

Understanding  
chromosome  
disorders

Unique



# 15q26 deletions



## Sources

The information in this guide is drawn partly from 41 cases in the published medical literature and other relevant papers (Roback 1991; Tönnies 2001; Okubo 2003; Biggio 2004; Dorkins 2004; Bhakta 2005; Castiglia 2005; Le Caignec 2005; Pinson 2005; Slavotinek 2005; Slavotinek 2006; Klaassens 2005; Klaassens 2007; Poot 2007; Clugston 2008; Davidsson 2008; Lurie 2008; Walenkamp 2008; Li 2008; Ester 2009; Veredice 2009; Bruce 2010; Lin 2010; Veenma 2010; Wat 2010; Choi 2011; Dateki 2011; Dhamija 2011; Rudaks 2011; Capelli 2012; Poot 2013). 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](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 the Decipher database (<https://decipher.sanger.ac.uk>) and on a survey of members of Unique conducted in 2013, referenced Unique. When this guide was compiled, Unique had 24 members with a pure deletion from 15q26. They ranged in age from 20 months to 19 years. Seventeen families completed a detailed survey in 2013.

## 15q26 deletions

A 15q26 deletion is a genetic condition that occurs when there is a small piece of genetic material (DNA) missing from one of the 46 chromosomes – chromosome 15. The genetic change usually affects development, growth, feeding, and sometimes health as well. But how much it affects individuals, and the ways in which it affects them, can vary a lot.

## Genes and chromosomes

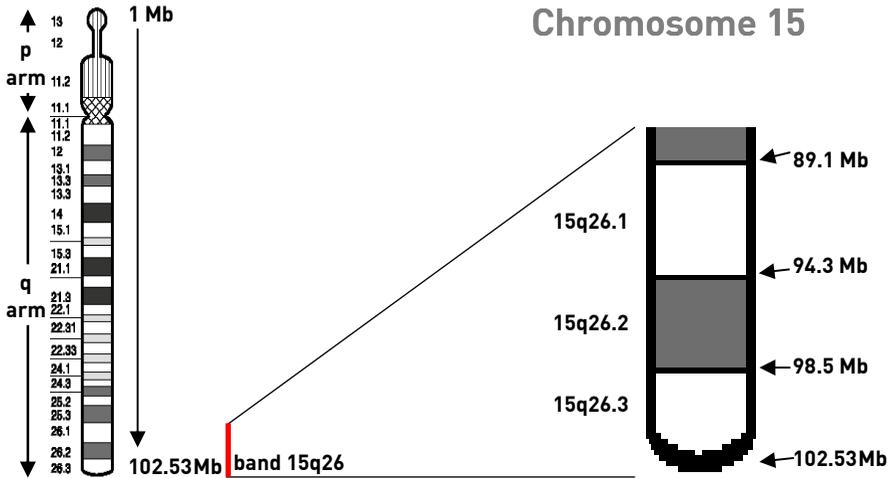
Our bodies are made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; this genetic information tells the body how to develop, grow and function. Genes are carried on structures called chromosomes. Chromosomes usually come in pairs, one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: (two Xs for a girl and an X and a Y for a boy). The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from largest to smallest. These are called autosomes. Each chromosome has a short (p) arm (from petit, the French for small) and a long (q) arm (see diagram, page 3).

In general, the right amount of genetic material is needed for correct development – not too little and not too much. How an individual develops, his/her personality, needs and achievements, are influenced by both the genetic material he or she has and the environment in which he or she lives.

## Looking at chromosome 15q26

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. In the diagram of chromosome 15 on page 3, you can see the chromosome bands are numbered outwards from the point where the long arm meets the short arm. You will find 15q26 at the bottom, divided into three bands – light (26.1), dark (26.2) and light (26.3). Each band 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. In all, 15q26 has about 13.4 million base pairs. This sounds a lot, but is actually quite small: the DNA in 15q26 on one chromosome 15 is about 0.2 per cent of the total in each cell.





## Genetic testing

Looking at chromosomes under a microscope, it may be possible to see the genetic material that is missing, if the piece is large enough.

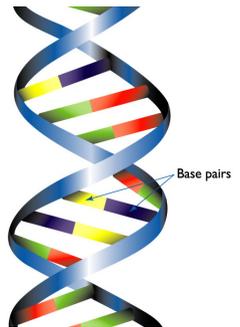
Molecular DNA technology gives a more precise understanding of the size and position of the deletion. This is important as scientists identify genes and pinpoint their location on chromosomes.

Techniques that are commonly used include FISH and microarrays:

- Fluorescence *in situ* hybridisation (FISH) uses fluorescent dyes to visualise under a microscope the number of copies of small sections of chromosomes. Unique publishes a separate guide to FISH

However, rare chromosome disorders may be caused by subtle changes in the chromosomes that are too small to see using a microscope.

- Microarray comparative genomic hybridisation (array CGH) is a sensitive technique which shows gains (and losses) of tiny amounts of DNA throughout the chromosomes. Array CGH identifies duplicated, disrupted or absent DNA. Unique publishes a separate guide to array CGH.



1 base pair = bp  
1,000 base pairs = 1kb  
1,000,000 base pairs = 1Mb

Your geneticist or genetic counsellor will be able to tell you about where the chromosome has broken in your child. The results are likely to read something like one of these four examples:

1. **46,XX,del(15)(q26.1qter)** 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 woman. **del(15)** means there is a deletion from chromosome 15. **q26.1** shows the band in the chromosome where the break was found; **qter** shows that DNA is missing from 26.1 to the end (terminus) of the chromosome, so this type of deletion is called **terminal**. The word 'terminal' does NOT imply that the child will die.

2. **46,XY,del(15)(q26.2q26.3)** This shows that the expected number of chromosomes (46) were found. It shows that an X and a Y chromosome were found, so this is a boy/ man. **del(15)** means there is a deletion from chromosome 15. **(q26.2q26.3)** shows that two breaks were found in the chromosome, one in the 15q26.2 band and the other in 15q26.3 and the DNA between them is missing. This type of deletion is called an **interstitial** deletion.
3. **46,XY,del(15)(q26.2).ish del(15)(wcp15+, D15S396-)** This result tells you that the expected number of chromosomes (46) were found. It shows that an X and a Y chromosome were found, so this is a boy or man. **del(15)** means there is a deletion from chromosome 15. **q26.2** shows the band in the chromosome where the break was found. **ish** shows that the analysis was by FISH. **wcp15+** shows that the chromosome was identified as 15 using a technique known as whole chromosome painting. **D15S396-** shows that a marker whose position on chromosome 15 is known is missing.
4. **arr [hg19]15q26.3(99187693-99507795)x1dn** This result tells you that array comparative genomic hybridization (**arr cgh**) showed that only one copy of part of the band known as 15q26.3 was found (**x1**). The normal number of copies is two. **hg19** tells you which version of the human genome was used to make these measurements. At present, hg19 is the latest version. The first base pair missing is **99187693** and the last is **99507795**. By taking the first number from the second, you can work out that there are 320,102 missing base pairs, or about 0.3 Mb of missing material. **dn** de novo (Latin for 'from the beginning') means that the chromosome change has not been inherited but has arisen 'anew' (*see* page 00).

## Has everyone with a 15q26 deletion lost the same amount of DNA?

No: everyone is different. So far as we know, there are no especially fragile places in the 15q26 region where the chromosome is likely to break. Some people have lost a lot of DNA, others only a tiny amount. Some people have lost DNA from the end of chromosome 15 (a **terminal** deletion) with a break in the 15q26.1 band, others in 15q26.2, yet others in 15q26.3. Other people have two breaks in the chromosome and have lost the DNA between them (an **interstitial** deletion). The different missing DNA and genes explain many of the differences between people who all have a 15q26 deletion, but not all of them. Some people with very similar missing amounts of DNA and genes are affected much more mildly than others. Some of these differences might be explained by the DNA on the other, intact chromosome 15. Other differences are not yet fully understood (Poot 2007; Veenma 2010; Poot 2013).

## Main features

The effects of a 15q26 deletion depend largely on what DNA and which genes have been lost. But there are still differences between people who have lost a similar amount of DNA.

- Babies who have lost the *IGF1R* gene from the 15q26.3 band are typically very small at birth, and remain very short for their age
- Many babies need a lot of help with feeding
- Children typically have developmental delay, although the degree can be extremely variable
- Some babies are born with a heart problem. This can be minor or more serious
- A defect in the diaphragm that separates the contents of the chest from those of the stomach (diaphragmatic hernia) has been found in a few babies
- Many children have unusually lax (bendy) joints

- Babies and children have some facial features that are different from the rest of their family
- Some children have had seizures. These are more common in those with a 15q26.1 or 15q26.2 deletion Other features are described on pages 11-13.

## First signs

Most commonly, babies are very tiny and their growth does not catch up

Among 34 babies and children reported in the medical literature, small size was the most common first sign of the chromosome anomaly. Most babies were identified during pregnancy, some with additional health problems. Seventeen babies and children – half of the total – were very small but had no significant health problems. Seven babies had serious health concerns, usually affecting the heart or the diaphragm (the sheet of muscle between the chest cavity and the abdomen). Three children were identified when they showed developmental delay, such as crawling late, and three had epilepsy. An additional reason for checking the baby's chromosomes was often some slightly unusual facial or hand feature, such as low-set ears, widely spaced eyes, or short or incurving fingers. In other children a persistent failure to gain weight prompted the genetic test (Roback 1991; Siebler 1995; Tönnies 2001; Okubo 2003; Biggio 2004; Dorkins 2004; Bhakta 2005; Le Caignec 2005; Pinson 2005; Slavotinek 2005; Klaassens 2007; Poot 2007; Rujirabanjerd 2007; Davidsson 2008; Li 2008; Walenkamp 2008; Ester 2009; Veredice 2009; Veenma 2010; Choi 2011; Dateki 2011; Dhamija 2011; Rudaks 2011; Capelli 2012).

Among 15 Unique members, seven were diagnosed because they were very short and their growth failed to catch up; two because of serious health problems; and three because of developmental delay. In two babies the first sign was areas of the scalp where the skin had not closed. One baby was born with a cleft lip and palate and later developed epilepsy. Some babies and children had other non-specific signs, such as a single palm crease (Unique).

## Pregnancy

Babies are very often small for dates and some have health problems. Some pregnancies are trouble-free

Where pregnancy was described, six Unique reports and three reports in the medical literature gave no grounds for concern. By far the most common concern was the size and growth of the baby (intrauterine growth restriction – IUGR), although this was only true for 4/14 Unique mothers. The baby's small size was noted from 22 weeks of pregnancy but may have been evident earlier. In one pregnancy a decline in growth rate was not noted until the last month. In four cases there was very little amniotic fluid around the baby (oligohydramnios). Pregnancy anomaly scans showed a variety of major and more minor health concerns, including heart problems, diaphragmatic hernia (a hole in the wall of muscle separating the chest cavity from the abdomen), a cystic hygroma (a cyst-like swelling containing clear lymphatic fluid) and clubfeet. Other features noted by Unique mothers include reduced fetal movement and some bleeding. Other features, such as rib pain, extreme sickness, back pain, high blood pressure, Group B streptococcus infection and a low-lying placenta are unlikely to be connected with the chromosome anomaly (Roback 1991; Siebler 1995; Tönnies 2001; Okubo 2003; Bhakta 2005; Pinson 2005; Slavotinek 2005; Poot 2007; Rujirabanjerd 2007; Davidsson 2008; Walenkamp 2008; Bruce 2010; Veenma 2010; Choi 2011; Dateki 2011; Rudaks 2011; Unique).

## New babies

New babies are typically very small and have feeding difficulties

Babies with a growth or health problem have been closely monitored in the second half of pregnancy and some delivered a few weeks early by Caesarean section. Among babies born at or near their due date, two-thirds were very small and others quite small for gestational age, although a few babies are born an appropriate length and weight for their age. Among babies reported in the medical literature, birth weights at or near term ranged from 1.263kg (2lb 13oz) to 2.89kg (6lb 6oz) (Roback 1991; Ester 2009). Among Unique babies born at or near term, birth weights were on average higher than reported in the medical literature for 15q26 deletion. The lowest was 2.03kgm (4lb 8oz); the highest 2.69kg (5lb 15oz) (Unique). Babies were generally proportionate, short as well as light, and with a small head (microcephaly). Babies with a birth weight within the normal range have typically lost part of the 15q26 bands, but have retained the *IGF1R* (insulin-like growth factor 1 receptor) gene intact (*see Genes* pages 24-25).

Apgar scores (a 0-10 scale of a baby's wellbeing at birth) were typically low but in most showed an improvement after five and 10 minutes.

The umbilical cord usually has three blood vessels – two arteries and a vein. In a few cases, babies with a 15q26 deletion have had a single umbilical artery (Slavotinek 2005; Klaassens 2007; Unique). Some babies were born with evident anomalies, including talipes (clubfeet), padded 'rocker bottom' feet, areas on the skull where the skin had not closed, brownish 'café au lait' skin patches, birthmarks, a dimple at the base of the spine, dislocated joints or other joint problems. Other babies had no sign that would be obvious to a parent that anything was wrong. Many babies needed support with their breathing in the first hours and some needed care for some weeks or even months after birth, partly because of their small size and feeding difficulties and partly due to their medical problems. Babies with a serious heart problem or a diaphragmatic hernia generally needed breathing support on a ventilator until the extent of the health problems had been clarified and in some cases surgical correction carried out. Babies with more minor health problems, or none at all, were generally able to go home after a few days in hospital.

Nearly all babies lost more weight after birth than expected, a concern since they were generally very small, and needed a lot of support with feeding. They found it difficult to latch on or suck and while a few, generally with a smaller deletion from 15q26.3, were able to feed slowly from the breast or bottle, many needed to take feeds intravenously or from a nasogastric tube fed through the nose and down the food pipe to the stomach. Some babies were able to feed independently before leaving hospital, while others went home with the nasogastric tube in place.

(Roback 1991; Siebler 1995; Okubo 2003; Poot 2007; Rujirabanjerd 2007; Davidsson 2008; Rump 2008; Ester 2009; Veenma 2010; Decipher; Unique)

"Tiny, lethargic baby, did not wake for feeding, only fed a very small amount and would not stay awake." 15q26.2 terminal deletion

## Growth

Babies and children remain short. Growth hormone helps some.

Babies who have lost the *IGF1R* gene from the 15q26.3 band (*see Genes* pages 24-25) typically grow unusually slowly in the womb, are born obviously light and short for their age and their growth fails to catch up later. Typically, they are proportionately small, with

a small head and somewhat under weight or with a body build that is 'about right'. However, the family genetic background also plays a role, so a child with tall parents might be of average height rather than very short.

The *IGF1R* gene is involved in growth regulation. A normal growth pattern is determined by a complex of factors, including the processing by the body of chemicals known as growth factors. Children who have lost the *IGF1R* gene are usually resistant to one of these growth factors, a hormone known as insulin-like growth factor 1 (IGF-1). As a result, levels of this hormone may be very high, but the body is unable to make use of them. Children should be referred to a paediatric endocrinologist with a special interest in growth. When treated with growth hormone, most children, though not all, show at least modest catch-up growth, though complete catch-up may not be possible. The potential benefit of giving growth hormone means that early recognition and diagnosis are important (Klaassens 2007; Poot 2007; Ester 2009; Veenma 2010; Dateki 2011; Rudaks 2011; Poot 2013).

Unique families whose children have been treated with growth hormone report mixed success. Some children have grown a little faster; others have not. Other benefits reported include extra strength. Disadvantages reported include the daily injection; and headaches (Unique). None of the 3 Unique teenagers took growth hormone and all are short: a boy of 15 is 162 cm (5' 4") tall; a girl of 16 is 152 cm (just under 5 foot). Over time, some children remain short but put on too much weight (Bruce 2010; Unique).

"F is now 3 foot (90cm); his build is about right. He has had growth hormone from 2 years with very good effect. He is catching up on growth, and is not far behind his peers. He is finally on the last centile line on the chart, never reached before growth hormones. No drawbacks." 15q26.3 deletion, 3 years

"He has been on growth hormone since the age of 2 with very little progress but during trial periods off it has shown virtual growth failure, so we were advised to keep him on it. He is now 48" (120 cm) tall and weighs 50 pounds (23kg) and we recently took him off growth hormone due to lack of success." 15q26.3 microdeletion, 10½ years



Left, boy, 15, with a 15q26.2 deletion, with his mother, brothers and sister

## Feeding

Young babies have difficulty feeding and can have great difficulty putting on weight. The evidence from Unique is that most babies have needed a lot of long term support to establish effective feeding. With a few exceptions, babies may show no interest in feeding at first, lack a sucking reflex, be unable to suck effectively or to coordinate the actions of sucking with swallowing. Many babies were fed intravenously, through a nasogastric tube or a gastrostomy tube direct into the stomach for weeks, months or even years. Just a few babies have succeeded in breast or bottle feeding; others have taken breast milk by tube. Babies able to take milk from a bottle typically fed extremely slowly, sometimes falling asleep while feeding, and usually needed a teat designed for babies with feeding difficulties or a special bottle, such as a Haberman feeder.

Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food pipe and may cause choking, vomiting and discomfort, affected some babies. Reflux raises a baby's risk of inhaling food contents and setting up an infection in the lungs known as aspiration pneumonia. 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 and counteract any acidity. Babies who have continuing problems can have a surgical procedure called a fundoplication to improve the action of the valve at the junction of the food pipe and stomach. Where feeding and reflux problems are persistent, a gastrostomy tube (PEG, button) can be inserted to allow direct feeding into the stomach until the baby is sufficiently mature to tolerate feeding by mouth. Some children still rely on a gastrostomy tube as toddlers and at school for all or some of their feeds.

All babies known to Unique have made slow but steady progress with feeding, with most eventually learning to drink through a teat or a spouted cup. Progress to solids has also been delayed and children have spent months or even years taking liquidised, puréed or mashed foods or naturally smooth foods such as yoghurt before learning to tolerate lumps and tiny bites of solid food. Children given lumps they could not swallow might hold them in their mouth, so need frequent sips of drink to help the food down. Some teenagers still needed their food puréed, chopped or cut up, but could eat a varied, healthy diet. Even the most competent feeders needed a sauce to enable them to swallow dry food.

Lack of appetite appears to be persistent, with many children continuing to eat very small quantities. Many babies are unable to maintain their weight or a satisfactory weight gain. Enriched milks, energy supplements and high-calorie foods are usually needed. The evidence from Unique suggests that babies whose weight gain is satisfactory have usually not lost the *IGF1R* growth gene from 15q26.3.

Some children have needed therapy to increase their oral tolerance and allow activities such as tooth brushing, with generally good results.

Young children are often unable to feed themselves and need to be fed, usually from a spoon. Some need a specially adapted chair (Unique families have used Heathfield, Samba, Tripp Trapp) so that they are supported and safe while feeding.

More than half of Unique families reported that their baby or child had significant constipation. With medical advice, families tried probiotics, with mixed results. Medication was generally successful, as was adding fibre to a baby's milk, and families found that constipation eased once their child became more mobile. Older children on a mixed diet were helped by drinking water and fruit juice and eating fruits and salads. Families should expect to receive expert feeding support throughout their child's early years. (Unique)

"He had no feeding difficulties and was breastfed but did have difficulty putting on weight." 15q26.2q26.3 deletion, 2½ years

"C did not do well with breast feeding and we tried many different types of bottle.

Ultimately we had to squeeze his cheeks so he could get enough suction. Today he eats what we eat, though he seems to be sensitive to hot temperature and has a bit of a hard time with hard foods (choking and/or not chewing thoroughly)." 15q26.2 terminal deletion, 6 years

"H didn't take to breast feeding and did not take much formula. She never finished more

than a 4 oz bottle and never had more than 16 oz in one day. After her heart surgery at 2 years old she began to thrive and her appetite improved. She now enjoys a variety of foods, particularly foods that are salty.” 15q26.2q26.3 deletion, 11 years

“A was fed intravenously at first. She has been tube fed and had a gastrostomy tube placement as well as a fundoplication.” 15q26.1 terminal deletion, 14 years

“Quantity consumed was very small and there was no progression; the effort of feeding would tire J rapidly. Bottle fed, woken at 3-hour intervals, nappy changed mid-feed to wake him. Today, he eats normal foods – but food has been by far our biggest problem. J will eat anything he finds and then hide the evidence. He is banned from the local shop having taken money from my purse and spent it on chocolate. Our kitchen cupboards are locked and in many respects we treat the problem as if he had Prader-Willi syndrome. He is diagnosed as hyperphagic. J’s excessive weight is going to be an issue as he gets older as his joints and back already hurt. Although he understands the need to lose weight, he has very little will power.” 15q26.2 terminal deletion, 15 years

“C couldn’t feed as a baby; she didn’t know how to suck. We really struggled to get her to take a small amount of milk and she lost weight rapidly at first. We must have tried 50 types of teat and she couldn’t breast feed. She has had issues with food ever since and still doesn’t chew food, but she can eat chopped foods and now enjoys a varied diet.” 15q26.1 terminal deletion, 16 years

## Appearance

Babies and children are likely to have some facial features that are different from the rest of their family. Doctors may notice what are known as ‘dysmorphic features’ which may or may not be obvious to a parent. Most of these are facial features of little or no importance to the baby but they do help doctors to reach the correct diagnosis.

Some of the most common features seen include a triangular face with a relatively small chin and lower jaw that may be set back against the upper jaw; or alternatively a round face; wide set eyes; a thin upper lip; and low set ears that may be large and may be tilted backwards. Other features seen in a few children include a prominent nose or wide bridge to the nose; a flat or short groove between the nose and upper lip (philtrum); and a short neck. Additionally, a baby’s head is often unusually small, but in proportion to the rest of their body.

## Hands and feet

Minor anomalies of the hands and feet are relatively common in children with chromosome disorders. These may just be cosmetic or they may make it harder for the child to use their hands. The most common features affecting the hands include incurving fifth fingers; short fingers, sometimes with a single crease; small or short hands and an unusual placement of the thumbs lower down the wrist than normal. One child had an extra finger (Robak 1991; Siebler 1995; Okubo 2003; Biggio 2004; Bhakta 2005; Castiglia 2005; Pinson 2005; Poot 2007; Rump 2008; Ester 2009; Lin 2010; Veenma 2010; Choi 2011; Rudaks 2011; Decipher; Unique).

“The palms of H’s hands are red and she has a single crease across the palm.” 15q26.2q26.3 deletion, 11 years

“C has calluses on her hands as she tightens them and squeezes her fingers when stressed or anxious.” 15q26.1 deletion, 16 years

Children’s feet are typically small and may be so small that weight-bearing and walking is difficult. In some cases the feet are very flat or they may have a curved sole, like a

rocker on a chair. A few children are born with one or both feet turned in and 12 children were born with club feet that needed correction by surgery, strapping, casting or physiotherapy. Additionally, two babies were missing one joint in one of their toes, and two more had unevenly implanted toes or small, underdeveloped nails (Roback 1991; Bhakta 2005; Pinson 2005; Slavotinek 2005; Poot 2007; Rujirabanjerd 2007; Davidsson 2008; Rump 2008; Ester 2009; Rudaks 2011; Unique).

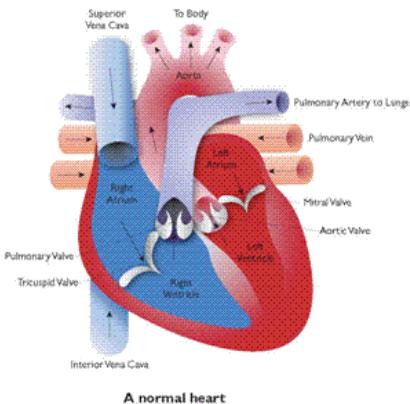
"V's feet are big and chubby and turn inwards when she stands without shoes. We try to use supporting shoes and also do other exercises." 15q26.1q26.2 deletion, 20 months

"A has small, puffy feet. She has had a partial bilateral talipes repair." 15q26.1 deletion, 14 years

"J has had ingrowing toe nails removed on both feet. His toes are calloused, and they sometimes become sore." 15q26.2 deletion, 15 years

## Health

### ■ Heart



A normal heart

Both minor, self healing problems and complex anomalies are found

Some babies with a 15q26 deletion are born with strong, healthy hearts, but defects in the structure of the heart are seen quite commonly. The problems range from ones that self-correct in time to major, complex ones that need surgical correction.

The *NR2F2* gene in the 15q26.2 band is known to be involved in heart development and it has been suggested that absence of one copy of it may give rise to some specific heart problems, including holes between the upper and lower chambers of the heart (atrial and ventricular septal defects); narrowing of the blood vessel that takes the blood

from the heart to the rest of the body (coarctation of aorta); blockage (stenosis) of the left pulmonary artery and underdevelopment of the valve that regulates blood flow between the chambers on the left of the heart (hypoplastic mitral valve) (Poot 2007).

The range of other heart problems seen in people with a 15q26 deletion includes an unusual formation, narrowing, blockage or enlargement of valves in the heart that regulate blood flow; a right-sided aorta; persistent ductus arteriosus (PDA), where a channel between the aorta and the pulmonary artery that takes blood to the lungs remains open instead of closing shortly after birth; double outlet right ventricle (DORV), where the aorta and pulmonary artery both arise from the right side of the heart; unusual ventricular left wall; and transposition of the great vessels (TGA), where the aorta arises from the right and the pulmonary artery from the left ventricle; and hypoplastic left heart syndrome, where the left side of the heart has not developed properly and is very small and the aorta, the artery that takes blood from the heart around the body, is tiny and blood can only reach it through the ductus arteriosus, a blood vessel that normally closes within days of birth (Tönnies 2001; Biggio 2004; Dorkins 2004; Bhakta 2005; Le Caignec 2005; Slavotinek 2005; Poot 2007; Davidsson 2008; Ester 2009; Decipher; Unique).

The approach to a child's heart problem depends on its severity and can include monitoring, medication and surgical correction.

Among Unique members, around two-thirds of children were born with a heart problem. "She had open heart surgery at 3 days old to correct her cardiac problem - coarctation of the aorta and multiple ventricular septal defects, and put on a pulmonary artery band. Complications included wound breakdown, delayed healing, and osteomyelitis. Given her extreme complications first time around, a decision was made not to pursue further heart surgery, and she was in palliative care from about the age of ten months." 15q26 deletion "V's ventricular septal defect does not affect her, we are just following the situation. No treatment needed." 15q26.1q26.2 deletion, 20 months  
"He had a heart murmur at birth but later was scanned and there was nothing to be concerned about. He has an enlarged pulmonary valve, which is monitored every 6 months but has no effect on him." 15q26.2 deletion, 4 years  
"H did a lot of coughing with a rattling sound in the chest as an infant, which we thought was allergies. After her 9 month visit to the pediatrician we saw a cardiologist and discovered she had an atrial septal defect. After the surgery at 2 years of age the cough and rattling sound disappeared. She recently saw the cardiologist and she asked him if she will always have to see him. It is nice that she is starting to ask questions herself. She will see a cardiologist for the rest of her life to keep an eye out for things like atrial fibrillation." 15q26.2q26.3 deletion, 11 years

### ■ Diaphragmatic hernia

A diaphragmatic hernia is a hole in the muscular wall separating the heart and lungs from the contents of the abdomen. Part of the bowel, stomach or liver can take up space in the chest, potentially depriving the lungs and heart of room to develop properly. The 15q26 region contains a cluster of genes expressed in the developing diaphragm and quite a few babies with a 15q26 deletion reported in the medical literature have been born with abnormal diaphragm development. However, other babies with a similar deletion have been unaffected. Among Unique's 24 members with a 15q26 deletion, 23 are unaffected and one has abnormal diaphragm development, but not a hernia. She has a right-sided diaphragm eventration, in which there is no hole in the diaphragm, but all or part of the muscle is replaced by fibrous elastic tissue. By the age of 14, this has not needed treatment.

When a baby is born with a diaphragmatic hernia, it is known as congenital, or, abbreviated, as CDH. CDH is a defect that should be able to be visualised on a mid-pregnancy anomaly scan. A baby born with CDH is likely to have life-threatening respiratory distress. Once its condition has been stabilised, usually on a ventilator, the hernia may be surgically repaired and breathing support given for as long as needed. However, the consequences of a diaphragmatic hernia are not always recoverable and the doctors may wish to discuss the surgical intervention with the baby's family. (Biggio 2004; Slavotinek 2005; Slavotinek 2006; Klaassens 2005; Klaassens 2007; Clugston 2008; Wat 2010; Unique)

See [Genes](#), page 24

### ■ Kidneys

A baby with a 15q26 deletion will probably have a careful check of the kidneys in case they are affected. A range of possible effects has been seen: one kidney may be found in an unusual position (ectopic) but be working normally; one or both kidneys may be unusually small and have reduced function; one kidney may contain fluid-filled sacs that affect its function (cystic dysplasia); the kidneys may be enlarged (hydronephrosis); or the tubes leading to the bladder may not be properly formed. The medical literature suggests that

as many as two babies in three may be affected, but among Unique members, the frequency is one in three and there may be no effects on the child's health (Lurie 2008; Unique).

"One kidney is located in the pelvis, the other in the normal place. This has no clinical effects." 15q26.1 terminal deletion, 12 years

"She has hypoplastic kidneys and right hydronephrosis. The anus is closer to the vagina than usual, which may explain her frequent urinary tract infections without evidence of bladder reflux." 15q26.1 terminal deletion, 14 years

"C had a lot of urine (and ear) infections when younger. It is thought that overzealous treatment with fluids may have caused kidney scarring. She has regular urine tests by the school nurse but no treatment is needed." 15q26.1 terminal deletion, 16 years

## ■ Spine

Unique records show that most children with a 15q26 deletion have normally developed spines with no additional features. The most common finding is a small hollow (dimple) near the base of the spine. This has been seen in eight children (Roback 1991; Bhakta 2005; Ester 2009; Decipher, Unique). If the dimple is shallow and the end can be seen and it is in the crease between the buttocks, it is not usually a sign of any underlying problem. All the same, matter from a dirty nappy can lodge inside, so it is important to keep it clean and cover it well with barrier cream. An ultrasound scan can show whether the pit is deep or connects with the spinal canal or the colon.



In two children the spinal cord was 'tethered' (Bhakta 2005; Unique). In this condition, the bottom end of the spinal cord that usually floats freely in a pool of spinal fluid is attached instead. As the child grows and moves, this causes the spinal cord to stretch, leading to symptoms such as muscle weakness, loss of sensation and difficulties with bowel and bladder control. Three children had a significant spinal curvature. The curve may be sideways (scoliosis), forwards (kyphosis) or backwards (lordosis) (Decipher; Unique).

"A's tethered cord was released when she was four years old. Her kyphosis worsened drastically at the onset of puberty and she had a spinal fusion when she was 12. She now has less range of motion in her spine but more in her neck and seems more comfortable." 15q26.1 terminal deletion, 14 years

## ■ Genitals

Minor anomalies of the genitals and reproductive system appear to be somewhat more common among babies and children with a chromosome change than among others, and this is true of those with a 15q26 deletion. However, most babies are born with normal genitals. Among the anomalies seen in boys are testes that have not descended into the scrotum and may need to be brought down and fixed with surgery (2/11 boys in Unique); hypospadias, where the hole usually at the end of the penis is on the underside (2/11 Unique); a very small penis, with a very small opening. Among girls the anus may be placed close to the vagina, and both a double vagina and a divided uterus have been seen (Le Caignec 2005; Slavotinek 2005; Choi 2011; Rudaks 2011; Decipher; Unique).

## ■ Skin

Three babies, all with a 15q26.2 deletion, have been born with open areas of scalp (aplasia cutis). These areas close naturally but without hair follicles (Slavotinek 2005;

Unique). More minor skin changes have also been seen, including café au lait spots, light skin colouring or albinism, and skin tags. These changes have been seen with break points across the 15q26 bands (Okubo 2003; Poot 2007; Rump 2008; Veenma 2010; Capelli 2012; Unique).

### ■ Other internal or external problems

Among the other birth problems are three accessory spleens (Unique); an abnormal distribution of the major internal organs in the abdomen (Le Caignec 2005); cleft palate/lip (Slavotinek 2005; Unique); tongue tie (Unique); an extra nipple (Ester 2009).

## Development

Expect some delay – but the range is very broad

So far, everyone with a known 15q26 deletion has shown some degree of developmental delay but the range is extremely broad. At one end of the spectrum are people whose delay is scarcely noticeable on first meeting. Other children are late to reach their baby developmental milestones; in some children, the delay is obvious in mobility, play, responsiveness and communication. In more subtle cases, the delay may be more obvious to family than to professionals, and may only show in complex later activities such as riding a scooter. In children with significant health problems, any delays may be explained at first by their ill health and time spent in hospital. Once a delay has been confirmed, early intervention services are extremely helpful.

“S didn’t crawl or walk when the age for the milestone passed, but did at 3 years. He had no sounds or words and still has no speech. His communication was zero, it is improving but very, very slowly. He was unable to do a lot of things other children could do at his age.” 15q26.2q25.3 deletion, 4 years

“Many people would not notice anything unusual about J on first encounter. He takes himself to school each day, about 40 minutes walk each way and he is able to take our Labrador for a walk. In school he is well behaved and today has been made a prefect. Years ago, they said he wouldn’t go to mainstream school. His projected GCSE results (UK exam taken at 16) are good: he should get 5 A-C grades. He can prepare a meal, do his own washing and ironing and after much prompting keep his room reasonably tidy. He understands most of the dangers of a kitchen, although it didn’t stop him putting a metal knife in the toaster recently. Fortunately he survived!” 15q26.2 terminal deletion, 15 years

## Sitting, moving, walking (gross motor skills)

Many babies hold their head up, sit, stand, move and walk late

Babies and children with a 15q26 deletion typically face delay in reaching their mobility milestones but the extent of the delay is extremely varied. Some children show no delay in gross motor skills and sit up and walk at the expected age for a typically developing baby (Walenkamp 2008; Bruce 2010; Veenma 2010; Rudaks 2011; Unique). Part of the difference between individual babies is due to underlying health problems, such as heart conditions, and part also due to features such as feet that need surgical correction before walking becomes possible. Generally speaking, those with larger deletions starting in the 15q26.1 band are more delayed than those with smaller deletions starting in the 15q26.3 band, and those with small microdeletions are less affected than those with larger deletions, but this is not a hard and fast rule. Some babies also have low muscle tone but with maturity and physiotherapy, this generally improves.

Joints are typically hypermobile and children may need support in the form of splints, supporting boots, standers or walkers, to become mobile and for some years afterwards.

Babies in this group learned to hold their heads steady between one month and 6 months of age; roll over between the ages of 5 months and 2 years and were able to sit up between 6 and 30 months. Babies became mobile between eight months and three years, either by crawling, scooting or bottom shuffling. The earliest walkers were on their feet around their first birthday, and walking independently by the middle of their second year, but others were significantly delayed. While one girl learned to walk within 2 months of her club feet being corrected shortly before her third birthday, and most others were walking by 3 or 4, at least one child was not yet walking at the age of 7. Most Unique families reported that their child had an unusual or unsteady walking style, and that this was more obvious when running, when they could become unsteady and fall.

Early intervention and physiotherapy are important for children showing significant delay and some children have shown some catch up in motor skills (Okubo 2003).



15q26.2q25.3 deletion, 4 years

“As a young baby, V didn’t learn to hold her head up as usual and kicked in only one direction; however, she turned on her belly and back on time. She sat supported from 7 months. Today she cannot sit herself down, but when we put her in a sitting position she gets out of it herself. Indoors she crawls, outside mainly sits in her baby carriage.” 15q26.1q26.2 deletion, 21 months  
 “Unsteady walking style and clumsier than other kids. Stumbles and falls easily but getting better with balance issues.” 15q26.2q26.3 deletion, 2½ years

“S didn’t crawl or walk on time. Today he loves to walk around and is constantly on the move, but walks like a child is learning to walk and walks with his legs apart. He is sturdy indoors but outdoors is very wobbly, tends to try to run and ends up falling. S has problems with putting his feet flat to the ground and tends to walk on tiptoes. His Achilles tendons have not developed properly due to late walking and not using the whole foot, so we do daily exercises to help. The inner arches of his feet are collapsing and he is awaiting special needs shoes. S uses a rollator and wheelchair, mainly outdoors. Proper shoes and encouragement at home worked best for getting him mobile.” 15q26.2q25.3 deletion, 4 years

“M has caught up in gross and fine motor skills and today moves normally indoors and out. He is very active and social and has boundless energy. He is really good at kicking soccer balls and hitting baseballs with a bat. For the struggles he had starting out he really has some great athletic skills.” 15q26.3 terminal deletion, 5 years

“M reached all his milestones within normal limits but does have an unsteady walk.” 15q26.1q26.1deletion, 9 years

“Nimble and athletic.” Microdeletion from 15q26.3, 10 years

“While H’s milestones came late as a toddler, her strong determination enabled her to ride a bike before she turned 7 years old (much sooner than her sister who does not have a deletion).” 15q26.2q26.3 deletion, 11 years old

“P has gained strength, maybe due to the growth hormone she takes daily.” 15q26.1 terminal deletion, 12 years

“J is fully able to walk, but tends to walk with his toes clawed and has orthotics for his school shoes. He doesn’t walk in a straight line and has no awareness of those around him; if he is walking next to you, he tends to walk across you. He hates sport and physical education at school.” 15q26.2 terminal deletion, 15 years

"C was delayed but walked independently by the age of 6 and was climbing stairs by 8. She just took her time to become mobile, and now walks well. She can run but with a wide gait and is prone to falling if she runs too fast. Her walking is steady but her running unsteady. She did wear splints to support her ankles as both had quite a pronounced inversion; this improved and she stopped wearing them when she was 13. She now enjoys swimming and playing in the garden." 15q26.1 terminal deletion, 16 years

## ■ Hypermobile joints

Lax or overly flexible ('bendy') joints are common in all young children but even more common in children with a 15q26 deletion. Around half of Unique families reported this, and it was repeatedly observed in the medical literature. Virtually any joints can be affected: hips, knees, hands, feet and elbows were mentioned most often. Joints are usually not so loose that they can actually dislocate, although this can happen (Okubo 2003; Poot 2007; Rujirabanjerd 2007; Rump 2008; Ester 2009; Unique). Others have reported contracted joints (Okubo 2003; Unique); and intermittently swollen joints for which no explanation has yet been found (Unique).

"S's ankles, heels and feet are not developed properly and are currently being investigated." 15q25.3q26.2 deletion, 4½ years

"P tore the anterior cruciate ligament in her knee, which is rare for children of her age." 15q26.1 terminal deletion, 12 years

"J's hands, feet, knees and elbows are lax, but do not dislocate. His excess weight gives problems compounding the laxness of his joints." 15q26.2 terminal deletion, 15 years

## Using their hands: fine motor and co-ordination skills

Extremely varied abilities

Information from Unique shows that children's fine motor abilities are extremely varied. Hand and eye co-ordination skills such as holding and playing with small toys and holding implements such as cutlery and writing implements does not necessarily develop in line with gross motor skills. Some children are dexterous and well coordinated; others find gripping and grasping difficult and unrewarding. Children with weak hands or very flexible joints in their hands find holding objects especially difficult. Early intervention with play and occupational therapy to stimulate hand use is almost always very helpful, and parents recommend keyboards and toys with lights and music for early skills and stringing beads and cards for more advanced development. Individual children have particular problems: one girl found it hard to hold her hands with the palms upwards and preferred to push with her thumbs than her fingers; another held her hands tight shut and need stimulation to open them.

This range of skills impacts on children's ability to feed themselves, to use a spoon and fork, to dress and wash, and later to use an implement such as a pencil for drawing and writing. Children who have mastered play skills well and on time may still need support from occupational therapy for handwriting.

"V has very sensitive hands and has not being willing to use them much. However, she was able to grasp with a pincer grip almost on time. She started pointing to objects and eating with her hands at year and 9 months. She can hold little things if she wants. However, she often still holds her hands clenched and won't grasp anything she thinks to be disgusting. We (parents and physiotherapist) try to stimulate her hands using exfoliating gloves, a baby brush and vibrator." 15q26.1q26.2 deletion, 20 months

"E has poor fine motor skills, and doesn't hold a pencil correctly. At mealtimes she uses her fingers and sometimes a fork and spoon." 15q26.1q26.2 deletion, 4 years

"M has caught up in gross and fine motor skills and doesn't need support any more."

15q26.3 terminal deletion, 5 years

"When coloring as a child, H's hand would hurt because she pressed down too hard on the paper with the crayon. She would sometimes break crayons from holding them too tightly. We put a stack of paper under the coloring page to ease the pressure and encouraged her to loosen her grip and hold the crayon with her fingers. She has a tight grip on her pencil when she writes and her hand grows tired. We have tried many types of pencil grippers, but she does not feel comfortable with any of them." 15q26.2q26.3 deletion, 11 years

"A's fine motor skills have improved somewhat in the past five years; she is better at puzzles." 15q26.1 terminal deletion, 14 years

## Personal care

Daily tasks like getting dressed and undressed, washing and brushing teeth will also be difficult, although using stretchy clothes, Velcro fastenings and slip-on shoes helps.

Children gradually progress with daily repetition, cues, prompts, reminders, laying out clothes, recognised routine and bribery but, as ever, some get very much further than others. Children's ability with personal care directly reflects their fine motor skills and the enjoyment they take in the activity. There is an enormous range of ability, with some children needing little more than gentle reminders, while others are almost totally dependent.

Typically, children use their hands for eating, graduating late to toddler cutlery, and many needing special easy grip implements. Even with these, they may drop food liberally or throw it rather than feed themselves.

"He can dress himself with a little help with his top, zips and buttons, and puts trousers and socks on without help. He goes to the potty by himself but needs help up on to the toilet. He can wash himself in the bath and helps wash his own hair. He brushes his hair and washes his hands with help at the sink." 15q26.2 terminal deletion, 4 years

"S is unable to do anything for himself, but has learned recently to lift his arms up when we are undressing him. If we hold his hairbrush out, he knows it is for brushing his hair and will rub his hair. He loves having baths: having a secure insert in the bath allows you to wash him and use the other hand to prevent him from eating bubbles and trying to bang his head on the side of the bath." 15q26.2q25.3 deletion, 4 years

"M is completely independent but will still ask for help from time to time. He seems to need extra attention and 'babying'. I attribute this to the fact that for so long when he was a baby we didn't know what was 'wrong' with him and he was our first child so we did everything for him and probably created a learned dependency." 15q26.3 terminal deletion, 5 years

"Very independent. Does not always listen to directions, however." Microdeletion in 15q26.3, 10 years

"H had some occupational therapy, but was tying her shoes in kindergarten –due to her outstanding drive and determination. She has been dressing herself and showering independently since about 7 years old. She does not like to pick out her own clothes, possibly because she has so many 'hand-me-down' clothes that she is overwhelmed and cannot put together an outfit. I set up outfits for her in a closet organizer that has 5 slots – one for each school day. Setting up the outfits for the week in the closet is wonderful. She enjoys being organized and loves the independence." 15q26.2q26.3 deletion, 11 years

"Fully independent, but needs constant prompting. Sees no importance in washing and

“C had special cutlery until about 8 years but doesn't need it now. She does need help with all aspects of personal care and lots of encouragement to use the toilet; she wears pads day and night. She can wash and dry her hands with lots of prompts.” 15q26.1 terminal deletion, 16 years

## Toilet training

11/17 children were dry and clean in the day time, and the great majority of them acquired the skill between the ages of 2 and 4 years. Overall, the size and position of the 15q26 deletion did not appear to impact on toilet training, although two teenage girls still wearing pads have large deletions with a break point at 15q26.1. Older children unable to achieve toilet training may still stay clean and dry during the day if they are taken to the toilet regularly (Unique).

## Communication

Children start speaking late

A delay in communication, speech and language is to be expected, but Unique's experience is that with speech therapy children do generally learn to use words and phrases. Overall, the picture is varied, however, and while some use words and short phrases and supplement their communication with signing, eye contact, facial expressions, gestures, vocal noises, pushing, patting and pulling, shouting and crying, others acquire fluent understanding and conversational skills. Among 16 Unique members, 6 children, all aged 5 or less, are still essentially non-verbal or use single words – and some of these may well go on to become fluent talkers; 5 children aged 3 to 16, use phrases; 4 children aged 5 to 15 years have fluent speech; and one has a diagnosis of speech apraxia (a speech disorder in which the person has trouble saying what s/he wants to say correctly and consistently).

Among those communicating at most with single words, social smiles emerged at 2-8 months; babbling (making speech-like sounds) at 3-12 months and first words at 13 months to 4 years. At first, words could be non-specific: dada and mama could be interchangeable. The most common sounds of speech that children had difficulty with were *s*, *f* and *r*, but these can vary. One child had significant difficulty making speech sounds (Bruce 2010). But even those who are non-verbal can be good communicators.

“Despite her medical condition and delayed development, she is interactive, happy, smiles easily and is a pleasure to be around. She makes use of many facial expressions and is clearly able to show her delight in an activity or interaction.” 15q26 deletion, 18 months

“Communication is improving very, very slowly. He is starting to babble, but not like 'ordinary' babbling, more sounds now. He understands words like yoghurt, icepop, milk, sleep that we use constantly: repetition does work. Some days he understands everything I say, looks me straight in the face (not common as he avoids eye contact) and has an understanding look on his face. Other days he has no understanding at all. He has learned quite a bit through speech therapy. Using children's microphones (echo types) encouraged him to use sounds and he likes to hear his own voice. Using one word rather than sentences works better for understanding.” 15q25.3q26.2 deletion, 4 years

Among those communicating in phrases, speech therapy, signing, picture exchange systems, communication boards and dyspraxia cards were helpful communication aids. Understanding was generally ahead of expression, but children typically had difficulty

understanding abstract or complex speech. Two older teenagers communicating in phrases have large terminal deletions from 15q26.1; younger children have smaller deletions.

"F uses words, pushing/ pulling and 2-3 word phrases. He has just started speech therapy." 15q26.3 terminal deletion, 3 years

"C doesn't understand a lot that is said unless it is clear, plus simple requests such as 'C bedtime' or 'C toilet'. She can ask for food, drink, play, outside, parents, family, friends, space. She has some phrases eg: Gran and grandad's house; Don't want tea; Cottage pie; Dinner time; Ride in car. She mainly just takes her time to learn to talk and communicate." 15q26.1 terminal deletion, 16 years

Among those communicating with fluent conversation, babble emerged between 4-12 months and first words at 16-22 months. There is no apparent link between fluency and the size or position of the deletion: children with terminal deletions from 15q26.1, 15q26.2 and 15q26.3 all have fluent speech.

"H uses full speech and while retelling a story can be difficult for her, putting the words together is becoming easier as she gets older and her language skills improve. She speaks VERY loudly and did some screaming as a toddler before she had speech. We learned to ignore the screaming and would only answer 'call me with a soft voice and I will answer'. She eventually stopped. Her speech is now clear and she no longer uses sign language." 15q26.2q26.3 deletion, 11 years

"J's conversation which has always been well in advance of his age, as is the content. His verbal communication is excellent, although clarity still leaves some to be desired." 15q26.2 terminal deletion, 15 years

One child with a terminal deletion from 15q26.3 babbled on time but struggled with words and was diagnosed with speech apraxia.

"He can usually get people to understand him, but if he can tell they don't know what he's saying after repeating it he will act it out if he can. Otherwise he says 'Never mind'. He can have conversations but at times we're not sure what he's saying. He fully understands everything but has a hard time expressing it. He sees a speech therapist twice and we got an iPad from an Apraxia group with some helpful apps." 15q26.3 terminal deletion, 5 years

## Learning

Children need support

Children with a 15q26 deletion are very likely to need some support with their learning, although the extent varies widely. Evidence from the medical literature and from 15 Unique families shows a scattered pattern, with great variation in the skills achieved. Out of three teenagers, one is expected to do as well as the top 60% in national school tests at 16, while two others are not reading. Five Unique children were considered to be learning at a level appropriate to their age or to have a mild disability, in 3 it was moderate; in 3 severe; and in 5 children as yet unspecified. The only Unique child with a formal learning score had the most significant learning disability: he performed less well than a child with Down syndrome. Many children have a scattered range of skills, with some significant strengths, such as understanding how things work; reading; art; science; subjects with a practical application. While there is a tendency for children with larger deletions including 15q26.1 to need more learning support, and for children with smaller deletions from 15q26.3 to have fewer difficulties, it is not possible to predict the

level of difficulty from the diagnosis or the karyotype. Among Unique families, around half the children attend a mainstream/ regular school, and half attend a special school; some children switch between the systems; all children in mainstream schools have some level of learning support, ranging from extra time and special provision for public examinations, through inclusion classrooms to full 1: 1 support. Many families stress how well their child learns 1: 1; or when learning through something they are passionate about; and having high, but realistic expectations. Families stress their child's determination as a factor in learning success, and many families say their child has a good memory. Concentration is a problem for many children (Okubo 2003; Ester 2009; Dateki 2011; Poot 2013; Unique).

"He reads a lot of board books and can draw a spiral." 2½ years

"F loves books and can draw circles and a spider." 3 years

"S can return to something and remember how to do it, eg turning on things, knowing where the on/off switch is. Repetition, as simple as it sounds, does work." 4 years

"E is very good at puzzles. She likes to be busy, but concentration is poor." 4 years

"A lot of things are a struggle for M, but he's probably learning at just a year behind. He can sound out words but not read; write his name and draw 'rough' animals and figures. He attends a traditional private school with therapists who pull him out of class or meet him afterwards. M can do great things and has huge potential. If he can't do it, we back off, but we've never had anything he couldn't do." 5 years

"C can almost write his name." 6 years

"M has an excellent photographic memory. He reads well but does not immediately understand what they are reading." 9 years

"He has a mild auditory processing disorder and was in a competitive private school for kindergarten and 1st grade but transferred in the 2nd grade to a school specialising in learning disabilities where he is thriving. We anticipate that he should be able to access mainstream when older." 10 years

"H works very hard and sometimes surprises us. Math and reading are biggest struggles. She often does well on science, social studies and vocabulary tests. Often I try to relate the study material to something she is very familiar with. They are doing pre-algebra in math now and she managed to get a 62.5 on her test, which made me very proud. Last week she came back with a 94 on a science test about the earth, volcanoes and earthquakes. She studied for about 5 nights. Most of the test involved writing, which is why we needed so much time to prepare. Writing is also a big struggle. She has more drive than many children to succeed. She wants to do well for herself more than to please others. She recently won an art contest at school, and was selected to receive an award. She has an Individualized Education Plan which gives her preferential seating, tests read to her, inclusion setting classroom, simplified assignments, extra time on tests." 11 years

"P has excelled in reading. She has a maths tutor." 12 years

"A knows that M is for Mommy and understands initial letter sounds." 14 years

"J has maintained his position in mainstream schooling and is expected to gain A/B for science subjects at GCSE (public exam in UK at age 16) and C/D for maths/ English. He is far better at learning subjects where the emphasis is on hands-on such as catering, design technology and science where he can relate what he is learning to everyday things. He still struggles with the volume of work and concentration can be poor. J has exam support: laptop in use, writing slope, extended time for rest periods and a scribe if necessary." 15 years

"C can draw simple circles and enjoys practical work." 16 years

## Behaviour

Children are generally friendly but difficulty concentrating is common

When Unique asked families how their child behaved on a normal day, they said they were generally happy and friendly. Typical comments are: 'The happiest and most smiling child I have ever seen; very eager to make contact with other children; very interested in her environment' (20 months); 'happy and chatty, a very keen babbler and very interactive - an absolute treasure of a girl, a happy little sister with amazing stamina' (20 months); 'playful, social and friendly' (2½ years); 'can be helpful when asked' (3 years); 'mostly very good' (4 years); 'extremely happy; wakes with a smile' (4 years); 'very loving and kind' (5 years); 'very happy and sociable' (6 years); 'very patient and calm' (12 years); 'content for the most part' (14 years); 'excellent social skills, exuberant, mischievous, polite & well-behaved with both young and adult' (15 years). Children may lack social boundaries and risk being too friendly, so they invade other children's space, or have no stranger awareness. They may seek physical contact or be somewhat immature and have difficulty maintaining friendships; some children prefer adult company. They may have difficulty reading social cues and maintaining age appropriate conversations.

"J is a happy boy who can be moody, argumentative and sometimes a little aggressive but out of the house and in school this is a side they barely see. He doesn't understand the difference between bullying and teasing and can get very wound up very quickly. He does tell jokes, though they are not always very funny, and he really doesn't understand social etiquette or the niceties of social interaction, so when we are going somewhere I like to check that he understands what will be acceptable behaviour and how others might behave.

He is outspoken, always believes his opinion is right and will turn the conversation to suit the outcome he wants; regularly interrupts. He will inflict his desire to talk, whether appropriate or not. J does get on well with his siblings, although he can be very loud and instead of asking politely will bellow at them. He doesn't do this in school." 15 years

"Very outgoing and well-liked by her peers and the teachers adore her bright and positive personality. She makes people smile everywhere she goes. She truly shines, and has a contagious laugh. Her big sister wonders why she is 'so popular' at school." 11 years

"He does quite well socially, although he is aware that he doesn't communicate the same as the others and will often become shy in a new setting. He also struggles with sensory issues and if the setting is quite loud or has flashing lights he will draw back." 5 years

The most common problem, mentioned by 10/17 families is difficulty concentrating. Four children have a diagnosis of ADHD (attention deficit hyperactivity disorder) and 4 others are considered overactive or hyperactive. Two children take medication to help them concentrate at school, with positive results. Temper outbursts affect around half, and around one in 3 has an unusual fixation, such as refusing food unless it is on a certain plate; tipping things; fixing on buttons, doors or latches or particular toys.

Among other problems that families mentioned were being stubborn ('Can cry without stopping to get his own way' - 3 years; 'absolutely relentless: if she has something on her mind she will not quit asking until she either gets it or gets a very firm answer' - 11 years; 'very single minded' - 15 years); whining and complaining (3 years; 5 years; 7 years); self injury: one child wears a protective helmet, and is now trialling a weighted jacket (4 years; also 16 years); attention seeking (9 years); unable to complete an activity (14 years); occasional aggression (4 years; 15 years; 16 years).

Five children have a diagnosis of an autism spectrum disorder, including one teenager

with Asperger syndrome, and repetitive behaviour is common: 'He likes to say the same things when saying good-bye, and at night goes through the same routine. If interrupted, he will start again.' In one child the features of autism became obvious after the age of 8. Overall, there are marked behaviour differences between individual children and one teenage girl has significant behaviour problems and needs clear boundaries and routines and calm handling as well as professional management. (Pinson 2005; Poot 2007; Ester 2009; Dhamija 2011; Capelli 2012; Poot 2013; Decipher; Unique)

## Other issues

### ■ Sleep

Most Unique families say that their child has no sleep problems. Three children aged 3-6 years wake frequently at night, and in one child the problem is significant and has not resolved with melatonin.

### ■ Eyesight

The most common eye problem, seen in 15 children, was a squint (strabismus). This may affect one eye or both and the direction may be inward or outward. Severity also varies, with the condition resolving naturally in some babies, requiring monitoring and surgical correction in others. Four children reported in the medical literature and two Unique children were shortsighted; it has been suggested that the *IGF1R* gene may be involved in the development of the eye and lens (Rump 2008; Walenkamp 2008; Veenma 2010; Choi 2011; Capelli 2012; Unique). Among other vision disorders seen are long sight in two children; lazy eye; and astigmatism (an abnormal curve of the cornea (the clear cover over the iris and pupil)) in two children (Li 2008; Unique).

"S has been diagnosed with being far sighted and will need glasses but they can't carry out the test as they need him to be able to communicate. He has had drops put into the eyes but the other part of the test involves him to point out pictures and he doesn't understand this. He also has blocked tear ducts: his eyes get red, swollen, sticky, hard crusted and close when he gets a cold or is run down. He is awaiting surgery to have tubes inserted into the tear ducts." 15q25.3q26.2 deletion, 4 years

"H's strabismus was corrected at 6 years. She sees the ophthalmologist annually to check on any reverse of the surgery." 15q26.2q26.3 deletion, 11 years

### ■ Hearing

Young children are vulnerable to the fluctuating, temporary hearing loss caused by a build-up of fluid within the middle ear behind the ear drum. This was found in seven young children with a 15q26 deletion and successfully treated by inserting aeration tubes into the eardrums (Ester 2009; Veenma 2010; Unique). One child, with a 15q26.2-q26.3 deletion, was found to have anomalies of the inner ear with hearing loss (Decipher) and two further children had a permanent hearing loss (Rump 2008).

### ■ Teeth

Dental disorders appear to be more common among children with a chromosome disorder than among typically developing children. Unique records show that around half the children have normal dental development and among the others, the most common feature is late teething, with the back teeth emerging before the front teeth (Ester 2009; Unique). Other unusual features include missing teeth, extra teeth, crowded teeth, short, spaced teeth, baby teeth late to fall out, crooked teeth and discoloration due to high calorie formula (Dhamija 2011; Capelli 2012; Unique).

## ■ Epilepsy

Five people in the medical literature and five Unique members have had seizures (fits). Three further patients on the Decipher database have had seizures. Apart from two of the Decipher patients, who have deletions from 15q26.3, everyone has a deletion from 15q26.1 or 15q26.2. Brain scans have generally been normal or shown non-specific findings, although in one child the corpus callosum linking the two hemispheres was thinner than normal, and the subarachnoid space around the brain was enlarged; in another child there were cysts at birth which resolved by 3 years (Pinson 2005; Unique). The seizures are of varying types, and Unique's experience has been that seizures are generally well controlled with anti-epileptic medication; one child had an idiosyncratic response to medication; another child had a single fever fit and has not been treated. In two children, however, the epilepsy was hard-to-treat, in one case with eyelid jerking and absence seizures; in another child the seizures were only partly controlled. Another child only had two febrile seizures. One child outgrew their epilepsy and was treatment-free by 30 months (Pinson 2005; Li 2008; Veredice 2009; Dhamija 2011; Capelli 2012; Unique).

It has been suggested that the *RGMA* gene in the 15q26.1 band may underlie seizures in some people with a 15q26 deletion, and that a further gene, *ST8SIA2*, situated at 92,937,058 – 93,015,640 in 15q26.1, may also be involved (*see* Genes, pages 24–25). But there is clearly more to be discovered, since other Unique members and people on Decipher have lost one or both of these genes, but not experienced epilepsy, while others have lost neither gene but still had epilepsy (Dhamija 2011; Capelli 2012; Decipher; Unique).

## ■ Diamond-Blackfan anaemia

Diamond-Blackfan anaemia (DBA) is a rare blood disorder in which the bone marrow fails to make red blood cells. One type is caused by a mutation (change) or deletion of the *RPS17* gene in 15q25.2 (OMIM 612527; Wat 2010). One Unique member with a well-characterised 15q26.1q26.2 deletion developed DBA.

“This has affected our lives most during these two years, and we still have follow ups every now and then. DBA was first treated with red blood cell transfusions (from 2 to 6 months), after that high-dose cortisone (prednisolone) treatment was given (from 6 months to 1 year 1½ months).”

## General wellbeing and outlook

There are very great differences in health and wellbeing between individual children with apparently similar deletions from 15q26. Clinical differences explain much of the difference: babies born with serious heart, lung, kidney or diaphragm problems in general have a harder time than those born reasonably healthy. But even children with severe health problems in babyhood and early childhood can go on to be robust and healthy later. Sadly, this is not possible for all, and three of Unique's 24 members with a 15q26 deletion have died; one at 10 months; one at 17 months with heart and lung problems; and one with complex heart problems at 20 months.

Out of 15 further children for whom we have detailed information, 14 were reported to be now quite or very healthy and rarely ill, although many of these had repeated respiratory tract and/or urinary infections when younger and were more ill than typically developing children when they caught an infection. A girl of 20 months has Diamond-Blackfan anaemia (see above); a boy of 2 was hospitalized with an illness, still undiagnosed,

causing swollen joints, fever and a severe rash; a boy of 9 with a small deletion from 15q26.1 has been diagnosed as hypothyroid and takes replacement thyroid hormone; a boy of 15 who is overweight has insulin resistance which is treated with metformin (Unique); a girl of 10 has had repeated episodes of low blood sugar (Okubo 2003).

“E is overall a healthy and active little girl.” 15q26.1q26.2 deletion, 4 years

“Overall, M is very healthy. If he gets a cold or a cough he is more likely to develop pneumonia or bronchitis, but otherwise he is healthy.” 15q26.3 terminal deletion, 5 years

“C is healthy but seems to catch every virus going around school and seems to get the virus worse than others.” 15q26.2 terminal deletion, 6 years

“A had pneumonia four times by age 3. She was very fragile in her first 3 years with lots of respiratory illness and urinary tract infections but since then has only had colds and childhood stomach viruses. She is now rarely sick eg with a cold but this is not a problem any more.” 15q26.1 terminal deletion, 14 years

## Puberty



11 years old

Both the medical literature and Unique records suggest that puberty usually proceeds normally in girls. In one boy it was slightly late but otherwise normal (Walenkamp 2008; Dateki 2011; Poot 2013; Unique).

## Why did the 15q26 deletion occur? Did my baby get it from me?

15q26 deletions usually occur out of the blue for no obvious reason. Less often, they can be caused by a change in either the mother's or the father's chromosomes. The only way to be certain is to check the chromosomes of both parents. If both parents have chromosomes without any relevant changes, the 15q26 deletion is a new occurrence. The genetic term for this is *de novo* (dn). A new 15q26 deletion has been caused by a mistake either when the parents' sperm or egg cells were formed or in the very earliest days after fertilisation. As a parent there is nothing you could have done to change or control this. In a few families, one parent has a structural rearrangement of their own chromosomes. This is usually balanced so that all the genes and chromosome material are present and the parent is entirely healthy. However, these families have an increased risk of having another affected child. Whether the deletion is inherited or *de novo*, there is nothing you did as a parent to cause the 15q26 deletion. No environmental, dietary, workplace or lifestyle factors are known to cause these chromosome changes.

## Can it happen again?

In families where both parents have been tested and have chromosomes without relevant changes, the risk of having another child with a 15q26 deletion is minimally higher than anyone else's risk.

If a blood test shows that either parent has a balanced chromosome rearrangement involving 15q26, the possibility of having other affected pregnancies rises considerably. Someone who themselves has a deletion of 15q26 has a possibility of passing it on of

about 50 per cent in each pregnancy and a 50 per cent chance of a pregnancy with normal chromosome 15s. Your genetics centre should be able to offer counselling before you have another pregnancy and if you already have a child with the 15q26 deletion, prenatal diagnosis will be possible if that is what you choose.



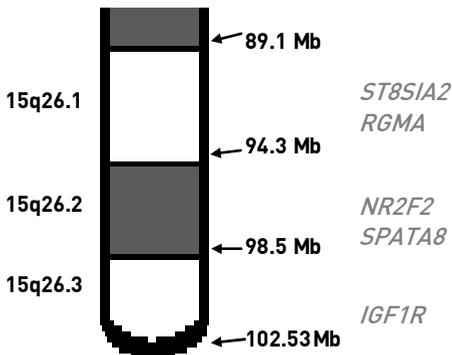
Girl with 15q26.1 deletion, 11, feeding baby brother

## Can my child have children of their own?

It isn't yet known whether the condition affects fertility, but most girls with 15q26 deletions generally seem to go into puberty at the expected age and have periods normally which suggests they are likely to be fertile. Anyone with a 15q26 deletion has around a 1:2 (50 per cent) chance in each pregnancy of passing it on.

## Genes

We don't know yet what most of the genes in the 15q26 region do, but the role of some is becoming increasingly clear.



*IGF1R*, the insulin-like growth factor 1 receptor gene, is situated within the 15q26.3 band at 99,192,760-99,507,758 (see diagram, above). This important gene is vital to proper growth, so when it is disrupted, deleted or displaced, people are typically, although not always, unusually short (Ester 2009; Choi 2011; Rudaks 2011). We don't yet know the full role of *IGF1R* and different research teams have suggested other roles, such as that it contributes to unusual facial and skeletal features, and mild early developmental delay (Veenma 2010; Dateki 2011); to the development of the eye and lens (Walenkamp 2008; Veenma 2010); to brain development and carbohydrate metabolism (Rudaks 2011); and to hearing (Ester 2009). There is uncertainty whether it plays a role in heart development (Dateki 2011). One research group has suggested that *IGF1R* may act with *FBN1*, a gene outside the 15q26 region in 15q21, to produce joint hypermobility and growth failure (Ester 2009). Apart from being short and having some speech delay, some people who have lost the *IGF1R* gene have developed normally (Walenkamp 2008; Rudaks 2011).

The 15q26 region contains a cluster of genes expressed in the developing diaphragm. *NR2F2*, a gene also called *Coup-TFII* and situated in the 15q26.2 band at 96,869,167 – 96,883,492, is believed to be essential for normal diaphragm development (Slavotinek

2005; Klaassens 2007; Clugston 2008; Poot 2013). However, losing the *NR2F2* gene does not always cause abnormal diaphragm development, so other factors must be involved.

*NR2F2* is also known to be involved in heart development and its absence may cause the heart defects reported in 15q26 deletions. However, losing it doesn't give rise to a specific heart defect and complex heart problems may be caused by absence of one gene unmasking changes in the remaining *NR2F2* gene on the other chromosome 15. Other genes may be involved in heart problems as well (Slavotinek 2005; Poot 2007; Dateki 2011; Rudaks 2011; Poot 2013).

Two genes in the 15q26.1 band have been suggested as 'candidate genes' for epilepsy. *RGMA*, situated at 93,586,636 – 93,632,433, plays an important role in the development of the nervous system and because of this role, *RGMA* may be a candidate for both learning disabilities and seizures (Li 2008; Capelli 2012).

*ST8SIA2*, situated at 92,937,058 – 93,015,640 in 15q26.1, may also be involved in epilepsy, although some individuals with epilepsy have not lost this gene, so clearly more remains to be discovered (Dhamija 2011; Capelli 2012).

Currently little is known about the function of the *SPATA8* gene, situated in 15q26.2 at 97,326,619-97,328,845, but it has been suggested that it may have a role in determining how severely people are affected by deletions of 15q (Rudaks 2011).

While identifying the gene(s) responsible for certain features of a 15q26 deletion is valuable and may help guide future studies, it does not lead directly to immediate improved treatment. Also, 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.

## What is special about your child?

Very sweet and compassionate. She has taught our family patience – she gets so excited when she accomplishes a task.

The most enthusiastic child I have ever met: she has such drive and determination that I know she will be successful in whatever she chooses to do. Genuinely concerned for others. Does not judge people for what makes them different.

Such a sweet boy. He is very loving, loves to tell you that he loves you and gives out hugs to family, friends and teachers.

One of the sweetest children you could meet.

A very loving little girl.

A happy, interesting child – my friend.



Boy, 8 years, with interstitial deletion from 15q26.1

## We wish we'd known ...

That there are people out there to help, talk to and listen. Our geneticist had almost nothing for us to read or anyone to get in touch with.

That doctors don't know everything!

That paediatric occupational therapy would be the best thing for her development. I wish she had had it earlier.

I wish I had not been so hard on myself, I wasn't to blame. I should not have kept comparing him to other children his age. While we all worry about our children, a lot of the time that could have been spent enjoying him, I was worrying myself sick.

That it is not so negative as doctors led us to understand. They drew a very difficult future for us. We know now that we need to live with uncertainty but at some level you can get over that and accept it. We also would have liked some guidance from hospital staff towards peer support such as Unique.

I wish people had listened to us when she was a baby and she had had help earlier.



Boy, 3 years, with 15q26.1 deletion

## What do children enjoy?

Flowers, leaves and baby DVDs. 17 months

Things that make a noise, banging things together and scrunching and tearing paper. Bathtime and playing with older sister and moving arms around and clapping hands. 18 months

Playing her 'instruments' (drums, xylophone, piano) and read (look at) her books. She is usually doing something: if she is on the floor and looking at a book she also moves her feet etc. When excited, she begins to move her head back and forth on the floor. She follows a vacuum cleaner when we clean the house. She likes to dance when she is on the lap of her grandma or grandpa. 20 months

Books; Pink Panther DVD; painting; Lego; parks. 3 years

Playing, reading, drawing, music and loves cooking and watching cooking shows. Enjoys the iPad to watch shows and play apps too. 4 years

Anything that has lights, plays music and has buttons. The music channels on TV. 4 years  
Music and watching DVDs. 4 years

Playing outside! He loves bugs and animals and water and in the summer is quite happy to dig in the sandbox, find bugs, play with the water table or go to the beach. Inside he usually plays with his toys and has different little scenarios going on with them. He has a great imagination. He also really loves the iPad, but we try to limit that. 5 years

Computers Music TV Anything real Electronics iPod, etc. 6 years

TV, videos, computers, music, playing with other people, puzzles. 9 years

TV, video games, pets, sports, playing sports with others. 10 years

What all kids love – the ipod and computer. Music. Basketball and helping her father work outside. 11 years

Swimming class and playing games on the computer. 12 years

Puzzles, computer games, music. 14 years

Computer, internet, and watching the same TV programme repeatedly. 15 years

Swimming; brightly coloured toys; taking things apart. 16 years



Girl, 10 years old, with 15q26.2 interstitial deletion



naughty

happy

sleeping

cute



handsome

crying

irritated

kissing



silly

"yeah"

surprised

smart



"what"

playful

tasty

smiley



Boy, 2 years, with 15q26.2 interstitial deletion

## Support and Information



### **Rare Chromosome Disorder Support Group,**

G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

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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 Professor Anne Slavotinek, Professor of Clinical Pediatrics, University of California, USA; by Professor Christopher Barnett, Head of Paediatric and Reproductive Genetics, South Australia Clinical Genetics Service; and by Dr Martin Poot, Department of Medical Genetics, University Medical Center Utrecht, The Netherlands.

2013 Version 1 (PM)

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