deletion told *Unique* that autism undermined their child's development more than other symptoms of the chromosome disorder. It is likely that families of children with ring 2 should also be alert to this (Smith 2001; Aldred 2004).

How and why did the chromosome disorder happen?

It is not known why the ring chromosome forms in the first place but when parents' chromosomes are tested, they are usually normal. Rearrangements occur in chromosomes as part of evolution. They affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. So there is no reason to suggest that your lifestyle or anything that you did caused the ring to form.

After conception, when the cells in the embryo that will become the baby are dividing and multiplying, the ring may not divide readily, and this will leave some cells with one ring, others with no ring, and yet others with two rings, entangled rings or double sized rings. This process, known as dynamic mosaicism, is particularly common with rings of the long chromosomes such as chromosome 2. The cells containing odd numbers of rings or no ring at all may die off and this constant loss of cells during growth is probably what causes the slowed growth rate in children with a ring chromosome disorder.

Can someone with ring 2 pass it on?

There are a number of families where a ring chromosome has passed from parent to child but none yet involving a ring 2 (Gardner & Sutherland 2004).

■ Hearing

Most children with ring 2 have normal hearing. Glue ear, causing a temporary conductive hearing loss, is common among all young children including those with ring 2. If it is long-standing, it is usually treated with tubes (grommets) until the child outgrows it. Two children have been diagnosed with a permanent hearing loss but this may not be caused by their chromosome disorder (Lacassie 1999; U).

■ Eyes and vision

Most children with ring 2 have normal vision. Squint (strabismus) may occur, as it does in other children, and so may minor errors of refraction that can be corrected with prescription glasses. One child was diagnosed with a disorder of the retina but this may not be due to the chromosome disorder (Maraschio 1979; U).

Therapies

Unique's experience is that children for whom occupational and physiotherapy (physical therapy) was provided early have improved development. Most children also benefit from speech therapy both to improve their self feeding skills and speech development.

Behaviour

There is little information on behaviour in children with ring 2. A 10-year-old boy was described as immature. The evidence from *Unique* comes from two families. In each case, behaviour has become hard to manage. On the one hand, the child can be friendly and lovable but can also become aggressive and destructive.

The information available on children with 2q37 deletions suggests that, in some children at least, behaviour issues may be important. Families of children with a 2q37 deletion may face a range of extreme behaviours. There appears to be no one personality type and many aspects of behaviour in children with 2q37 deletion syndrome are well known to any parent of a small child. However, the behaviours are more intense, more extreme, they last longer and parents need extra ingenuity and energy to cope with them. In the largest series of 35 people with a 2q37 deletion, eleven (31 per cent) had some level of disorder including repetitive behaviour, hyperactivity, autism and attention deficit disorder. This high rate means that families should have rapid access to behaviour management support (Lacassie 1999; Aldred 2004).

Families say ...

“ He can be aggressive and destructive and can't leave anything alone. He throws everything and particularly likes emptying bedroom contents downstairs. He likes any reaction to his behaviour, good or bad, and terrorises animals including horses, cats, dogs, spiders and bees, despite being stung three times – age 7.

“ The greatest problems are with his behaviour, social development, speech, making contact, imitation, play and staying calm. He tends to stereotypy in play; has a short attention span; reacts well to intensive stimulation but still does not concentrate - age 3.

Other features

Other features shown by a child with ring 2 are likely to vary partly depending on whether or not genes have been lost from either end of the chromosome when the ring formed. When a ring chromosome forms, either the tips fuse with no loss of genes or chromosome material, or the chromosome breaks at each end and the 'sticky' broken ends join to form a ring. Your geneticist or paediatrician should be able to tell you whether some chromosomal material has been lost when the ring formed in your child's case and this will usually be marked in the karyotype (chromosome description) and some additional studies from the genetics laboratory.

In almost all children known so far where genes have been lost, the short arm of chromosome 2 has broken at band p25 and the long arm has broken at band q37 (see diagram). A deletion (loss) from chromosome 2q37 is a more common chromosome disorder than a ring 2. Most of the features in the list below have been found in some children with 2q37 deletions and have also been found in some children with ring 2; others have only been seen in children with ring 2.

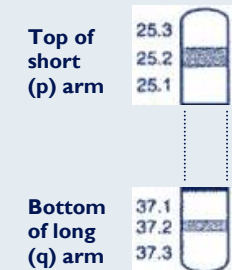
- Developmental delay.
- Learning difficulties, usually mild or moderate.
- Feeding difficulties in babies and young children, usually minor.
- Hypotonia (showing as floppiness) in babyhood and possibly in early childhood.
- Short hands and feet.
- Hernias, especially umbilical and inguinal (in the groin).
- Vulnerability to behaviour difficulties, including autism.
- Heart conditions.
- Small genitals, occasionally with minor anomalies.
- Usually minor foot anomalies.
- Variable number of coffee coloured patches on the skin (café au lait spots).
- Loose, flexible joints.

(Lacassie 1999; Dee 2001; Aldred 2004; Alkuraya 2005; U)

Outlook

It is hard to suggest an outlook for children with ring 2 when so few are known. The oldest child described in the medical literature was 10 years old and the oldest known to *Unique* was 11 years old at the time of writing. A child without serious birth defects or health problems could usually expect a normal lifespan and *Unique's* members have usually been healthy. *Unique's* experience has been that one child had a complex heart condition as well as other birth defects and died before the age of one. A baby born with a similar heart condition had successful surgery at five days of age (Lacassie 1999; Alkuraya 2005; U).

Ends of chromosome 2



Pregnancy

Out of 11 pregnancies we know about, four were described as normal. In four cases there was very little amniotic fluid (oligohydramnios). In five cases, the baby's body, the head or both were found to be small for the gestational age (number of weeks of pregnancy). In one case, the umbilical cord contained two blood vessels instead of the expected number of three. In this case, the fluid filled spaces within the baby's brain were found to be enlarged (Lacassie 1999; Dee 2001; Aldred 2004; U).

Birth and the newborn period

Birth appears to usually occur at or near term or slightly early. Of 11 pregnancies, eight births were at or near term while three babies were born around 35 weeks. Babies were typically very small, with a range of birth weights from just below 1500g to just above 2500g at term (3lb 5oz to 5lb 8oz).

There is little information on babies' health at birth and as problems tend to be reported more often than non-problems, this is a generally good sign. One especially tiny baby (birth weight below 1500g at 35 weeks) needed ventilation after developing respiratory distress syndrome; another required facial oxygen; one had recurrent urinary tract infections and two babies needed heart surgery, one of them also needing a colostomy (a surgical operation to create a temporary outlet from the rectum, usually until a full surgical repair is completed) as the anus was sealed over (imperforate) (Dee 2001; Alkuraya 2005; U).

First signs

A baby's very small size, small head and in some cases some unusual facial features may alert doctors to consider a chromosome disorder. Other features mentioned by some *Unique* families included incurved fifth fingers (clinodactyly) and a wide space between the nipples on the chest.

Will a child with ring 2 look different from other children?

Apart from their small size, children usually look healthy and normally proportioned, although the head may appear particularly small, especially if this was noticed at birth.

Some children with a deletion from the long arm of chromosome 2 look very similar to each other and this facial appearance has also been seen in children with ring 2.

A child with ring 2



A child with a 2q37 deletion



■ Bones and skeleton

People with a 2q37 deletion are susceptible to a condition known as Albright's hereditary osteodystrophy (AHO)-like syndrome. AHO is a condition that affects the way the body lays down calcium and is caused by a gene that resides in a different chromosome. It is uncertain whether individuals with ring 2 are also susceptible to this, but suggestive signs would include short fingers (see below).

People with AHO have subtle physical changes including short stature, a round face and a tendency to put on too much weight. Some bones in the hands and feet are unusually short. Up to 50 per cent of people with a 2q37 deletion have unusual hands and feet, very similar to people with AHO, showing that genes found at 2q37.3 must also be important for skeletal development. If this is true, then some people with ring 2 would be expected to show the same features. One child with ring 2 was found to have bony outgrowths on each elbow (Wilson 1995; Smith 2001; U).

■ Joints

Occasionally children have been found to have very flexible joints at the wrists, ankles and feet. This can make hand control for feeding and writing more difficult but improves with therapy (Sutherland 1978; U).

Other health concerns

When very few children have been described with a particular chromosome disorder, it can be uncertain whether any birth defects or health concerns are caused by their disorder or not. The concerns listed here have been found occasionally in children with ring 2 and have also occurred in children with a 2q37 deletion: unusual position or formation of the kidneys; frequent childhood infections; seizures. Two out of five *Unique* children with ring 2 had a spinal curvature, treated in one child with a brace (U).

■ Hands

It has been observed that in one series, all children with ring 2 had incurved little fingers. In *Unique's* experience, this feature – very common in children with chromosome disorders and also found in other children – may occur but is not universal. Other children have been found to have very long fingers and thumbs or, in one case, a child had thumbs in which the final joint was divided (bifid thumb). This can be surgically reconstructed (Alkuraya 2005; U).

■ Skin

Children with a mosaic form of a chromosome disorder (see page 2) are sometimes found to have one or more coffee coloured skin patches (café au lait spots). These are not harmful, but they may increase over time and pale skin patches may also appear (Lacassie 1999; Dee 2001; U).

Medical concerns

Many babies and children with ring 2 are perfectly healthy. However, some medical conditions and birth defects are more common in a group of babies and children with ring 2 than in other children. This does not mean that your baby will necessarily be affected, rather that the paediatricians who care for your baby's health will be especially alert to these conditions.

■ Heart conditions

Heart conditions are known to occur fairly commonly in children with a small deletion from the end of the long arm of chromosome 2 (2q37 deletions) and may be even more common in babies with ring 2. The range of conditions is broad – holes between the lower chambers of the heart (ventricular septal defects), persistent ductus arteriosus (persisting structure of the fetal circulation), coarctation (narrowing) or displacement of the aorta, the blood vessel that leads from the heart to the body. Some babies have a single condition, while others have more than one defect. While some conditions resolve naturally with time, a few babies will need surgery (Maraschio 1979; Conrad 1995; Alkuraya 2005; U).

■ Genitals

In around three quarters of the babies, some unusual feature of the genital area was noticed, although it was usually minor and did not need treatment. Most commonly, in boys, the genitals were relatively small, although this only became apparent in one boy by his first birthday. The testicles might not have descended into the scrotum at birth. They may descend later; if not, they can be brought down in a simple surgical operation called orchidopexy. Two girls were noted to have underdeveloped skin folds at the entrance to the vagina. Two children had a more severe or complex condition: in one, there was a channel connecting the vagina with the rectum and a boy with small genitals also had hypospadias (where the hole usually at the penis tip is on the underside of the shaft) and a scrotum divided in two (Maraschio 1979; Vigfusson 1980; Jansen 1982; Wyandt 1982; Lacassie 1999; U).

■ Limbs and feet

Six babies out of 15 were born with an unusual position or formation of one foot or both. A number of different anomalies have been noted, including rocker bottom feet (the sole is curved like a rocker), club foot (talipes), flat feet and a tendency for the feet to roll outwards or inwards. Stretching and physiotherapy will usually bring some improvement but occasionally a surgical operation is needed to improve the position of the foot (U).

Families say ...

“ No treatment needed, as he is very mobile – age 7.

Facial features

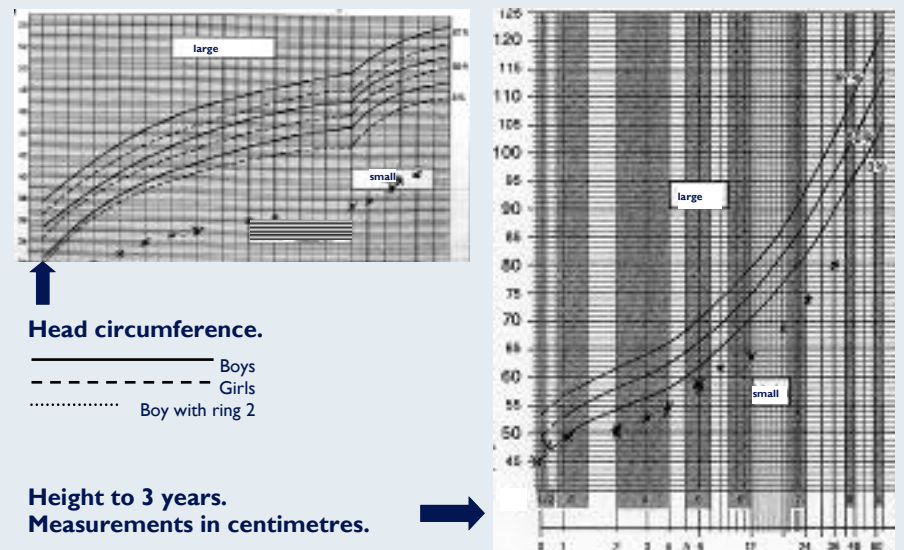
Doctors may identify facial features that are different from the norm. These are usually quite subtle and nothing that on its own would make your baby or child stand out. Taken together, however, they can show a pattern that is typical of a particular chromosome disorder and this pattern helps doctors towards a diagnosis. Most children will have some of these features, but not all of them.

Those described in the medical literature include a flat back to the head (occiput); a bulge down the middle of the forehead where two plates of the skull meet at a join called the metopic suture; high arched eyebrows; upslanting and wide set eyes; tiny skin folds across the inner corner of the eye (epicanthic folds); ears that are set below the line of the eyes; a small horizontal opening of the eye (blepharophimosis). A baby's neck may be unusually short and in many cases the lower jaw and chin are small. Occasionally, babies and children with a mosaic chromosome disorder (see page 2) may have a somewhat asymmetrical appearance (Dee 2001; U).

Growth

Growth delay is usually obvious during pregnancy and continues after birth, with the typical growth rate on a baby's height and weight chart tracking the lowest curves on the chart or falling below them (see image). In one child with ring 2, partial growth hormone deficiency was identified and the recommendation made that children should be evaluated for growth hormone deficiency and treated where appropriate. Among *Unique* members, growth hormone evaluations in a baby showed a normal outcome. Other children were not evaluated (Lacassie 1999; U).

Growth charts of a child with ring 2



Food and eating

Much of the information on feeding problems comes from *Unique*, where the experiences of three member families with children aged up to 7 showed that any feeding problems were usually relatively short-lived and by early childhood children could be expected to be eating a wide range of healthy foods. Hypotonia plays a role and other factors may be important as well as was seen in a baby of 16 months who had mild gastro oesophageal reflux that was not severe enough to cause distress and additionally experienced delayed emptying from the stomach to the intestines. Nonetheless, at 16 months he was eating healthily, taking small portions every three hours and including fruit and vegetables in his chosen foods. A five year old had no feeding problems and ate a range of healthy foods including apples and carrots, while a seven year old who as a baby had sucked weakly and tired easily at the breast but nonetheless breastfed for six months, was eating widely but remained fussy over new tastes and textures. He had been delayed in accepting lumpy foods.

Overall, there is no clear pattern of feeding difficulty and plenty of evidence that children usually eat healthily (Sutherland 1978; Vigfusson 1980; Wyandt 1982; U).

Learning

The evidence from the medical literature and from *Unique* is that children can face a broad spread of ability to learn, with some children apparently unaffected cognitively while one or two children have severe and complex learning needs. One child who needed most support with learning had a mosaic pattern of chromosome disorder, as did one child with no apparent learning difficulties. One child with no apparent learning difficulties had breakpoints at 2p25 and 2q37.3.

Families say that their children learn best in a 1:1 situation or in a small group; performance may be undermined by difficulties with concentration and attention (Sutherland 1978; Vigfusson 1980; Wyandt 1982; Cote 198; Lacassie 1999; Dee 2001; U).

Speech and communication

There is little evidence from the medical literature on speech development. However, in one child studied to the age of 10, speech improved markedly with therapy, resulting in a strong recommendation that this service should be offered to all affected children (Lacassie 1999; U).

The *Unique* experience is of a wide range of ability that generally mirrors a child's learning skills. A child with complex learning needs was able to speak in 2 to 3 word sentences by the age of 7, but also used picture symbols to communicate. A 5 year old had difficulties with social communication and imitation and was evaluated for autistic tendencies but was making good progress by the age of four. He had a small but effective and growing vocabulary of around 10 words (Sutherland 1978; Vigfusson 1980; Wyandt 1982; Lacassie 1999; U).



Sitting, moving, walking

Some delay in reaching the typical baby developmental 'milestones' is typical of children with chromosome disorders, but in children with ring 2, this seems to be usually slight and at least one child in *Unique* showed no delay in what are known as gross motor skills. The *Unique* experience is that babies rolled over between four and 10 months, sat alone between eight and 18 months, started to shuffle or crawl between 13 and 15 months and to walk during their second year, with an age range of 12 to 25 months. An individual child may

develop gross motor skills somewhat later than the upper ages given here.

Unique's experience has been that once mobile, children move fast and if anything tend to be overactive. They are likely to be best placed in a learning environment where their relatively good gross motor skills are encouraged, maximised, praised and harnessed to manage any difficulties they may face with attention or concentration.

Using their hands

Hand use seems to be typically only slightly delayed and in one family's experience, an early delay was overcome by the age of 7. Children benefited from physiotherapy (physical therapy) and occupational therapy (Lacassie 1999).

Families say ...

“ He walks, runs and climbs like a monkey
- age 5.

“ He runs everywhere, fast
- age 7.

“ He can open a bottle or a banana, but his hand use is not so advanced as his gross motor skills
- age 5.