

14q13 deletions



14q13 deletions

A chromosome 14 deletion means that part of one of the body's chromosomes (chromosome 14) has been lost or deleted. If the deleted material contains important genes, learning disability, developmental delay and health problems may occur. How serious these problems are depends on how much of the chromosome has been deleted, which genes have been lost and where precisely the deletion is. The features associated with 14q13 deletions vary from person to person, but are likely to include a degree of developmental delay, an unusually small or large head, a raised risk of medical problems and unusual facial features.

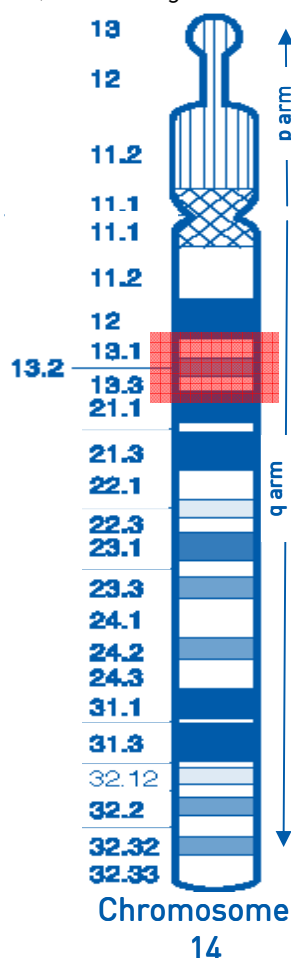
Genes and chromosomes

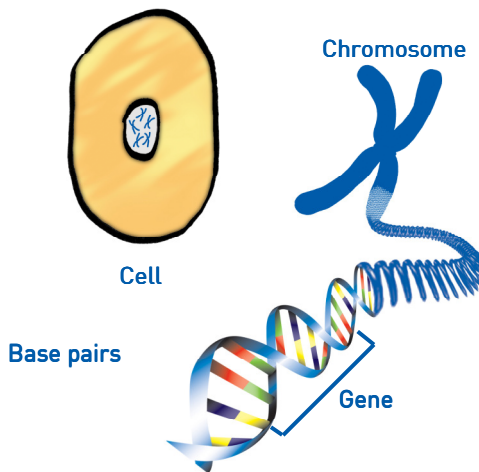
Our bodies are made up of billions of cells. Most of these cells contain a complete set of thousands of genes that act as instructions, controlling our growth, development and how our bodies work. Inside human cells there is a nucleus where the genes are carried on microscopically small, thread-like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

Chromosomes come in pairs of different sizes and are numbered from largest to smallest, roughly according to their size, 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 has 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 it 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 band numbered q13 is divided into three smaller bands, numbered q13.1, q13.2 and q13.2. The neighbouring bands are numbered q12 and q21.





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**. These techniques can be used to precisely map microdeletions, and are making it possible to find more precise genotype-phenotype correlations - that is, the link between a specific deletion and the clinical features observed. 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 will show which base pairs and which genes are missing.

The deletion may be within the bands numbered 14q13, or it may be larger, extending to neighbouring bands.

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.

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). Articles consulted include: Florian 2011; Kortüm 2011; Torgykes 2011; Fonseca 2012; Piccione 2012; Santen 2012; Perche 2013; Peall 2015; Gentile 2016. If you wish, you can obtain abstracts and most articles from Unique. The leaflet also draws on Unique's database. When this leaflet was updated in 2016, Unique had 179 members with a 14q deletion, of whom 17 had a deletion involving 14q13 with no other chromosome involved.

Test results

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

del 14q13 pat

This tells you that the missing material comes from the band of the long (q) arm of chromosome **14** that is numbered **13** (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)(q13.1q21.1)

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. **(q13.1q21.1)** shows the bands in the chromosome where the missing material starts and finishes; in this case, the DNA is missing between band q13.1 and the band next to q13, which is q21.1 (see diagram, page 2).

46,XY,ish del(14)(q13.3)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 **q13.3** 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] 14q13.3(33164371-36689248)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.

14q13.1q13.3 The chromosome involved is 14 and the deletion starts in band q13.1 and ends in band q13.3

[33164371-36689248]

The base pairs between **33164371** and **36689248** have been shown to be deleted. Take the first long number from the second and you get 3,524,877 (3.52Mb). 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 14q13 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 (see page 4).

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 documented 14q13 deletions are de novo. Where a microdeletion is very small, it is sometimes also found in the mother or father (Decipher). The parent is usually unaffected by it, or only mildly affected. Whatever the situation, there is nothing 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 14q13 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 14q deletion is very unlikely to happen again.

There is a remote possibility that both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 14q13 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 14q13 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

“ He smiles and reacts to his parents and his sisters, but he doesn't cry.

“ It's not easy living but he is lovely. We call him “pieszczoch” which means a darling and lovely person you want to hug.”

14q13q21 deletion, 23 months

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.

What are the effects?

The clinical manifestations of 14q13 deletions can vary, depending on the size of the deletion, the number of genes deleted and precisely which genes are deleted. Broadly speaking, it is suggested that there are two groups of people with a 14q13 deletion: those with mild symptoms, and those with severe symptoms (Santen 2012).

Deletions involving the NKX2-1 gene cause an extremely variable pattern of disorders known as brain-lung-thyroid syndrome. Learning difficulties are most typically mild; there may be difficulty with involuntary and uncontrolled movements (choreoathetosis); the thyroid is underactive (hypothyroidism); and the lungs don't work properly, causing breathing difficulties and respiratory infections. A deletion of the neighbouring PAX9 gene can cause hypodontia (missing teeth). See [Genes](#), pages 18-19

When neighbouring bands are also involved, effects can be more severe, with the most serious features found in people with deletions extending to chromosome 14q12. The 14q12 band harbours a gene named FOXG1 whose absence causes a severe disability syndrome. When FOXG1 is included (or the deletion is relatively close to the FOXG1 gene), a range of clinical features including a small head (microcephaly), agenesis of the corpus callosum (the band of nerve fibres connecting the two sides of the brain fails to develop properly), unusual facial features, low muscle tone and seizures have been found (Torgykes 2011; Fonseca 2012; Piccione 2012; Santen 2012).

Most common features of deletions of chromosome 14q13 including NKX2-1

- Developmental delay
- Speech delay
- Variable degree of learning difficulty or disability
- Low thyroid levels at birth (hypothyroid)
- Involuntary, uncontrolled movements
- Possibility of breathing disorders

When the PAX9 gene is deleted

- Missing teeth (oligodontia)

(Santen 2012; Unique)



14q13q21 deletion, 3 years

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

- Developmental delay
- Difficulties with feeding, reflux and faltering weight gain (failure to thrive).
- Low muscle tone or a mixture of low and raised tone
- Breathing difficulties at birth
- MRI shows abnormal structures in the brain. The band of nerve fibres (corpus callosum) bridging the left and right sides may be small or missing.
- Seizures/jerky movements
- Frequent infections (pneumonias, middle ear infections). Pneumonias may be caused by reflux (aspiration)
- Repetitive (stereotypic) movements. If walking, may be unsteady
- Poor eyesight

(Kortüm 2011; Torgyekes 2011; Unique)

Pregnancy

In the medical literature most pregnancies were described as normal and went to term, and at Unique most pregnancies were problem-free. But in two, both where the baby had a large deletion extending beyond q13 to neighbouring bands, there was a suspicion of too little amniotic fluid (oligohydramnios). One baby was noted to be growing slowly (intrauterine growth retardation, IUGR) 4 weeks before the due date, and a cleft lip and palate were observed on ultrasound at six months in a baby with a 14q12q13.1 deletion.

Most pregnancies went to term and any problems were only noted after the delivery but one baby was delivered at almost 35 weeks after early separation of the placenta, and another at 36 weeks.

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).

According to the medical literature, babies with deletions extending into the neighbouring bands were born with very low (2108g/4lb 10oz) to average (3150g/6lb 15oz-3600g/7lb 15oz) birth weights, but several of these babies had chromosome disorders involving other chromosomes. At Unique, birth weights were generally low, although 3 babies were born early and 2 were pre-term. The range was 2.41kg (5lb 5oz) to 4.8kg (10lb 10oz), and 4/7 term babies were born weighing less than 2730g/6lb (Torgykes 2011; Fonseca 2012; Santen 2012; Unique).

Reports in the medical literature show that some babies were in good condition, with Apgar scores (ratings of general wellbeing after birth, on a scale 0-10) of 7 and above. Unique evidence supports this: a baby with a deletion from 14q12 to 14q13.1 had Apgar scores of 8, 6 and 10, and another with a large deletion between 14q12q13 had Apgar scores of 9, 9. Another baby with a 14q13.1q21.1 deletion had heart slowing during delivery, but was in a good condition at birth (Santen 2012).

However, an important group of babies with a deletion including 14q13 experienced severe respiratory distress at birth (mostly caused by NKX2-1 deletions), and one with a 14q13.1q21.1 deletion was born with a perforated lung. In some cases these babies showed heart rate slowing during delivery. These babies needed resuscitation and respiratory support, oxygen and intensive care, in some cases for weeks and months. One baby boy with a deletion of 14q12q21 had low Apgar scores at 1 and 5 minutes of 1 and 5 and needed a tube inserted into his windpipe to help him breathe (Devriendt 1998; Mehta 1999; Torgykes 2011; Piccione 2012; Santen 2012; Perche 2013; Unique).

Feeding

Feeding difficulties are common, although not universal with many babies unable to suck and swallow effectively at birth. With age, feeding improves but families need support, and the most affected babies need feeding through the nose (tube) or direct to the stomach (button) for some time. The Unique series shows that breastfeeding was exceptional. Among Unique babies with a deletion within the 14q13 bands, weak sucking, swallowing difficulties and reflux (see below) generally made feeding by mouth difficult but not impossible, but where the deletion extends to 14q21, tube or button feeding was universal except for one baby who left special care after two months on the breast, and went on breastfeeding for 2 years.

Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food passage, is common and while often improving with age, can be troublesome and persist into childhood. It can affect babies and children whatever the position or size of their deletion. Reflux raises a baby's risk of inhaling feeds and causing an infection in the lungs known as aspiration pneumonia. Reflux can be

“ He has a smile that will light up the room, he connects really well with people. He is a very happy and motivated boy. ”

14q13.2q13.3 deletion,
4 years old

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.

“ 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

“ He had a weak suck as a baby, but started feeding by bottle at one month. Now he eats puréed foods with some lumps, but still has a problem with chewing.” 14q13q21 deletion, 2 years

“ Had swallowing difficulties when younger which lead to several bouts of aspiration pneumonia. Took thickened feeds and was delayed in eating solids. This has mostly resolved itself now.” 14q13.2q13.3 deletion, 3 years

Difficulties with growth or weight gain

Among Unique children with a deletion within 14q13, 3/5 had difficulties putting on weight. In one child these problems had resolved by the age of 4, another child was described as of average height and weight by the age of seven years despite a low birth weight (6lb, 2.721kg), and another as big. Where the deletion was larger, extending to 14q12 or 14q21, growth slowing was reported in 3 children, all needing feeding by tube or button (Torgykes 2011; Fonseca 2012; Unique).

Reports in the medical literature confirm that children with deletions involving 14q12q13 are often relatively small, with weight and length measurements that generally fall below the 5th centile (the lowest 5% of the population), and slow growth typically persisting throughout childhood (Perche 2013; Fonseca 2012; Torgykes 2011).

“ He has been off the charts (big) since birth and has remained big.”

14q13.2q13.3 deletion, 3 years

“ Very small for her age.” 14q13.1q21.1 deletion, 3½ years

Thyroid function

Hypothyroidism, where the child's thyroid gland does not produce enough thyroid hormone may be identified from neonatal screening or, where this is not carried out, in childhood. Babies with hypothyroidism are often sleepy and difficult to feed, and other symptoms can include constipation, low muscle tone (floppiness), cold extremities, and poor growth. Some hypothyroid babies have prolonged jaundice (with an associated yellow skin) after birth. Six out of seven children with a 14q13 deletion in the medical literature, and 6/8 Unique children had hypothyroidism (Santen 2012). The gene that is important for normal thyroid functioning in this region is NKX2-1 (see [Genes](#), pages 18-19). This gene is also plays a role in the development of healthy lung function (see [Breathing](#), pages 11 -12). Children with abnormal thyroid function are successfully treated with thyroxine replacement (Devriendt 1998; Mehta 1999; Iwatani 2000; Krude 2002; Santen 2012; Unique).

Changes in muscle tone

An unusually low muscle tone, so that the baby or child feels floppy to handle, is common in 14q deletions involving 14q13, as in many other chromosome disorders. Babies with hypotonia tend to lie with their arms and legs loosely outstretched instead of bent at the knee or elbow. When held under the arms, their bodies easily slip through the hands.

Among Unique babies with a deletion within 14q13, hypotonia was a problem for 3/3. Among those with a larger 14q13 deletion involving neighbouring bands, hypotonia was a concern for 4/5, with mixed tone (low muscle tone in the body (trunk) and hypertonia (an increase in muscle tension so that muscles are unable to stretch properly) in the arms and legs the other typical pattern. The pattern of mixed tone is commonly found in babies with a 14q12 deletion, but has also been seen in babies with a pure 14q13 deletion (Piccione 2012; Unique).

Babies and children with hypotonia benefit from early intervention with physiotherapy. Where there is raised tone, early intervention is also vital as it may be progressive, putting affected children at risk of developing spasticity. 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).

Head and brain

Some babies and children with a 14q13 deletion have no structural brain anomalies (Fonseca 2012; Unique); but as particular anomalies are commonly found, your child may be offered an MRI scan to examine the brain's structures.

If you search on the internet, you may find information suggesting that a condition known as HPE (holoprosencephaly), where

developmental anomalies of the brain affect its division into two hemispheres, is associated with a 14q13 deletion. This is no longer thought to be the case (Santen 2012), although features associated with HPE are found, such as a small, short or missing corpus callosum (HCC/ACC), the band of nerve fibres connecting the right and left sides of the brain, a cleft lip or a single upper front tooth (Unique).

In the medical literature and Unique, brain anomalies were only reported in those with a larger 14q13 deletion: among 5 Unique families with a child with a deletion within 14q13, none reported any brain anomalies, although one family described 'underdevelopment' of the brain.

Among children with a 14q12q13 deletion, other brain anomalies may also be 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 brains of two children with large deletions extending to 14q21, and in another the ventricles (fluid-filled spaces within the brain) were larger than expected, though the brain's structure was normal (Kortüm 2011; Torgykes 2011; Perche 2013; Unique).

The range of outcomes for babies with head and brain abnormalities associated with a 14q13 deletion is quite broad; your child's neurologist or paediatrician is best placed to interpret what they are likely to mean.

"She has an amazing drive, she never gives up. When learning to walk, I never saw her give in. She has always had this mentality. She is very interactive with her younger brother, having a sibling has been very helpful for her."

14q13q21 deletion, 3½ years old

Breathing

Respiratory problems have been widely reported for babies, children and adults with deletions involving 14q13 (see also [At birth](#), page 8). Loss of the NKX2-1 gene in 14q13 (see [Genes](#), pages 18-19) is believed to underlie most of the

serious respiratory disorders, although some who have lost this gene are unaffected (Santen 2012; 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 (Devriendt 1998; Mehta 2001; Torgykes 2011; Fonseca 2012; Unique). One baby with a 14q13.1q21.1 deletion was born with a collapsed lung (Santen 2012). 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 (Devriendt 1998; Mehta 2001; Torgykes 2011; Fonseca 2012; Santen 2012; Unique). Sadly, three children are known to have died from pneumonia; two had a 14q11.2q13 deletion, and one a 14q12q13 deletion (Unique).

Breathing difficulties including deep panting (hyperventilation) can occur. A boy with a 14q12.2q13 deletion had a disturbed breathing pattern associated with episodes of very rapid deep breathing (Perche 2013).

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

A few babies have been born with a cleft palate (a split in the roof of the mouth) or a high and narrow palate (Unique). Among Unique babies, a cleft palate and lip were seen only in 2 babies with a large deletion extending to 14q12; no cleft was seen in any children with a pure 14q13 deletion.

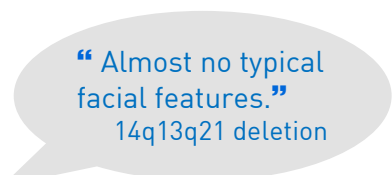
The hard palate at the front of the mouth may be split or the split may be found further back in the soft, fleshy tissue at the back of the top of the mouth. Occasionally the split is only seen in the tissue that hangs down above the tongue at the very back of the mouth (uvula, known as a bifid uvula when it is split). A cleft lip may also occur (see [Head and Brain](#) page 11).

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

There may be little sign in the appearance of some babies with a 14q13 deletion of the underlying disorder. 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'.

Children with a deletion involving chromosome 14q13 may exhibit unusual facial features which most commonly include heavy eyebrows; epicanthal folds (a skin fold across the inner corner of the eye); a low and wide bridge to the nose; a smaller or larger than average nose; small ears; and a mouth with an obvious Cupid's bow (Perche 2013; Piccione 2012; Fonseca 2012; Torgykes 2011; Unique).



“Almost no typical facial features.”
14q13q21 deletion

Hands and feet

Minor, non-functional anomalies of the hands and feet are relatively common in children with chromosome disorders. One child with a 14q13 deletion has 'unusual' hands; among those with a 14q12q13 deletion, one girl has shortened fingers and wide first toes; another has a single crease across the palm; another overlapping toes. A child with a deletion between 14q12q13 has overlapping toes. These can usually be corrected passively, using plastic splints; toe position may improve when a child starts to walk (Fonseca 2012; Unique).

Seizures

Although seizures are common in children with a 14q13 deletion, many children do not experience them. However, significant numbers of children have episodes of shaking or moving oddly that need investigation to distinguish them from the movement disorder that some children have. 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); tonic-clonic (the muscles tense, and then contract and relax rapidly); myoclonic jerks (sudden muscle contraction or relaxation).

Seizures are associated with deletions involving 14q12, the band next to 14q13, with 9/10 children in the medical literature affected (Bisgaard 2006; Papa 2008; Mencarelli 2009; Torgykes 2011; Allou 2012; Ellaway 2012; Perche 2013). They are also relatively common among Unique children with a 14q11.2 deletion that extends to 14q13 or 14q21. Two children with a deletion within 14q13 have also had seizures, although in one child no EEG anomaly was found (Unique).

Seizures can be associated with a brain anomaly such as a missing corpus callosum (see [Head and brain](#), page 11). Generally seizures are controlled with anti-epileptic medication but among Unique members one child experienced seizures that were hard to control.

Heart

Most babies, including all of those in Unique with a deletion within 14q13, were born with a normal heart structure and function. Two babies with a 14q12q13.1 deletion were born with a patent foramen ovale (PFO), when a hole between the two upper chambers of the heart fails to close as expected at birth. Another child with a larger 14q12q13.3 deletion was born with a patent ductus arteriosus (PDA), another persisting structure of the fetal circulation. PDA allows some of the oxygenated blood from the heart to shunt back to the lungs, potentially leaving the baby short of breath and causing pulmonary hypertension, which makes the heart work too hard (Fonseca 2012; Torgykes 2011; Unique).

If mild, heart conditions can be monitored at first to see whether they resolve naturally. If needed, they can be corrected surgically.

Eyesight

Deletions involving 14q13 have been linked to a range of problems. A girl with a 14q12q13.1 deletion had underdeveloped optic nerves in both eyes and was essentially blind (Torgykes 2011). A boy with a 14q13.1q21.1 deletion had a range of symptoms including an extremely small right eyeball (microphthalmia) accompanied by abnormality of the lens and an underdeveloped optic nerve. His left eye was larger than the right one, but was still smaller than normal; however, the optic nerve was normal (Piccione 2012; Torgekes 2011).

Among Unique children with a deletion within 14q13, one child has cortical visual impairment, where the visual systems in the brain do not understand or interpret what the eyes see. This was also found in a child with a larger 14q12q13 deletion.

Hearing

Hearing appears to be generally unaffected, with just three children diagnosed with middle ear dysfunction caused by the build-up of fluid. This is known as glue ear and is treatable where necessary by drainage and the insertion of tubes in the eardrum. Glue ear is common in all small children, and even more so in children with a cleft palate. One girl with a 14q12q13.1 deletion had mildly impaired hearing and one child with a 14q11.2q21 deletion had poor hearing in his left ear (Torgykes 2011; Unique).

“Conductive hearing loss in the first year - 50 dB bilaterally at first, gradually improving and having disappeared by the age of 1.” 14q13q21 deletion

Missing teeth

Oligodontia is a rare anomaly of development where six or more teeth are missing. When oligodontia has been specifically investigated, 4/4 people with a 14q13 deletion were affected. This feature only occurs if the PAX9 gene located on 14q13.3 is deleted or non-functional (Santen 2012) (See [Genes](#), pages 18-19).

However, among Unique children, none had oligodontia, although two, both with large deletions between 14q12/3 and 14q21, had a single central front tooth, a possible sign of the very mild form of HPE (Fonseca 2012; Santen 2012; Unique) (see [Head and brain](#), page 10).

Development

■ Sitting, moving - gross motor skills

Babies and children with a large 14q13 deletion typically appear to face considerable delay in reaching their mobility milestones, although there is a wide variation in how much a child is affected. This seems to depend on how big and where the deletion is. Most children have altered muscle tone, usually low, which can make it harder to learn to control the body. Some have a movement disorder called choreoathetosis, where they make twisting, writhing and contracting movements that they cannot control. At least one child has been

diagnosed with benign hereditary chorea. Others have ataxia, with difficulty controlling their movements, making it hard to learn to sit, move and walk, and increasing the likelihood of falls (Santen 2012; Unique). It is possible to treat the movement disorder with physiotherapy and medication, which you should discuss with your child's paediatrician.

Among Unique families and children reported in the medical literature, virtually all children were affected, and one family said that gross motor skills were the area of greatest delay. One child held her head steady by 7 months; children first sat up between 9 months and 2 years; one baby crawled by 19 months while another was scooting on her back indoors at the age of seven; children started walking between 2 and 4 years, but were at risk of ataxia with difficulty controlling movements and frequent falls. Muscle control and mobility were however not possible for all: two children, aged 4 and 12, developed spastic paraplegia (where the muscles usually in the legs get increasingly stiff and weak); the 4-year-old was unable to roll, while a 2½ year old boy could only move like a baby of 2 months (Torgykes 2011; Santen 2012; Piccione 2012; Fonseca 2012; Perche 2013; Unique).

“ At 5 months he did not roll onto his tummy, had no interest in toys and contact with others was minimal. At 7 months he had no gross motor skills and almost inactive legs. At 21 months he has started to follow people and toys with his eyes. He can grasp a toy when sitting in a chair. His legs are very active and he grasps his feet and plays with them when lying on his back or sitting. He can sit with support and can now last longer in this position. His hand/eye coordination is now quite good. He is doing well with lying with his toys.” 14q13q21 deletion, 2 years old

For all children, early physiotherapy input is vital to assess needs for therapy and equipment and to guide families to stimulate early activity. Adapted seating and other aids may be helpful in extending children's range of mobility. Children with hypotonia are likely to also benefit from support.

■ Using their hands: fine motor and coordination skills

Hand and eye coordination skills such as holding a bottle and playing with small toys may not develop in line with gross motor skills. A child who is late to hold his head steady may still reach for toys. Where there is a delay early intervention by occupational therapy to stimulate hand use is vital.

“ At 14 months she started reaching and grasping for toys; at 15 months she started taking and shaking rattles. We are thrilled! ” 14q13q21 deletion



“ Very smart for his age; learns quickly.”
14q13.2q13.3 deletion, 3 years

■ Learning

We only have limited information relating to learning, but it is clear that most children with a 14q13 deletion - although not all - are likely to need support. The amount of support needed will vary, with some children only having mild difficulties. Two Unique families told us that their child had no learning difficulties. The larger the deletion and particularly if the FOXP1 gene (see [Genes](#), pages 18-19) at 14q12 is included, the greater the probability that any learning difficulties will be more marked (Santen 2012; Unique).

A child with a 14q13.1q13.2 deletion is described as having a good memory and learning by her own persistence and when she is happy; she has a learning disability characterised as severe. A 7 year old girl with a 14q13.1q21.1 deletion was one year behind at a mainstream primary school. Her IQ was assessed at 76, with a verbal IQ of 105. A woman of 36 year old with a 14q13.1q21.1 deletion had mild learning difficulties and attended a special school as a child (Santen 2012).

■ Speech and communication

Generally, speech and language reflect the level of learning disability and children with greater learning difficulties appear to use less speech. Understanding is also affected but children generally understand more than they can express. There is a very wide spectrum, from children with above-average speech and language skills, to others who mostly communicate using vocal noises. Where 14q12 is involved, speech is most likely to be severely affected. The evidence from Unique suggests that understanding may also be limited, despite unimpaired hearing, but children can learn to respond to familiar voices, signs and phrases with interventions including speech therapy and sign language have sometimes proved successful.

Among Unique families, 2 children with a 13q13.2q13.3 deletion report no speech delay, and a third child with a deletion within 14q13 was 'speaking fluently' by the age of 9 after delays in early childhood. In others, delay ranges from mild to severe. Among those children who have started to speak, first words emerged between the ages of 18 months and 3 years.

Among children reported in the medical literature, a girl of 7 with a 14q13.1q21.1 deletion had a verbal IQ of 105. A child with a small deletion within 14q13 spoke her first words at 32 months and was speaking in six-word phrases by the age of 4. A boy of 14 with a 14q13.1q21.1 deletion was speaking, but used repetitive phrases and had echolalia (repeating heard words and phrases without meaning), and he could understand and carry out simple tasks.

Less encouragingly, a girl with a 14q12q13.3 deletion had a delay in speech development and a vocabulary of 10 words; however, her speech later deteriorated and at the age of 6 she could pronounce only one word. A boy of 2½ with a 14q12q21.1 deletion had the language skills of a six-month old baby, and

a girl of 4 with a 14q12-q13.1 deletion was unable to respond to her name, and a boy of 12 with a 14q12q13 deletion was also unable to talk (Torgykes 2011; Fonseca 2012; Piccione 2012; Santen 2012; Perche 2013; Unique).

It has been suggested that losing the RALGAP1 gene from 14q13.2 (see [Genes](#), pages 18-19) may underlie speech regression (Caliebe 2011).

“ Not speaking but he can make sounds including some vowels and consonants and makes throaty noises. He responds in his own language when people talk to him but sometimes he does not react. He doesn’t cry.” 14q13q21 deletion, 2 years

“ Teachers observe that his responsive language is more advanced than most kids of his age; any delays in speech tend to be due more to tone (quality of breath etc).” 14q13.2q13.3 deletion, 3 years

Behaviour and autism

Children and babies with a 14q13 deletion are described as generally easy-going and happy. Although one boy with a 14q13.1q21.1 deletion was described as being irritable and aggressive, he seems to be an exception (Piccione 2012). Among Unique families, one child with a small deletion within 14q13.2 has a diagnosis of autism, and a further child has autistic features but no formal diagnosis.

“ Interacts with adults and has great eye contact. She loves interacting with her peers in school and is getting braver with each day. She has the best personality, always has a smile and greets everyone with a loud Hi.” 14q13.1q21.1 deletion, 3½ years

“ She is just so active, happy, committed and living in the present. She loves everything around her, she studies everything she finds in nature and she has such a good time.” 14q21.1 deletion, 3½ years

“ Even though he is 4 years and 4months old, he acts younger. He gets overwhelmed in large crowds. A lot of the time he speaks his own language, but seems happy-go-lucky. He is so loving. He loves to cuddle. He is happy most of the time. He is just entertaining. He brings us all a lot of joy.” 14q21.1q21.3 deletion, 4 years

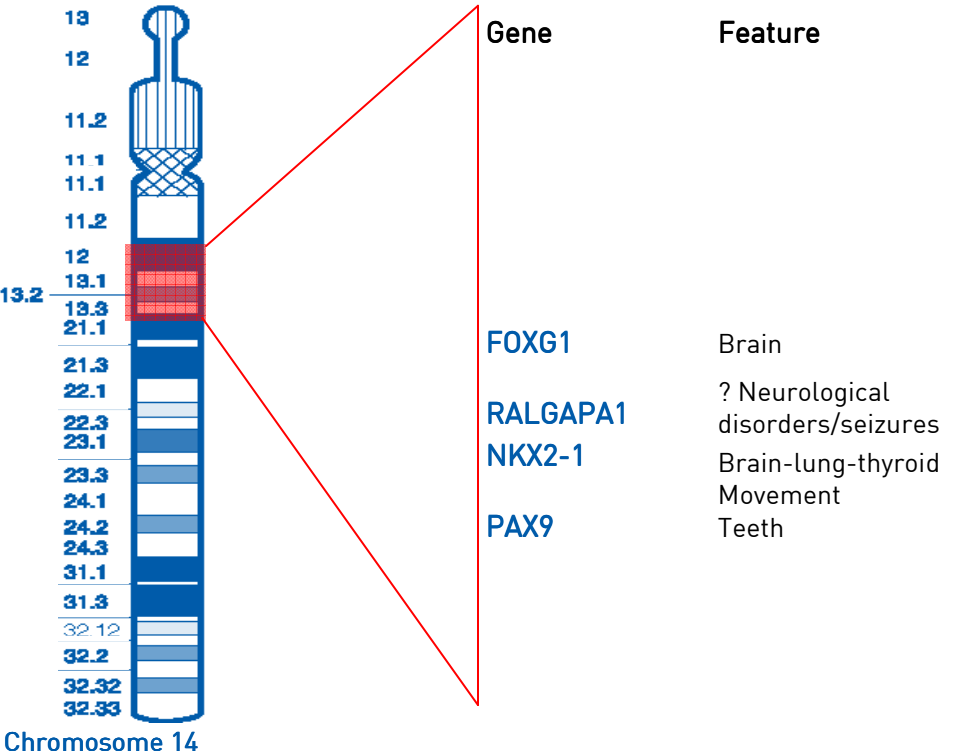
Sleep

Sleep problems may occur, but as far as we know, they are not necessarily to be expected. At 3½, a young boy with a 14q13.1q13.2 deletion only slept for short spells. A 4-year-old girl with a 14q12-q13.1 deletion had sleep apnoea, corrected by having her adenoids and tonsils removed.

Among Unique children with a 14q11.2 deletion extending to 14q13, two families report a sleep problem. In one child it is thought to be due to an underlying anxiety. In the other child, with a large 14q11.2q21 deletion, the cause is physical, in that he has sleep apnoea where he stops breathing for short spells (Torgykes 2011; Santen 2012; Unique).

Apart from removing swollen tonsils and/ or adenoids in a child with obstructive sleep apnoea, sleep difficulties can be helped by sleep training and difficulties in settling can often be helped by giving the hormone melatonin.

Genes



FOXG1

14q12 28,767,071-28,770,276

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, or there is a mutation (change) in the gene. In children with the features of FOXG1 syndrome where the FOXG1 gene is not deleted or mutated, 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).

RALGAPA1

14q13.2 35,538,351-35,809,303

RALGAPA1, also known as TULIP1 and GARNL1, has been suggested as a gene causing 14q-linked neurological disorders. Children with only one copy of the gene share common characteristics with children with mutations (changes) within the gene, such as intellectual disability, language regression during childhood, autistic behaviors, developmental delay, and hypotonia (Shapira 1994; Kamnasaran 2001; Petek 2003; Schwarzbraun 2004; Kamnasaran 2005; Shimojima 2009; Caliebe 2011; Fonseca 2012; Piccione 2012; Decipher). It has also been suggested that malfunctioning of RALGAPA1 could be linked with seizures (Shimojima 2009; Caliebe 2011).

NKX2-1

14q13.3 36,516,396-36,520,224

This gene, the thyroid transcription factor-1 gene (NKX2-1), plays a role in the development of healthy lung function and its absence or malfunction causes 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/benign hereditary chorea, see [Sitting, moving](#), pages 14-15), lung dysfunction and breathing problems, and low levels of thyroid hormone (Santen 2012). It is also 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; Peall 2015).

PAX9

14q13.3 36,657,567-36,677,806

Changes (mutations) in the PAX9 gene are a known cause of missing teeth (oligodontia when six or more teeth are missing). Losing part or all of the gene can also cause oligodontia (Fonseca 2012; Santen 2012).

“ He is the best kid ever! He’s very funny; very sweet (kind to other people – always sharing); has a firm grasp on what is going on around him (asks lots of questions); exceptionally smart (totally understands what we’re saying and can carry on conversations); he loves to play with other kids (although he can get frustrated by his lack of mobility); has a good imagination. He brings us constant joy and is quite simply the greatest thing to ever happen to our lives! ”

14q13.2q13.3 deletion, 3 years

Support and Information



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Please help us to help you!

Facebook group for Benign hereditary chorea

www.facebook.com/groups/761402783950511

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. It was compiled by Unique and reviewed by Dr Gijs Santen, clinical geneticist in training, Leiden University Medical Centre, The Netherlands.

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