12q14 microdeletions
12q14 microdeletions
A 12q14 microdeletion is a very rare genetic condition in which a tiny piece is missing from one of the 46 chromosomes – chromosome 12.

Chromosomes are made up mostly of DNA and are the structures in the nucleus of the body’s cells that carry genetic information (known as genes), telling the body how to develop, grow and function. Chromosomes usually come in pairs, one chromosome from each parent. Of these 46 chromosomes, two are a pair of sex chromosomes, XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm (shown at the top in the diagram below) and a long (q) arm (the bottom part of the chromosome). People with a 12q14 microdeletion have one intact chromosome 12, but the other is missing a tiny piece from the long arm and this can affect their learning and physical development. However, a child’s other genes and personality also help to determine future development, needs and achievements.

Looking at chromosome 12q
You can’t see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. Even if you magnify the chromosomes as much as possible, to about 850 times life size, a chromosome 12 with the microdeletion at q14 often looks normal. People who have missing material on a chromosome are said to have a deletion but when the amount is so small that it can’t be seen even under a high-powered microscope, it is called a microdeletion. The 12q14 microdeletion can be found using molecular techniques such as multiplex ligation-dependent probe amplification (MLPA) and array comparative genomic hybridisation (array-CGH) or by cytogenetic fluorescent in situ hybridisation (FISH) techniques using fluorescent DNA probes targeted to gene markers within the involved chromosome 12q14 region. These techniques usually show whether the microdeletion is present or not and which genes are deleted (size of the deletion). It is believed that the effects are caused by the presence of only one copy of these genes instead of two, as expected normally. The 12q14 region is denoted by the red bar on the diagram opposite.

Band 12q14 contains around 9 million base pairs. This sounds a lot but it is actually quite small and is only seven per cent of the DNA on chromosome 12.

Chromosome 12 has around 132 million base pairs and is about four per cent of the total DNA in our cells. Base pairs are the chemicals in DNA that form the ends of the “rungs” of its ladder-like structure. The size of the microdeletion is variable and reported sizes range from 1.28 megabases (Mb) to 10.12Mb.

1 base pair = bp
1,000 base pairs = 1kb
1,000,000 base pairs = 1Mb
Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point where the chromosome has broken in your child. With a 12q14 microdeletion, the results are likely to read something like the following example:

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arr[hg19] 12q14 (55344266-58329514)x1
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- **arr**: The analysis was by array-CGH
- **hg19**: Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new “builds” of the genome are made and the base pair numbers may be adjusted
- **12q14**: The chromosome involved is 12q14
- **(55344266-58329514)x1**: The base pairs between 55,344,266 (around 55Mb) and 58,329,514 (around 58Mb) have been shown to be deleted. Take the first long number from the second and you get 2,985,248 (3Mb). This is the number of base pairs that are deleted. x1 means there is one copy of these base pairs, not two – one on each chromosome 12 – as you would normally expect

Emerging phenotype: what to expect

When only very small numbers of people have been identified, we can’t yet be certain what the full range of possible effects of the microdeletion are. The features that are most striking and most common are:

- Growth delay in the womb and/or afterwards leading to short stature
- Feeding problems
- Children are likely to need support with learning. The amount of support needed by each child will vary, although most benefit from supportive services for special needs
- Speech delay
- Osteopoikilosis (a rare bone disorder where a person’s bones have small areas of denser than normal bones) in some people
- Heart problems in some people

What is the outlook?

We can’t be sure yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan.

Is there a 12q14 microdeletion syndrome?

In 2007 researchers described three people with similar features and problems and a deletion from band 12q14. Since people with this deletion show similar features it is now often referred to as 12q14 microdeletion syndrome [Menten 2007; Buysse 2009; Mari 2009; Spengler 2009; Lynch 2011].

Sources

The information in this guide 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 [http://www.ncbi.nlm.nih.gov/pubmed/].

If you wish, you can obtain most articles from Unique. In addition, this guide draws on information from a survey of members of Unique conducted in 2011, referenced Unique. When this guide was written Unique had 6 members with a 12q14 microdeletion and a further 13 people are described in the medical literature. These people range in age from 2 to 20 years.
**Pregnancy**

Many mothers carrying babies with a 12q14 microdeletion experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. There is information available on ten pregnancies of mothers carrying a baby with a 12q14 microdeletion. Four had no pregnancy problems and no unusual findings on ultrasound scans. Three babies had intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed resulting in babies that are smaller than expected for the number of weeks of pregnancy. Two mothers had oligohydramnios (an unusually low volume of amniotic fluid). In one of these mothers the placenta failed in later pregnancy and she delivered her baby by caesarean section at 34 weeks. One mother had hyperemesis (severe morning sickness) but delivered her baby at term (Menten 2007; Buysse 2009; Mari 2009; Lynch 2011; Unique).

**Newborn**

Newborns with 12q14 microdeletion syndrome may not have any signs or symptoms. However, quite a lot of babies (9/14) had feeding difficulties from birth and were described as failure to thrive. As a result of these difficulties some babies needed a stay in the neonatal unit at hospital for a few days after birth (Unique).

**Feeding and growth**

Babies are often, but not always, born small and light for dates. Birthweights recorded at Unique and in the published medical literature show a considerable variation with an average of 2.59 kilos (5lb 11oz). Around half of the babies have a normal birth weight, however, around half (8/15) had a low birth weight (below 2.6 kilos or 5lb 12oz) at term (Menten 2007; Buysse 2009; Mari 2009; Spengler 2009; Lynch 2011; Unique).

**Range of birth weights (at or near term):**

1.9 kilos (4lb 3oz) to 4.08 kilos (9lb 16oz)

Feeding difficulties appear to be common in those with a 12q14 microdeletion and many babies have feeding difficulties particularly in the newborn period. The hypotonia (floppiness) that affects some babies with 12q14 microdeletions can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Three babies have a high palate which can mean the action of sucking and swallowing is difficult. One baby benefited from having a temporary nasogastric tube (NG-tube, passed up the nose and down the throat) and one baby had a gastrostomy tube (a G-tube, feeding direct into the stomach) (Menten 2007; Buysse 2009; Mari 2009; Lynch 2011; Unique).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). Three children in the medical literature had GO reflux but none of those children surveyed by Unique were affected. GO reflux can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Menten 2007; Lynch 2011).

Many children, although not all, have growth delay resulting in short stature. The **HMGA2** gene has been proposed as the gene responsible for the growth delay and
those children whose deletion does not include this gene seem to have normal growth [Ongoing research involving 12q14, page 10].

One child had growth hormone treatment without any obvious benefits. Another child had growth hormone treatment and after 10 months he had a better growth rate (Buysse 2009; Mari 2009).

“He has had a poor appetite since a newborn and still doesn’t eat much. He still drinks Pediasure [a total nutrition milk]. He started drink it at 14 months when blood tests showed he was slightly malnourished. It was a godsend for us because it was stressful trying to get him anything at all and he took to drinking his pediasure well” – 3 years

“He has never had any issues with eating” – 3 years

Appearance
Your child with a 12q14 microdeletion will most likely look like other members of your family. However, children sometimes have one or two unusual facial features. They often have a prominent forehead and the bridge of the nose is often wide, which can make the face look a bit triangular in shape. They may have widely spaced eyes (hypertelorism) or deep-set eyes with long eyelashes. They may also have thin lips.

Development: sitting, moving, walking (gross motor skills)
Often gross motor skills are affected in those with a 12q14 microdeletion and this means that it may take a little longer for children to roll over, sit, crawl and walk. From the limited information available, children sat unaided between the ages of six and 18 months (average 12 months). Independent walking was mastered by most between 13 months and four years (average two years and one month). One girl has not mastered independent walking at three years but sat unaided from 18 months. One girl bottom shuffled until she walked aged four. A 14-year-old girl has an unusual way of walking (gait). A 3-year-old boy and 16-year-old girl are described as having no motor problems at all. Children may need considerable support while learning to walk (Menten 2007; Buysse 2009; Mari 2009; Spengler 2009; Lynch 2011; Unique).

“He loves jumping on the trampoline and pedalling his trike around” – 3 years

“He was always interested and engaged as a baby but not very active. He never really rolled over as an infant. He sat up on time (6 months) but walked very late (first independent steps at 20 months and consistent independent walking at 23 months). At 36 months he does not jump or pedal a trike” – 3 years

“She walks, runs and skips around the house. She is not still for long” – 3½ years

Development: hand-eye co-ordination and dexterity (fine motor skills) and self care
Fine motor skills in children with 12q14 microdeletions may also be affected and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be
especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch screen computer can often be easier. Two 3-year-olds have good fine motor skills. An 11-year-old girl can dress herself and manage basic hygiene. Toilet training is also likely to be affected (Menten 2007; Lynch 2011; Unique).

“His fine motor skills seem above average. He holds a pencil with the correct grip. His self-help skills are normal for his age” – 3 years

“Grasping and pincer grip developed normally. He can use a pen/chalk; easily build with large Lego™; complete puzzles; throw and catch a ball and use a spoon and fork independently. He has never waved ‘hello’ or ‘goodbye’ and started pointing late (24 months) and then frequently with his middle finger” – 3 years

“She has no problems. She can brush her teeth, feed herself and wash herself” – 3½ years

Speech and communication

Almost all those with 12q14 microdeletions described so far have a delay in language skills. The experience of Unique members is: a 3-year-old talks reasonably well; another 3-year-old has language delay but has a core vocabulary of around 25 words and a 6½-year-old has a good understanding of vocabulary and commands and uses vocal noises, gestures and visual aids to communicate but has no words. In the published medical literature many children (8/11) are described as having speech delay. A 2-year-old has many words. A 3-year-old has no words but babbles. A girl who is 3 years and 8 months has no speech but can express herself by showing what she wants. A 6-year-old boy has no speech. At 6 years and 9 months one boy developed the use of single words which he uses with defining action very well. An 11-year-old had significantly delayed speech when younger but now speaks in full sentences in both English and Polish. A 14-year-old is very articulate. A 16-year-old girl has a squeaky voice (Menten 2007; Buysse 2009; Mari 2009; Spengler 2009; Lynch 2011; Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. Those with a high palate may also have specific difficulty with perceiving and producing certain sounds. An ABR test in one Unique child revealed unusual auditory waveforms and a large and long-lasting cochlear microphonic in both ears. This means that while sound is going into his ear it is being distorted. A picture exchange communication system (PECS) and/or sign language can help children communicate their needs and speech therapy can be enormously beneficial.

“He talks reasonably well in three-word sentences” – 3 years

“His main delay is language. He has said as many as 70 different spontaneous words but his core vocabulary is just about 25 words, giving him an expressive vocabulary of a typical 18-month-old. His receptive language is better. He has said a couple of two-word phrases such as ‘help pull’ but these are rare. He also has a couple of two-word frozen phrases, as in ‘all done’. His words are mainly single syllable utterances, with the tail end of the word deleted, as in ‘wah’ for ‘water’. Also we have noted that he frequently speaks out of the side of his mouth. He is very responsive to funny sounds
and music. He has recently been diagnosed as having unusual auditory waveforms and a large and long-lasting cochlear microphonic in both ears. One doctor has theorized that it may sound to him as though sounds are blending together. This would likely contribute to his speech delay, as it would make it difficult to pick out individual words in a sentence” – 3 years

“She has no problems with speech and uses complete sentences” – 3½ years

**Learning**

Learning difficulties are a common finding in children with 12q14 microdeletion syndrome. As a rule, the larger the deletion the more likely the child will have learning difficulties. However, a 3-year-old has no learning difficulties and is doing well in a mainstream nursery and a 16-year-old girl is at a selective school. Children often have mild to moderate learning difficulties. A 6½-year-old cannot read but loves books and will point to writing in a story and knows if it is not being read correctly. He attends a special educational school and has 1:1 assistance in the classroom. An 11-year-old cannot read or write but can recognize colours and is good at jigsaws. She likes singing and music. An 18-year-old has mild learning difficulties and is taking applied mathematics but having problems with English at school. A child with a learning difficulty is likely to need some learning support. Many children benefit from attending a special educational school. Repetition, visual aids and 1:1 assistance are reported by parents to help children learn best (Menten 2007; Spengler 2009; Lynch 2011; Unique).

“He has a great memory and seems bright. He loves books and knew all his colours by the age of 2. He could count to 10 by 2½ years. Knows some of his letters and sounds” – 3 years

“He definitely has a learning difficulty but at this time it is difficult to gauge how severe it is. It is also difficult to tell how much of his learning delay is cognitive and how much is specifically language-related. He can definitely be taught. He is very interested in identifying letters and numbers. He can identify the sounds for about half the letters in the alphabet and he is learning the numbers from 1 to 10. He imitates his parents (putting washing in the washing machine etc). He learned to drive his remote-control car straightaway. He has an intense focus on books and music” – 3 years

“She is very smart. She cannot read yet but knows her letters and numbers and can write her name with help” – 3½ years

**Medical concerns**

- **Osteopoikilosis**

Osteopoikilosis is a rare bone disorder where a person’s bones have small areas of denser than normal bone. Osteopoikilosis literally means ‘spotted bones’ and an affected person’s bones have a mottled appearance on X-ray examination. Apart from the unusual appearance of the bones, osteopoikilosis usually has no other effects. Osteopoikilosis has been shown to affect three people in the medical literature but has not been seen in any Unique members (Menten 2007; Mari 2009; Unique).

However, osteopoikilosis may be absent at a young age as the three people who are affected were diagnosed between the ages of 14 and 18 years. The LEMD3 gene has been shown to be responsible for osteopoikilosis (see Ongoing research into 12q14 on page 9) [Menten 2007].
Skin
One child has thin skin with patches of irregular lesions (mark or growth on the skin) which are described as being reminiscent of Buschke-Ollendorff syndrome (a very rare skin disorder characterised by skin lesions). Another child has yellowish areas of skin and one has areas of increased pigmentation (Menten 2007; Buysse 2009).

Heart
Heart problems have been reported in several children with 12q14 microdeletion syndrome, particularly those with larger deletions. One child has a ventricular septal defect (VSD) which is a hole in the wall between the two pumping chambers of the heart (ventricles). Two children have an atrial septal defect (ASD) which is a hole between the two filling chambers of the heart (atria). Treatment for a hole in the heart is determined individually. Small holes may close spontaneously; a larger hole usually needs surgical repair. One child has a patent ductus arteriosus (PDA) which occurs when the ductus arteriosus (channel between the aorta and the pulmonary artery that takes blood to the lungs) fails to close after birth. Two children have hypertension (high blood pressure). Two children had mild pulmonary stenosis (a narrowing of the pulmonary valve (a flap-like structure that allows blood to flow in one direction), meaning that the heart has to work harder to pump blood which results in breathlessness), one of whom outgrew the problem (Menten 2007; Mari 2009; Unique).

Hands and feet
Children with 12q14 microdeletion syndrome may have hands that look different. Three children have curved little fingers (clinodactyly). Two children have hypermobility (laxity) in their small joints. One child has a single palm crease on her left hand; one has large thumbs; one has broad hands and one has short, broad fingers. These features do not usually cause medical problems but in a few cases do have an impact on functionality (Spengler 2009; Lynch 2011; Unique).

The feet of children with 12q14 microdeletion syndrome may also not be perfectly formed. Two children have puffy feet; one has short, broad toes; one has large heels and one has flat feet with toes that are fused (syndactyly) (Menten 2007; Lynch 2011; Unique).

Teeth
Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. A Unique child had late eruption of teeth with the first tooth appearing at 16 months. An 18-year-old boy has six secondary (adult) teeth missing. Regular and high quality dental care is recommended (Menten 2007; Unique).

Vision
Eye findings in 12q14 microdeletion syndrome do not appear to be common. Three children have strabismus (a squint) where one or both eyes can turn inwards, outwards or upwards and one has hypermetropia (long sight) (Lynch 2011; Unique).

Other
Other findings have been described in only one or two children and so may not actually be caused by the 12q14 microdeletion: two Unique children had glue ear (fluid in the middle ear) and required grommets; one Unique child suffers from constipation and a 4-year-old in the medical literature had constipation when younger (Lynch 2011; Unique); one child has kidney disease (nephropathy) and one child has ectopic (unusually positioned) kidneys (Menten 2007); two children have an intention tremor (a tremor which is worse during voluntary movement) (Menten 2007; Buysse 2009); two children have mild scoliosis (curvature of the spine) (Menten 2007; Lynch 2011); one child has unusual body
hair, mostly on his back (Unique); one child has an unusual shaped chest and one child has pyloric stenosis (the passage between the stomach and the small bowel becomes narrower resulting in persistent vomiting) which was corrected surgically (Lynch 2011).

**Behaviour**

In general children with 12q14 microdeletion syndrome are happy, affectionate and sociable. However, they are as vulnerable to frustration as other children with a communication difficulty and a small minority succumb to temper tantrums and aggression. One child is described as naughty but popular. She is hyperactive but can concentrate and has a pleasant and friendly personality. A 6½-year-old boy is hyperactive and is thought to be on the autistic spectrum. He interacts well with people around him but has recently started to bite his arms and get frustrated with communication at times (Lynch 2011; Unique).

Attention deficit hyperactivity disorder (ADHD) which is characterised by restlessness and a short attention span and difficulties with concentration has been reported in children with 12q14 microdeletion syndrome. Autistic spectrum disorder (ASD) has also been reported in two people with 12q14 microdeletion syndrome. A diagnosis of autism can be extremely helpful in accessing services and tailoring the educational and behavioural therapy to meet the child’s specific needs (Mari 2009; Lynch 2011; Unique).

“ He seems to have a magnetic personality – people are drawn to him. He gets a lot of attention when we are out and about. He is very affectionate. He loves music and drawing and colouring. He loves jigsaws and can sit and do them over and over ” – 3 years

“ He is charismatic and has a sense of humour. He is an affectionate, loving child who makes excellent eye contact. He has a baby sister and he treats her gently and with love. He is very interested in his peers but he is isolated from them by his inability to speak. As a baby and small toddler he spent a lot of time spinning things (such as pot lids) and rolling things (such as bottles). He also did some strange ‘tapping’ and ‘flicking’ motions that led some professionals to suspect autism. Now, he does this much less, unless he is very tired or agitated. He loves books and also has a number of Broadway musicals. He will become entranced and will listen, transported, for as much as an hour at a time. This is not an automatic or thoughtless reaction. He has favourite songs and responds to them with clear emotions. He also has a portable mp3 device on which his mum has recorded herself reading books to him. Now, he will talk back to the recording, filling in the missing word whenever there is a pause ” – 3 years

“ She loves books and puzzles; playing outside and swimming. She has no behavioural problems and is very pleasant to be around ” – 3½ years

**Sleep**

Most children with 12q14 microdeletion syndrome have no trouble going to sleep and staying asleep. However, a 6½ year-old seems to need little sleep (Lynch 2011; Unique).

**Puberty and fertility**

Due to the small numbers of people so far reported with 12q14 microdeletion syndrome, there is no information on puberty. One Unique father has passed the 12q14 on to his daughter.
Adults with 12q14 microdeletion syndrome

Two adults have been described in the medical literature. One is an 18-year-old man who has mild learning problems and is in school studying applied mathematics. Another is a 20-year-old man who is in a special educational school. One Unique father discovered that has a 12q14 microdeletion after his daughter was diagnosed. He has no health problems or developmental delay but is 165cm (5 foot 5 inches). There are certainly more people, including adults, with 12q14 microdeletion syndrome. As the molecular techniques which are needed to detect this microdeletion become more commonplace, further people are very likely to be diagnosed (Menten 2007; Lynch 2011).

Ongoing research involving 12q14

The features of a 12q14 microdeletion are the result of the loss of a number of different genes found in this region. The 12q14 microdeletions range from 1.28 to 10.12Mb in size. Despite the varying breakpoints, the microdeletions reported so far all overlap. Determining the exact size of the deletion is necessary for identifying critical regions and genes that may contribute to the features of 12q14 microdeletions.

The HMGA2 gene is likely to be responsible for the growth problems seen in 12q14 microdeletion syndrome. Those children who did not have HMGA2 missing had much better growth. In addition, a boy with a deletion only within the HMGA2 gene itself (no other genes were missing) has been described in the medical literature and has short stature. Also mice which are missing this gene have growth retardation (Buysse 2009; Spengler 2010; Lynch 2011).

GRIP1 gene is a possible candidate for the learning difficulties as the girl whose deletion did not include this gene did not have any learning difficulties and GRIP1 is predominantly expressed in the brain. DCTN2 and KIF5A have also been suggested as candidates for the developmental delay seen in those with 12q14 microdeletions (Spengler 2010; Lynch 2011).

Congenital heart problems have been reported only in those with deletions that extend towards the centromere (see diagram on page 11) therefore a candidate gene for heart problems is likely to lie in this region (see diagram on page 11) (Lynch 2011).

The LEMD3 gene has been shown to be associated with osteopoikilosis although several people reported in the medical literature have LEMD3 missing but do not have osteopoikilosis (Menten 2011).

It is important to remember that while identifying the gene(s) responsible for certain features of a 12q14 microdeletion may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, 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 often have a role in determining the presence or absence of a particular feature.
Why did this happen?
A blood test to check both parents’ chromosomes is needed to find out why the 12q14 microdeletion occurred. In all reported cases so far the microdeletion occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means ‘new’. *De novo* 12q14 microdeletions are caused by a change that occurred when the parents’ sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined.

As a parent there is nothing you did to cause the 12q14 microdeletion and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

Can it happen again?
Where both parents have normal chromosomes, it is unlikely that another child will be born with a 12q14 microdeletion or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 12q14 microdeletion. This is called **germline mosaicism** and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the deletion.

In families where the 12q14 microdeletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 12q14 microdeletion rises to 50% in each pregnancy. However, the effect of the microdeletion on the child’s development, health and behaviour cannot be reliably predicted.

Your genetics centre should be able to offer counselling before you have another pregnancy.
Inform Network Support

Unique

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

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This leaflet 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. It was compiled by Unique and reviewed by Dr Sally Ann Lynch, National Centre for Medical Genetics, Ireland; Dr Geert Mortier, Department of Medical Genetics, Ghent, Belgium and by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK.

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