Understanding chromosome disorders

Unique

14q12 deletions

rarechromo.org

14q12 deletions

A chromosome 14 deletion means that part of one of the body's chromosomes (chromosome 14) has been lost or deleted. If the material that has been deleted contains important genes developmental delay, learning disability, and health problems may occur. Recently the *FOXG1* gene has emerged as the gene underlying the main effects of a 14q12 deletion, and a new, distinct FOXG1 syndrome has been proposed. The syndrome has some similarities with a different syndrome known as Rett syndrome (Florian 2011; Kortüm 2011; Allou 2012; Ellaway 2013).

People with 14q12 deletions frequently show a similar range of effects to each other, but these can vary in severity, so some are more mildly affected, others more seriously. The reason for this variation is still not completely understood, but depends largely on whether particular genes are included in the missing part (Bisgaard 2006; Papa 2008; Florian 2011; Kortüm 2011; Torgyekes 2011; Allou 2012; Fonseca 2012; Santen 2012; Ellaway 2013; Perche 2013; Unique).

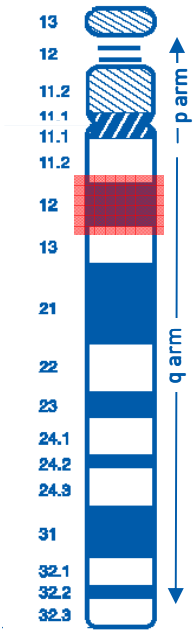
Genes and chromosomes

Our bodies are made up of billions of cells. Most of these cells contain a complete set of thousands of genes that act as instructions, controlling our growth, development and how our bodies work. Inside human cells there is a nucleus where the genes are carried on microscopically small, thread-like structures called chromosomes.

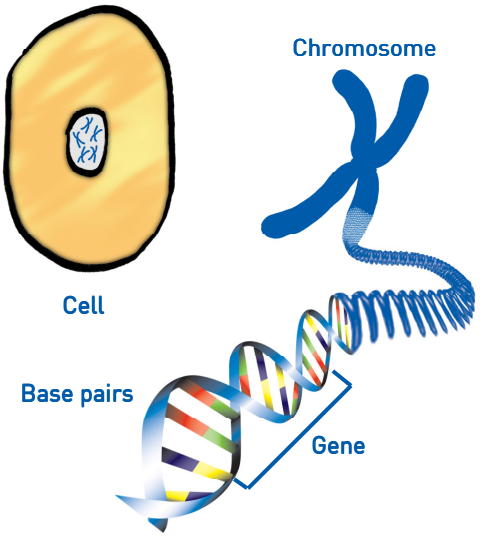
Chromosomes come in pairs of different sizes and are numbered from largest to smallest, from number 1 to number 22. In addition to these so-called autosomal chromosomes there are the sex chromosomes, X and Y. So a human cell has 46 chromosomes: 23 inherited from the mother and 23 inherited from the father, making two sets of 23 chromosomes. A girl will have two X chromosomes (XX) while a boy will have one X and one Y chromosome (XY).

Each chromosome has a short (p) arm (at the top in the diagram on the next page) and a long (q) arm (at the bottom of the diagram). In a 14q deletion, material has been lost from the long arm of one chromosome 14. The other chromosome 14 is usually intact. The short arm of chromosome 14 contains no unique genes, so losing material from the short arm generally does no harm.

You can't see chromosomes with the naked eye, but if you stain them and magnify their image with a computer or under a microscope, you can see that each one has a distinctive pattern of light and dark bands. The bands are numbered outwards from the point where the short arm meets the long arm, and in a 14q12 deletion, DNA has been lost from the band in the long arm numbered 12.



Chromosome 14



A small or very large piece of the chromosome can be missing. If the piece is visibly missing when the chromosomes are magnified it is called a **deletion**. If the missing piece is so small that the magnified chromosome looks normal, and it can only be found using enhanced techniques such as FISH or array CGH, it is called a **microdeletion**. A deletion close to the point on a chromosome where the short and long arms meet is called a **proximal** deletion.

Each band of each chromosome contains millions of **base pairs** of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. There are millions of base pairs in every chromosome. An array CGH test shows which base pairs and which genes are missing.

Your geneticist or genetic counsellor can tell you more about the genes and chromosome material that have been lost. You will be given the results of your child's genetic test, which will tell you what is missing.

The deletion may be within the band numbered 14q12, or it may be larger, extending to neighbouring bands.

Sources & references

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 (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain abstracts and most articles from Unique. The guide also draws on Unique's database. When this guide was updated in 2016, Unique had 179 members with a 14q deletion, of whom 16 had a deletion involving 14q12 with no other chromosome involved. Of these, 7 people have a deletion within the 14q12 band, and 9 have a larger deletion extending to 14q11.2, 14q13 or 14q21.

Test results

Your child's test results are likely to look like one of these.

del 14q12 pat

This tells you that the missing material comes from the band of the long (**q**) arm of chromosome **14** that is numbered **12** (see diagram, page 2).
pat means that the deletion has been inherited from the father; **mat** means that it has been inherited from the mother.

46,XX,del(14)(q12q13.1)

This result shows that the expected number of chromosomes [**46**] were found. It also shows that two **X** chromosomes were found, so this is a girl or a woman. del **(14)** means there is a deletion from chromosome 14. **(q12q13.1)** shows the bands in the chromosome where the missing material starts and finishes; in this case, the DNA is missing between one break in band q12 and one in band q13.1 (see diagram, page 2).

46,XY.ish del(14)(q12)de novo

This result shows that the expected number of chromosomes [**46**] were found, and there was an **X** and a **Y** chromosome, so this is a boy or man. The test used the FISH technique [**.ish**] and this showed that DNA was missing from chromosome 14 [**del(14)**]. The missing material was from the **q12** band. **de novo** means that the parents' chromosomes have been checked, and this chromosome change is a new occurrence [**de novo**] and has not been inherited from either the father or the mother. de novo is often shorted to dn.

arr[hg18] 14q12(27316236-32683942)x1

arr The analysis was by array (**arr**) comparative genomic hybridisation (cgh).
[hg18] Human Genome build 18. 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. The current build is hg38.
14q12 The chromosome involved is 14 and the position of the deletion is in band q12.
(27316236-32683942) The base pairs between **27316236** and **32683942** have been shown to be deleted. Take the first long number from the second and you get 5,367,706 (5.37Mb). 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 14 – as you would normally expect.

Comparing your child's genetic test results with others, both from the medical literature and within Unique, can help to build up a general picture of what to expect. But there will still be differences, sometimes quite marked, between your child and others with apparently similar deletions. It is very important to see your child as an individual and not to make direct comparisons with others with the same test results. After all, each one of us is unique.

How did it happen?

A blood test to check both parents' chromosomes allows parents to find out how the 14q12 deletion occurred. The child may have inherited a microdeletion from their mother or their father. However, where both parents have been tested and have normal chromosomes, the deletion occurred in the child for the first time and was not inherited. Geneticists call this de novo (new). De novo 14q deletions are caused by a change that occurred when the parents' sperm or egg cells formed, or possibly during formation and copying of the early embryonic cells.

The great majority of 14q12 deletions are de novo (Papa 2008; Florian 2011; Kortüm 2011; Torgyekes 2011; Fonseca 2012; Santen 2012; Ellaway 2013; Perche 2013). In one case the deletion was due to a family translocation involving chromosomes 8 and 14 (Santen 2012).

In a minority of cases where the microdeletion is very small, it has also been found in the mother or father (Unique). The parent is usually unaffected by it, or only mildly affected.

Whatever the situation, there is nothing that you, as a parent, did to cause the deletion, either before or during the pregnancy. Parents should feel reassured that no lifestyle change – environmental or dietary – would have prevented it from occurring.

Can it happen again?

In families where both parents have been tested and have normal chromosomes, the possibility of having another child with a 14q12 deletion is almost certainly no higher than anyone else's. So long as the parents have normal chromosomes, the extremely unusual sequence of events that led to a baby with a chromosome 14q12 deletion is very unlikely to happen again.

There is a remote possibility that a blood test would show normal chromosomes in both parents, but a few of their egg or sperm cells would still carry the 14q deletion. Geneticists call this germline mosaicism. It means that parents whose chromosomes are normal when their blood is tested can have more than one child with the deletion.

If either parent has a 14q12 microdeletion, there is a 50 per cent chance of passing it on and a 50 per cent chance of having normal chromosome 14s. The parent's ability to look after a child is very likely to be related to their own degree of learning ability.

Parents should have the opportunity to meet a genetic counsellor to discuss their specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo

biopsy; only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all these tests are available worldwide.

Can it be cured? How can it best be treated?

Unfortunately, there are no specific treatments at the moment to stop or reverse the progression of the effects of a 14q12 deletion. Managing the care of a child with 14q12 deletion focuses on their individual symptoms, making the very most of their abilities. A dynamic team approach works best, with specialist input from dietitians, physiotherapists and occupational therapists. Attention needs to be paid to nutritional problems and the development of spasticity, both of which can have a major impact on a child's and their parents' quality of life. Psychosocial support for the families plays a vital role. In terms of medication, seizures can be controlled with anti-epileptic drugs and melatonin can help with sleep disturbances (Florian 2011).

Most common features of microdeletions of chromosome 14q12

"She has a big, bright smile and the best laugh."

- Progressively slow growth of the head in babies and children, so it is unusually small (microcephaly)
- Developmental delay, sometimes with regression
- Difficulties with feeding and poor weight gain (failure to thrive)
- Constipation
- Abnormal muscle tone, with low tone (hypotonia), raised tone (hypertonia) and increasing spasticity
- Unusual facial features
- Walking and talking usually impossible
- Repetitive (stereotypic) movements
- Disturbed sleep
- Seizures
- Tooth grinding
- Cold hands and feet
- Curved spine (scoliosis)
- MRI shows abnormal development of part of the brain, the band of nerve fibres (corpus callosum) bridging the left and right sides
- Spells where a baby or child stops breathing (apnoea)

(Bisgaard 2006; Papa 2008; Florian 2011; Kortüm 2011; Torgyekes 2011; Allou 2012; Fonseca 2012; Santen 2012; Ellaway 2013; Perche 2013).

Most common features of microdeletions of chromosome 14q12-14q13.1

Many features are the same or similar to features of a deletion within the 14q12 band

- Developmental delay with possible regression, losing abilities previously gained
- Progressively slow growth of the head in babies and children, so it is unusually small (microcephaly)
- Difficulties with feeding and faltering weight gain (failure to thrive). Also severe, marked gastro-oesophageal reflux (GERD)
- Lack of speech
- Irritability and unexplained crying in babies
- MRI shows abnormal development of part of the brain, the band of nerve fibres (corpus callosum) bridging the left and right sides
- Vision loss due to cortical blindness and/or optic nerve atrophy
- Seizures/jerky movements
- Frequent infections (pneumonias, middle ear infections). Pneumonias may be caused by reflux (aspiration)
- Repetitive (stereotypic) movements
- Disturbed sleep

(Kortüm 2011; Torgyekes 2011; Unique).

Pregnancy

In the medical literature the majority of pregnancies were described as normal and went to term. Two babies were noted to be growing slowly (intrauterine growth retardation, IUGR) (Papa 2008) and a cleft lip and palate were observed on ultrasound at six months in a baby with a 14q12q13.1 deletion (Unique). The heart rate of a baby with a large deletion extending to 14q21.1 showed slowing just before delivery when the umbilical cord wrapped itself tightly round his neck (Torgyekes 2011). At Unique most pregnancies were also normal and went to term and any problems were only noted after the delivery. But one baby with a large deletion encompassing 14q12 was delivered early at almost 35 weeks after early separation of the placenta.

At birth

The range of normal birth weight in babies without chromosome anomalies is 2.5 kg (5lb 8oz) to 5kg (11lb). Average birth weight in babies without a chromosome anomaly is 3.4 kg (7lb 8 oz).

Birth weight and length for babies with a 14q12 deletion seem to be average or slightly below. Known birth weights ranged from 2.6kg/5lb 12oz to 4.4kg/9lb 11oz, and lengths from 46to 53 cm (18-21 inches). Head circumference ranged from normal to very small, but is typically in the low normal to borderline small range (Papa 2008; Kortüm 2011; Torgyekes 2011; Allou 2012; Ellaway 2013; Perche 2013; Unique).

Many babies with a deletion limited to the 14q12 band were in good condition at birth, with Apgar scores at one and five minutes after birth (ratings of general wellbeing, on a scale 0-10) of seven and above. The picture for babies born with deletions involving 14q13 is more complicated. Two babies with a deletion from 14q12 to 14q13 had Apgar scores of 9 and 9, and of 8, 6 and 10, showing that the second baby's condition 5 minutes after birth deteriorated before rallying; also 6, 7 and 10. One baby with a deletion including 14q13 experienced severe respiratory distress at birth and this has also been seen in the medical literature (Torgyekes 2011; Perche 2013). Two babies with a large 14q12q21 deletion experienced respiratory distress at birth, one needing a tube inserted into his windpipe to help him breathe. These babies needed respiratory support and intensive care, in some cases for weeks and even months (Devriendt 1998; Mehta 1999; Torqyekes 2011; Santen 2012; Unique).

Feeding

Feeding difficulties from birth onwards are very common with many babies unable to suck and swallow effectively at birth. The Unique series shows that breastfeeding was exceptional. With age, feeding improves but families need support, and the most affected babies require nasogastric tube feeds (tube through the nose to the stomach) or direct to the stomach (button, gastrostomy) for some time. Among babies in Unique with a 14q12 deletion, use of a feeding tube or button was only reported in babies with a larger deletion extending to 14q13 or 14q21.Tongue thrusting, which is often observed, interferes with feeding, and an inability to cope with semi-solid or solid foods can be persistent.
Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food passage, is also common and while often improving with age, can be severe and troublesome and persist into childhood. It can affect babies and children whatever the position or size of their deletion (Kortüm 2011; Torgyekes 2011; Fonseca 2012; Ellaway 2013; Perche 2013; Unique).

Reflux raises a baby's risk of inhaling feeds and causing an infection in the lungs known as aspiration pneumonia, very common in babies and children with a 14q12 deletion (Kortüm 2011). Reflux can be eased by careful semi-upright positioning during and after feeds, sleeping in a prescribed sleep chair rather than a bed, raising the head end of the baby's cot and if necessary by prescribed medication that helps to keep the feed within the stomach. Babies who have continuing problems can have a fundoplication, a surgical procedure to improve the action of the valve between the food passage (oesophagus) and the stomach. This complex of difficulties means that babies need an early referral to speech therapy for their feeding difficulties, and attention needs to be paid to nutritional

problems which can have a major impact on a child's and their parents' quality of life, and families should have specialist input from a dietitian (Florian 2011).

Constipation is common, and is particularly associated with 14q12 deletions, and many children need to take daily laxatives (Ellaway 2013; Unique).

Dribbling (drooling) can also occur (Papa 2008; Allou 2012). As well as hyoscine patches, a medicine called glycopyrrolate can be given by mouth. Some children have had Botox injections into the salivary glands in a specialist centre. Otherwise the salivary ducts at the bottom of the mouth can be tied off so saliva still comes from the top of the mouth but not the bottom.

" Breastfeeding didn't work for her. She was tube fed for six weeks, then bottle fed, and by six months was able to take cereal. Now at 14 months, she eats blended and minced food as part of a high calorie diet. " - *14q13q21 deletion, 14 months*

" She had severe reflux and two hospital stays for aspiration pneumonia. Her reflux was treated first with medicine, then a gastrostomy (button), then a G-J tube (a tube to the stomach and small intestine that allows air to vent), then a fundoplication. She has swallowing difficulties but no oesophageal anomalies and hasn't taken anything by mouth since birth. " - *14q12q21 deletion, 16 months*

Difficulties with growth or weight gain

While babies with a 14q12 deletion are generally of average or slightly below average weight and length at birth, as childhood progresses growth often slows, with a number of children becoming small and underweight. This slowdown in growth may be anything from mild to extremely pronounced, with weight and length dropping below the 3rd centile (the lowest 3% of the population). However, it is not universal: two Unique children with a deletion within 14q12, aged 2 and 8½, are growing at a normal rate (Allou 2012; Unique).

Children with deletions involving 14q12q13 are also often relatively small, with weight, length and head circumference generally below the 5th centile (the lowest 5% of the population). Slow growth has been found to typically persist throughout childhood (Torgyekes 2011; Fonseca 2012; Perche 2013; Unique).

There is however no evidence that growth hormone levels are low, or that treatment with growth hormone would help children with a 14q12 deletion.

" He can light up a room with his smile."

Hypotonia

Altered muscle tone is probably universal in deletions involving 14q12. The most typical pattern is low muscle tone (hypotonia) in the body (trunk), so that the baby or child feels floppy to handle, with raised tone (hypertonia, where there is an increase in muscle tension and muscles are unable to stretch properly) in the arms and legs. Less commonly babies may have generalised low tone throughout the body (Papa 2008; Fonseca 2012; Ellaway 2013; Unique). Every Unique family with a child with a 14q11.2 deletion who told us about their child's muscletone reported hypotonia. Among Unique children with a 14q12 deletion, three had low muscle tone, while 3 others either had mixed tone – generally low in the trunk, and raised in the arms and legs– or had generally raised tone. The raised tone in the arms and legs appears to be progressive, putting affected children at risk of developing contractures. This can have a major impact on a child's and their parents' quality of life, and affected babies and children need early specialist input from physiotherapists and occupational therapists (Florian 2011).

> **" She has the best laugh - she always makes others laugh when she starts."**

Head and brain

The growth of the head of a baby with a 14q12 deletion that includes the *FOXG1* gene (see **Genes**, page 18) slows down after birth. At birth, head size is typically in the low normal to borderline small range, but the head then grows increasingly slowly. Typically, it falls below the 3rd centile on the growth chart in the first year of life, and gets progressively smaller by 2 years, so it is obviously very small, looking more like a newborn baby's head at the age of 2 or 3 (Bisgaard 2006; Papa 2008; Mencarelli 2009; Kortüm 2011; Torgyekes 2011; Allou 2012; Ellaway 2013).

Magnetic resonance imaging (MRI) scans of the brain may be normal, but more commonly reveal absence or underdevelopment of the corpus callosum. The

corpus callosum is a band of nerve fibres joining the left and right sides of the brain. It can be missing altogether – called agenesis (ACC), or it can be thin, short and underdeveloped – called hypoplastic (HCC). The front part may narrow to a sharp point or hook, a distinctive feature of 14q12 deletions (Kortüm 2011). ACC and HCC are linked with a spectrum of disability ranging from subtle to severe depending on any other brain abnormalities.

Other brain anomalies have also been found, including a smaller amount of white matter (nerve fibres) in the frontal lobes than expected with loss of brain cells (neurones) and the connections between them, a delay in the laying down of natural fatty protection around the nerve sheaths (myelination), and larger than expected ventricles (the fluid-filled spaces within the brain). The surface of the brain in the frontal lobes may also be somewhat smoother than expected (mild frontal pachygyria). Among Unique members 'immaturity' was noticed in the brain of two children with large deletions extending to 14q21 (Kortüm 2011; Torgyekes 2011; Allou 2012; Ellaway 2013; Perche 2013; Unique).

Interpreting these findings is challenging, and your child's neurologist or paediatrician is best placed to explain to you just what the findings of any MRI imaging in your baby or child may mean.

Breathing

Respiratory problems have been widely reported for babies, children and adults with deletions involving 14q12 and/or 14q13 (see also **At birth**, page 7). Loss of the NKX2-1 gene in 14q13 (see **Genes**, page 18) is believed to underlie most of the serious respiratory disorders, although some children who have not lost this gene also have abnormal breathing patterns (Ellaway 2013; Unique).

Some babies have acute respiratory distress at birth and need ventilation, sometimes for weeks or even months. A few children remain dependent on oxygen after leaving hospital after birth. Apart from acute breathing difficulties at birth, some children may also have repeated chest infections including pneumonia and bronchiolitis that are serious enough for them to need hospital treatment. Sadly, four children are known to have died from pneumonia: two had a 14q11.2q13 deletion encompassing 14q12, one a 14q12 deletion, and one a 14q12q13 deletion (Devriendt 1998; Mehta 2001; Torgyekes 2011; Fonseca 2012; Santen 2012; Ellaway 2013; Unique).

Within Unique, most children with a 14q12 deletion did not have a breathing disorder, but one adult was diagnosed with asthma and frequently caught infections. Two children with a 14q12q13 deletion had repeated chest infections. Breathing disorders were common among children with a 14q13 deletion.

Some babies and children are also at risk of having short spells where they stop breathing (apnoeas). These may be caused by obstruction in the airways, or by the underlying neurological disorder (Torgyekes 2011; Fonseca 2012), but families need to be aware and to have appropriate monitoring equipment for children at home.

Breathing difficulties including deep panting (hyperventilation) can occur (Ellaway 2013). A boy with a 14q12.2q13 deletion developed a curvature of the middle part of the spine and had a disturbed breathing pattern associated with episodes of very rapid deep breathing (Perche 2013). Similarly, a girl with a deletion of 14q12 developed a curvature of the middle and lower part of the spine and also had episodes of hyperventilation (Ellaway 2013).

Partial or complete split in roof of mouth (cleft palate)

Although a cleft palate is not part of the typical 14q12 deletion syndrome, a few babies have been born with a cleft palate (a split in the roof of the mouth) or a high and narrow palate. Among babies with a 14q12 deletion, a cleft palate and lip were seen in 2/4 babies with a large deletion extending to 14q13 or 14q21 (Unique).

The hard palate at the front of the mouth may be split or the split may be found further back in the soft, fleshy tissue at the back of the top of the mouth. Occasionally the split is only seen in the tissue that hangs down above the tongue at the very back of the mouth (uvula, known as a bifid uvula when it is split). A cleft lip may also occur.

A cleft lip and palate causes difficulties both in feeding and in speech production. Your baby's caregivers will advise on how to minimise problems. Surgical repair is usually needed to ease these difficulties and eventually may eliminate them altogether.

Appearance

Babies with a 14q12 deletion may appear normal, and some may have a more subtle facial appearance. Doctors may notice what are known as dysmorphic features which are not always obvious to a parent. Each baby is an individual and some have almost no features considered 'typical'. All the same, babies may look subtly different to their parents and other family members.

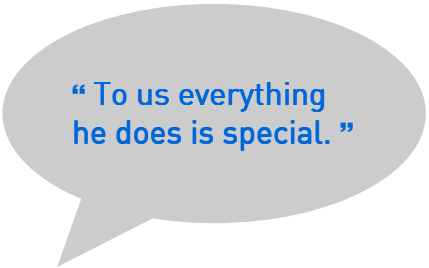
Children with a 14q12 deletion with FOXG1 syndrome (see Genes, page 18) have been reported to have a low nasal bridge and a bulbous tip to the nose; large ears; a full upper and lower lip, a protruding jaw and epicanthal folds (a fold of skin across the inner corner of the eye). These features may be more subtle in those with a smaller deletion. As a baby, some children may hold their mouth open, with their tongue pushing out and moving involuntarily. Missing teeth have been observed in a child with a large 14q12q13.3 deletion (Papa 2008; Kortüm 2011; Allou 2012; Fonseca 2012; Ellaway 2013).

These facial characteristics are subtle: no Unique family considered that their child with a deletion within 14q12 looked anything other than normal; where the deletion was larger and the child had a cleft lip, this is what was noticed.

Hands and feet

The hands and feet of children with a 14q12 deletion may feel cold to the touch (Papa 2008; Ellaway 2013). What is more, minor, non-functional anomalies of the hands and feet are relatively common in children with any chromosome disorder. Among those with a 14q12 deletion, observed features include relatively long fingers and toes, clinodactyly (inwards curve) of one or more toes or fingers, shortened toes, and small hands and feet. Among those with a 14q12q13 deletion, observed features include shortened fingers and wide first toes; a single crease across the palm; and overlapping toes (Fonseca 2012; Ellaway 2013; Unique).

Most hand and foot anomalies don't affect function or comfort, but overlapping toes can usually be corrected passively, using plastic splints if desired.
Flat feet are relatively common in children with chromosome disorders and may also occur in those with a 14q deletion. They are generally related to low muscle tone, but should be assessed, and if necessary your child can be prescribed shoes inserts or supportive footwear.



Seizures

Seizures are particularly associated with deletions involving 14q12 but do not affect everyone. Two/5 children in Unique with a deletion within 14q12 have epilepsy, while one Unique child with a 14q12q13 deletion was diagnosed with a movement disorder when a brain activity recording [an EEG] was normal during seizure-like attacks. Among Unique children with a 14q12 deletion that extends from 14q11.2 to 14q13 or 14q21, epilepsy is especially common.

In affected children, the first seizure was reported between 3 months and 11 years of age. Seizure types include absence seizures and infantile spasms (clusters of brief periods of movement of the neck, trunk, or legs that last for a few seconds and start before the age of 6 months), as well as tonic seizures (the body stiffens), tonic-clonic seizures (the muscles tense, and then contract and relax rapidly), and partial complex seizures (lasting 1-2 minutes, awareness is lost and automatic movements like lip smacking or picking at things may occur) (Bisgaard 2006; Papa 2008; Florian 2011; Kortüm 2011; Torqyekes 2011; Allou 2012; Ellaway 2013; Perche 2013; Unique).

Seizures are generally associated with a brain anomaly including a missing corpus callosum (see **Head and brain**, page 10-11) but can occur in children where a brain scan has found nothing. Generally they are controlled with anti-epileptic medication but among Unique members one child experienced seizures that were hard to control. In another child earlier failure to gain weight was corrected once he was on anti-epilepsy medications.

Heart

Most children were born with a normal heart structure and function. One Unique baby with a 14q12q13.1 deletion, was found to have a patent foramen ovale, the persistence of a hole between the two upper chambers of the heart that usually closes at birth. Another baby was born with a patent ductus arteriosus (PDA), another persisting structure of the fetal circulation, accompanied by a narrowing of the valve in the pulmonary artery that leads to the lungs (pulmonary stenosis), while a baby with a 14q12q13.3 deletion was found to have a PDA with severe secondary pulmonary hypertension (high blood pressure in the lungs (Fonseca 2012; Torgyekes 2011; Unique). Treatment of these heart conditions is decided on an individual basis but can include initial monitoring to see whether they resolve naturally and, if need be, surgical correction.

> **" She's a big ray of sunshine regardless of what's going on around her. "**

Eyesight

Some babies and children with a 14q12 deletion have normal vision, but babies will typically be late to develop a response to stimuli such as faces and patterns. The slow response may improve with time, but should be investigated as one child with a large deletion extending to 14q13 was shown to have underdevelopment of the optic nerves, affecting her ability to see (Papa 2008; Torgyekes 2011; Ellaway 2013; Unique).

Eye contact may also be only fleeting or absent. This is not a vision problem, but a possible feature of autism, (Florian 2011; Kortüm 2011).

Many children are long sighted and may also have a squint (strabismus). In one child the squint usually arose after a seizure (Kortüm 2011; Allou 2012; Ellaway 2013; Perche 2013). At Unique, 5/10 children had a vision impairment. In three, the impairment involved strabismus (a squint), sometimes together with long sight. In the other two, however, the difficulty was cortical visual impairment, where the brain does not understand or interpret what the eyes see, making the children effectively blind.

Hearing

Babies can be expected to be late to develop a response to noises. Hearing however appears to be generally unaffected, although the possibility of hearing impairment seems to be greater with large deletions. One girl with a 14q12q13.1 deletion had mildly impaired hearing and another with a 14q11.2q21 deletion had poor hearing in his left ear (Torgyekes 2011; Unique).

Development

Sitting, moving - gross motor skills

Babies and children with a 14q12 deletion typically face considerable challenges in reaching their mobility milestones, and these appear to be particularly difficult when the deletion extends to 14q13. Most children have altered muscle tone, often mixed, with low tone in parts of the body and raised tone elsewhere and this can make it harder to learn to control the body. Many children experience involuntary movements of parts of their body which also interfere with learning to sit, stand and walk. While less severely affected children may learn to take some steps, walk and even run, this will not be possible for many. Normal development may be seen in the first few months of life, but this can be followed by regression. Babies who learn to sit up have been shown to achieve this in their second or third year, followed by moving and standing some years later. The progressive stiffness that affects many children's arms and legs hampers their gross motor development, and early specialist physiotherapy input is vital to maximise a child's possibilities.

Among Unique children, one with a deletion within 14q12 was learning to sit at 26 months, and an 8 year old who started to walk at 18 months was able to run but was hampered by instability, involuntary movements and muscle weakness (Papa 2008; Florian 2011; Torgyekes 2011; Allou 2012; Ellaway 2013; Unique).

Using their hands: fine motor and coordination skills

While some children will learn to use their hands to a limited extent, this will not be possible for many. Hand control appears to be specifically targeted in babies and children with a 14q12 deletion, and while some babies may acquire some hand use, they may later lose these skills.

Less affected children may be able to reach out, pick up and hold onto objects and even to feed themselves with finger foods, while more severely affected babies and children may not develop the ability to pick things up with their thumb and forefinger (pincer grip). An additional difficulty for some children is habitual repetitive movement of their hands that they have no control over, such as hand wringing, hand waving and constant hand-to-mouth movements (Florian 2011; Torgyekes 2011; Allou 2012; Fonseca 2012; Ellaway 2013; Perche 2013; Unique).

In this situation early intervention by occupational therapy to stimulate hand use is vital.

Learning

Unfortunately we only have limited information relating to learning, but it is clear that children are likely to need considerable support. Evidence suggests that the larger the deletion, the greater the probability that any learning difficulties will be more marked. We don't have information about schooling, although Unique is aware that where children attend school, they generally go to a special school (Santen 2012; Ellaway 2013; Unique).

Speech and communication

Generally, speech and language reflect the level of learning disability and children with greater learning difficulties appear to use less speech. Some children with a 14q12 deletion learn a few words and signs, but this is not possible for all and the regression that can affect other areas of development can also affect speech and language so that children lose the words they had mastered. Instead of speech, babies and children may use other ways to communicate such as vocal noises, babbling, pointing, and assistive communication devices. Facial expression can be limited, making it hard for parents and caregivers to read a child's emotions.

Vocabulary is likely to be limited and the evidence from Unique suggests that understanding may also be limited, despite unimpaired hearing. However, children can learn to respond to familiar voices, signs and phrases with interventions including speech therapy and sometimes sign language.

Unfortunately, absence of speech appears to be a key feature of 14q12 deletions with 7/7 children reported in the medical literature affected (Kortüm 2011; Allou 2012; Fonseca 2012; Ellaway 2013; Perche 2013; Unique).

Where the 14q12 deletion does not include the *FOXG1* gene or any other DNA that regulates it, speech may be unaffected (Unique).

Behaviour

Children and babies with a 14q12 deletion are described as generally easy-going and happy. Two children with 14q12 deletions were said to have laughing 'happy' natures although they startled easily. Babies, however, can be irritable and cry for no understandable reason, although this gets better with time.

As children mature, a lack of social responsiveness resembling autism can become apparent and poor eye contact may be seen. Several children have been described as having autistic-like features, such as hand-wringing, scratching, pinching, patting, mouth and tongue movements and repetitively opening and closing doors. One child who is otherwise mildly affected has shown social communication delays. In one child poor eye and physical contact improved when music was playing .

Other difficulties include tooth grinding (known as bruxism) and hyperactivity, with laughing and crying for no apparent reason (Papa 2008; Kortüm 2011; Allou 2012; Fonseca 2012; Ellaway 2013; Unique).

" He's gorgeous. He can light up a room with his smile, and to us everything he does is special. **"** - *14q12 deletion, 2 years*

" She has a big, bright smile and the best laugh, she always makes others laugh when she starts. She's a big ray of sunshine regardless of what's going on around her. **"** - *14q12 deletion, 8 years*

Sleep

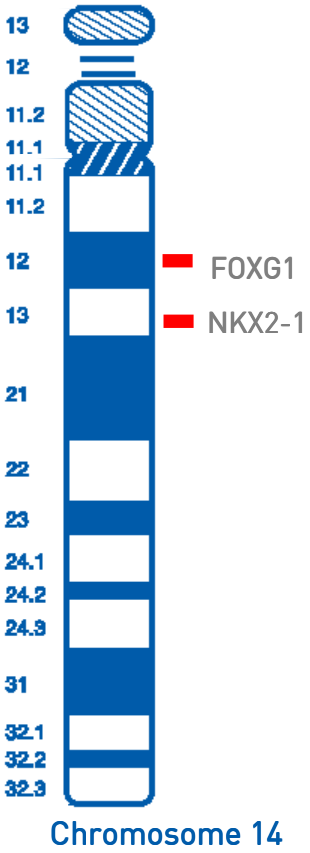
A disturbed sleep pattern has been reported for many children with 14q12 deletions and appears to be a feature where the *FOXG1* gene is deleted (see **Genes**, page 18). Frequent night time waking is typical. Investigations in several children have revealed sleep apnoeas, where the child stops breathing for short spells. Sleep apnoea is of two types: obstructive sleep apnoea occurs when there is a partial or full airway collapse during sleep, while central sleep apnoea is related to a central nervous system disorder which means the brain fails to trigger breathing when the person is asleep. If enlarged adenoids and/or tonsils are involved with obstructive sleep apnoea, they can be removed. Other treatment options include the hormone melatonin to help regulate sleep patterns. However, the disturbances can improve with age (Florian 2011; Kortüm 2011; Torgyekes 2011; Ellaway 2013; Unique).

Genes

FOXG1

The 14q12 band starts at base pair 24,600,001 and ends at base pair 33,300,000. The FOXG1 gene is located around the middle of the 14q12 band, between base pairs 28,767,071and 28,770,276.

The *FOXG1* gene plays a role in regulating the development of the forward-most part of the brain during development of the embryo and through to adulthood (Ellaway 2012; Kortüm 2011; Bisgaard 2006). Loss of the *FOXG1* gene is thought to be responsible for many of the neurological features of a 14q12 deletion including a missing corpus callosum, and to underlie a separate, specific FOXG1 syndrome. In most cases of FOXG1 syndrome part or all of *FOXG1* has been deleted. In children with the features of FOXG1 syndrome where the *FOXG1* gene is not deleted, it has been suggested that a region of chromosome 14q12 responsible for controlling the expression of *FOXG1* is missing, leading to a decrease in the expression of *FOXG1* gene (Allou 2012; Ellaway 2013; Gabau 2013).



NKX2-1

The 14q13 band starts at base pair 33,300,001 and ends at base pair 37,800,000. The NKX2-1 gene is located near the end of the 14q13 band, between base pairs 36,516,396 and 36,520,224.

This gene, the thyroid transcription factor-1 gene (NKX2-1), is thought to play a role in the development of healthy lung function and has been implicated in causing brain-lung-thyroid syndrome in people with 14q13 deletions. The effects of NKX2-1 malfunction or absence can vary from being so mild you would not notice to disablingly severe and even fatal. It is believed to underlie the typical movement difficulties (choreoathetosis), severe pulmonary insufficiency, where a valve in the heart is leaky and some blood may flow back into the heart instead of out to the lungs, and low levels of thyroid hormone (Santen 2012). It is also believed to be important for producing the surfactant that coats the surfaces of the air sacs inside the lungs and stops them from collapsing inwards. Babies are at risk of developing breathing problems at birth. Not all babies with a deletion at 14q13 are affected, however, probably due to variations in the level of expression of the gene (Santen 2012).

Notes

Support and Information

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

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www.rarechromo.org/html/MakingADonation.asp
Please help us to help you!

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