

## Support and Information



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Understanding Chromosome & Gene Disorders

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Understanding Chromosome & Gene Disorders

This guide was made possible by contributions from: Fonds NutsOhra, Erfocentrum, VGnetwerken and VKGN in the Netherlands.



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Version 1 2016 hg19. (LvD-PM)

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# 9q deletions including 9q33



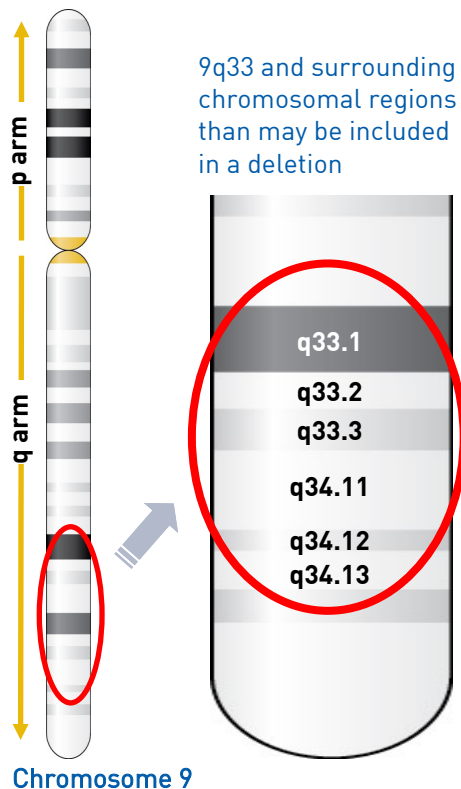
## 9q deletions including 9q33

A 9q interstitial deletion including 9q33 is a rare genetic condition caused by a missing part of one of the body's 46 chromosomes – chromosome 9. An **interstitial** deletion means that the chromosome has broken in two places and the broken ends have fused, leaving out the deleted segment. The size of the missing piece varies between different individuals.

For typical development, chromosomes should contain the expected amount of genetic material (DNA). Like many other chromosome disorders, having a missing piece of chromosome 9 may affect a child's health, development and intellectual abilities. The symptoms observed in people with a 9q deletion including 9q33 are variable and depend on a number of factors including what and how much of the chromosome is missing.

### What are chromosomes?

Chromosomes are made up mostly of DNA and are the structures in each of the body's cells that carry the genetic information (in the form of genes) that tells the body how to develop, grow and function. Chromosomes usually come in pairs, with one chromosome from each pair coming from the father and one from the mother.



Of the 46 chromosomes, two are a pair of sex chromosomes, XX (two X chromosomes) in females and XY (one X and one Y chromosome) in males. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 from largest to smallest.

Chromosomes have a short arm, named p (shown at the top in the figure left), and a long arm, named q (shown at the bottom in the figure). The two arms of a chromosome meet at a point called the centromere.

### Looking at chromosome 9q

You can't see chromosomes with the naked eye, but if you stain them and magnify them many hundreds of times under a microscope, you can see that each one has a distinctive pattern of light and dark bands.

There are three bands on chromosome 9q33: q33.1, q33.2 and q33.3. Looking at chromosomes under a microscope, it may be possible to see the genetic material that is missing if the piece is

the same deletion as the child or a chromosomal rearrangement that involves the long arm of chromosome 9. Each family situation is different and a clinical geneticist can give you specific advice on the chance of recurrence in your family and options for prenatal diagnosis and preimplantation genetic diagnosis. PGD requires the use of in vitro fertilisation and embryo biopsy, and 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.

### Results of the chromosome test

In an interstitial deletion 9q including 9q33, the result is likely to read something like the following example:

**arr [hg19] 9q33.3 (128,952,700-129,613,085)x1**

#### arr

The test was performed using the array technique: array CGH or SNP array.

#### hg 19

Human Genome build 19. This is the number of the DNA sequence as it was known at the time of the testing and was used to compare your child's DNA to. This build is subject to change as we learn more about the human genome. Scientists will then use a new DNA build to compare your child's DNA to.

#### 9q33.3

Chromosome 9 is involved and the band is band q33.3 on the long arm (q).

**(128,952,700-129,613,085)x1**

Our DNA consists of base pairs. All base pairs of a chromosome are numbered from the tip of the chromosome (top of the p-arm) to the end. In this example, the DNA between base pairs 128,952,700 and 29,613,085 is present once (**x1**) instead of twice. This is the deletion. If you subtract the smaller number from the larger number the result is 660,385 (approximately 0.66 million base pairs or 0.66 Mb). In conclusion this concerns a deletion 9q33.3, located between 128.95 and 129.61 Mb on chromosome 9 which is 0,66 Mb.

### Further research involving 9q

The features of a 9q interstitial deletion including 9q33 are likely to be the result of the missing genetic material and missing genes located on this part of the chromosome. It is important, therefore, to have the exact location and length of the missing material determined. When researchers compare the features in different individuals with the deletion, genes can be identified that contribute to the different features of 9q deletions.

As a result of earlier research, researchers have established that the NR5A1 gene between base pairs 127,243,516-127,269,709 in 9q33.3 is likely to be involved in the genital abnormalities. The LMX1B gene, located between 129,376,722-129,463,311 in 9q33.3, is associated with the nail patella syndrome and the STXBP1 gene is potentially involved in epilepsy and developmental delay. There are strong indications to suspect that a deletion of the ENG gene at 130,577,291-130,617,035 can cause ROW (Nambot 2015).

## If one person in a family with the 9q interstitial deletion including 9q33 is mildly affected, will others in the same family also be mildly affected?

It is difficult to answer this question as there are only a few families in which multiple family members have the deletion (Harrison 2013; Jiang 2014; Ehret 2015; Serati 2015). Four parents passed the deletion on to their children. The following information on these parents is known: one mother had mild intellectual disabilities and difficulties in speech and language development. Her daughter had severe developmental delay, epilepsy and several distinguishing facial features (Ehret 2015). Another mother had a son with mildly unusual facial features and hypertonía. She developed obsessive compulsive behaviour after his birth (Serati 2015). Another mother had a child with ambiguous genitalia. She went into premature menopause (Harrison 2013). A father and son share features of the nail-patella syndrome, but these are less clear in the father (Jiang 2014).

## How did the 9q interstitial deletion occur?

When children are conceived the genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. The term doctors use for this is *de novo*. This happens naturally and is not due to your lifestyle or anything you did to cause a change. Most parents of children with a 9q interstitial deletion including 9q33 are not found to carry the deletion.

Four children are described in the medical literature who inherited the deletion from one of their parents. In addition, one family is described in which the mother was found to carry a change involving chromosome 9q. The part of chromosome 9q that was deleted in her child was located on another chromosome in the mother (an insertion; Chien 2010). It is therefore important that both parents of a child with the deletion have their own chromosomes tested.

In either situation there is nothing you could have done to stop this. No one is to blame and nobody is at fault.

## Can it happen again?

The chance of having another child affected by a rare chromosome disorder depends on the genetic code of the parent. If the chromosomes in both parents are normal, the chance of having another child affected is very low.

Nonetheless, there is a small chance that part of the egg cells of the mother or part of the sperm cells of the father carry the deletion. You may hear doctors refer to this as '[germline mosaicism](#)'. It means that a blood test that shows the parents do not carry the deletion does not rule out a very small possibility of having another affected child. This has not been described in the medical literature in children with a deletion 9q including 9q33.

The chance of recurrence is much higher if one of the parents is found to carry

large enough. However, rare chromosome disorders can be caused by subtle changes that are too small to see using a microscope.

Molecular DNA technology gives a more precise understanding of the size and position of the deletion. Your geneticist will be able to tell you about the position where the deleted material can be found on the chromosome 9 of your child. More information on molecular DNA technology can be found on page 19.

## 9q deletions including 9q33

This deletion was first described in the medical literature in 1978 (Turleau 1978). As of 2015, 40 people with a 9q deletion including 9q33 have been reported (see [Sources & references](#) below). In an important subset of these people both band q33.3 and band q34.1 are deleted.

This does not mean that there are no other children with a deletion of 9q including 9q33. There are other children registered in international databases, but often with more limited information. There are also children with a deletion of 9q including 9q33 who have never been included in medical articles. At Unique when this guide was compiled there were 20 members with a 9q deletion that included part or all of 9q33.



## Sources & references

The information in this guide is drawn from the published medical literature. With the first-named author and publication date you can look for abstracts or original articles on the internet in PubMed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)). When this guide was written the full text of the articles was used as far as possible, but sometimes only the abstracts were available. As of 2015, 40 people with a 9q deletion including 9q33 have been reported in the medical literature (Turleau 1978; Farrell 1991; Park 1991; Schlaubitz 2007; Sellitto 2008; Kulharya 2008; Saitsu 2008; Tohyama 2008; van Silfhout 2009; Saitsu 2010; Chien 2010; Marini 2010; Mignot 2011; Campbell 2012; Saitsu 2012; Alfonsi 2013; Brandt 2013; Harrison 2013; Barcia 2014; Jiang 2014; Matsumoto 2014; Ehret 2015; Nambot 2015; Nicita 2015; Serati 2015). Quotations from some Dutch parents who have a child with this deletion and filled out a questionnaire are also included in this guide. When Unique formatted this guide, we had 20 members with a 9q deletion that included part or all of 9q33 with no other chromosome change. Eight families commented on this guide. Unique contributions are in grey boxes marked with the Unique logo.

## Main features in children with a 9q deletion including 9q33

The features mentioned in this guide have been described in the medical literature in children with a 9q interstitial deletion including 9q33. It is not known if all the features are actually caused by the deletion or if they are coincidental. Some of the features can also occur in children without the deletion.

Because only relatively few people with the deletion have been described, not all the effects of the deletion are known. The features can vary between children, but one or more of the following features can be present:

- Developmental delay and/or intellectual disability - pages 9-13
- Epilepsy - pages 13-14
- Ambiguous genitalia - pages 15-16
- Features of nail patella syndrome (NPS); a disorder in which abnormalities of the nails and the knee cap occur - page 9

For some of these features, specific genes within the deletion are thought to be causative. It is therefore important to know exactly which genes are included in the deletion (see also [Further research involving 9q](#), page 19).

## How common are 9q deletions including 9q33?

It is not known exactly how common the deletion is. As previously stated 40 people have been reported in the medical literature.

## Outlook

People with the deletion without major physical or health problems are likely to have a normal life expectancy. Four adults with the deletion have been described in the medical literature. One child has been reported in the medical literature who passed away 30 hours after birth as a result of severe oedema (fluid accumulation) in the lungs, abdomen and skin (Sellitto 2008).

When this guide was compiled Unique had 5 adult members.

## Pregnancy and birth

Many mothers of a child with a 9q interstitial deletion including 9q33 had a normal, uneventful pregnancy. Delivery was normal and they only discovered their baby was affected after birth.

The diagnosis was made during pregnancy in 2 unborn children and these couples chose to terminate the pregnancy. In one of these cases an ultrasound scan at 10 weeks of pregnancy revealed increased nuchal translucency. Progressive oedema (fluid accumulation) was observed at follow-up (Paoloni 2001). In the other pregnancy, extensive heart abnormalities were observed. The unborn child had female genitalia, but genetic testing revealed a male chromosomal pattern (Alfonsi 2013). Another child (see above) passed away shortly after birth as a result of oedema that was seen on earlier ultrasound examinations (Sellitto 2008).

One child was born after a Caesarean section at 27 weeks and 5 days of

by which blood vessels dilate and constrict. An 11-year-old boy had telangiectasias ('broken blood vessels', spider veins) on his cheeks (Nambot 2015). A 3-year-old girl had a dilatation of a blood vessel in the lungs (Campbell 2012). It is important for children with a 9q deletion which includes the ENG gene to receive check-ups for signs of ROW. Sometimes specific medications are prescribed for people with ROW before surgery.

One/8 children with a 9q34.1 deletion has broken blood vessels on her face and hands: they are not an issue for her. No families have reported frequent nose bleeds. Two children with a 9q33 deletion bruise easily.



## Other

These are some of the other features that have been described in people with a 9q deletion including 9q33. Three have asthma (Harrison 2013; Nambot 2015). A six-year-old boy had frequent (airway) infections (Campbell 2012). An eleven-year-old boy has dilatations of his airways (Nambot 2015). Three children had an umbilical hernia (Schlaubitz 2007; Matsumoto 2014; Nicita 2015). One of these children also had an inguinal hernia. One woman had a diaphragmatic hernia, where there is a gap in the sheet of muscle between the abdomen and the chest. She also had a slightly enlarged liver and diverticulosis (pouches) of the bowel. She was overweight, had type 2 diabetes and sleep apnoea (Harrison 2013).

A ten-year-old girl had hyperlaxity of her joints (Mignot 2011). Finally, one girl is described with an abnormal fat distribution and hypothyroidism (Kulharya 2008).

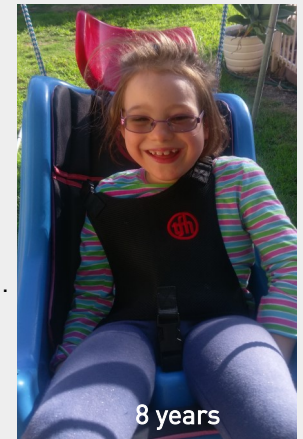
Other features observed at Unique include:

- Sleep problems (6) including frequent waking (3); difficulty falling asleep (2); very light sleep (1); and very little sleep (1). One child uses melatonin. The oldest child still with sleep problems is 12. A girl of 1 sleeps 'a lot, and like a log'.
- Dental problems (5) including late teething (3); crooked teeth (2); unusually decayed teeth (2); an unusual order of teething - molars before front teeth (1).
- Frequent infections in young children, including ear infections (5).

“ She gets repeated bacterial infections but has such a high pain tolerance it's hard to know when she has one. Her bowels and bladder hold too much which puts pressure on her stomach; she aspirates, causing a lung infection and enteritis, like a whole body infection. It's hard to find the seat of infection and then hard to find an antibiotic to treat her.” - 5 years

- Vascular ring (1). An artery was wrapped round the windpipe (trachea) and foodpipe (oesophagus). After surgery to correct this, the foodpipe 'bounced back', the trachea less so.

- Temperature regulation issues (1): feet and hands always cold.



inherited the deletion from his mother who entered the menopause prematurely. This could possibly be related to the deletion of the NR5A1 gene. The following genital abnormalities have also been described in four boys (Park 1991; Marini 2010; Saitsu 2012; Nambot 2015). An 11-year-old boy had a micropenis, underdeveloped scrotum and testes that were not located in the scrotum. A 19-month-old baby had a small penis. Another boy had an unusually bent penis and cryptorchidism (undescended testicles). Finally, a 28-year-old male had small genitalia. In 3 of these people, the NR5A1 gene was deleted. In a fourth this is not mentioned.

Only one boy at Unique had undescended testicles, and another has a very small penis: neither has lost the 9q33.3 band. No girls are reported to have any genital anomalies or problems at puberty.



#### ■ Skeleton

Aside from the hand and foot abnormalities mentioned on page 8, some children have additional skeletal abnormalities.

Five individuals had a sideways curvature of the spine (Schlaubitz 2007; Kulharya 2008; Marini 2010; Nambot 2015). Three had a sacral dimple or hairy spot located at the lower end of the spine (Kulharya 2008; Nambot 2015). One 5½-year-old girl had decreased bone mineral density. Two other children had a hip deformity known as coxa valga (Nambot 2015). Another boy had skeletal abnormalities that could possibly fit a diagnosis of nail-patella syndrome (Nambot 2015). One girl had delayed bone age, a short fibula (small bone in the lower leg) and a reduced number of ribs (Schlaubitz 2007). In an 18-year-old woman the length of her legs differed (Nambot 2015). In another girl there was fusion of some of the bones in her lower legs and feet (Tohyama 2008; Saitsu 2008, 2010).

Skeletal, spinal and joint anomalies known to Unique are almost all common: hip dysplasia at birth; a 6th vertebra in the lower back; and an out-turning of the leg from the knee down. One child has two missing ribs; in one boy the discs between the vertebrae in the lower back are worn.



#### ■ Blood vessels

One of the genes missing in some individuals with a 9q interstitial deletion including 9q33 is the ENG gene. This gene is found in the 9q34.11 band, between base pairs 130577291 and 130617035. Mutations in this gene can cause Osler-Weber-Rendu syndrome (ROW). In ROW, dilatations of small blood vessels can occur (telangiectasia) as well as nose bleeds. Sometimes dilatations of larger blood vessels occur (arteriovenous malformations). There are strong indications to suspect that a deletion of the ENG gene – which can occur in people with a 9q interstitial deletion including 9q33 that extends to 9q34.11 – can also cause ROW.

Two people in whom the ENG gene was deleted suffered from nose bleeds (Nambot 2015). In one of these children there were abnormalities in the process



pregnancy. This was carried out because there was bleeding between the placenta and the uterus and the baby was not growing well (Ehret 2015). In two other pregnancies there was premature rupture of the membranes (Barcia 2014; Nicita 2015). Both babies were born by Caesarean section, possibly because they had trouble getting enough oxygen in the uterus.

In three other pregnancies amniotic fluid levels were low (Schlaubitz 2007; Kulharya 2008; Nambot 2015). One of these babies had an abnormal heart rate (Nambot 2015). The second baby did not grow properly during pregnancy (Kulharya 2008). In the third pregnancy, the mother had high blood pressure (hypertension) and the baby was in breech position (Schlaubitz 2007).

Another baby also grew slowly during pregnancy (IUGR/ intrauterine growth retardation). The mother had HELLP syndrome, a variant of pre-eclampsia (van Silfhout 2009). The baby had low Apgar scores after birth and breathing difficulties. Yet another mother is described whose baby showed little movement during pregnancy (Kulharya 2008).

Unique has information on 9 pregnancies, most uncomplicated bar one where the baby was quiet and did not move much, another where there was too much amniotic fluid (polyhydramnios), and another where the mother had food poisoning at 12-14 weeks. Four babies were delivered normally, one of them at home. One baby was delivered at 42 weeks by emergency Caesarean section after developing fetal distress. Three babies were induced: one at 37 weeks, one at 38 weeks, and one at 41 weeks. This baby was found on early pregnancy scan to have a cystic hygroma (increased nuchal translucency), but nothing abnormal was found on diagnostic tests and the hygroma regressed.



#### Newborn babies

Mean birth weight in 10 babies born after a pregnancy of at least 37 weeks was 2.667 kg (5lb 14oz) (range from 2.134 kg/4lb 11oz to 3.14 kg/6lb 15oz) (Chien 2010; Saitsu 2012; Matsumoto 2014; Ehret 2015; Nambot 2015; Nicita 2015; Serati 2015). In another child, a twin, born around term, birth weight was 1.82 kg/4lb (Saitsu 2008; Tohyama 2008; Saitsu 2010).

One girl had mild jaundice after birth. She was re-admitted to hospital shortly after birth because of sinusitis (Kulharya 2008). Another baby, a girl, had breathing difficulties after birth. She had meconium stained amniotic fluid. Meconium is the baby's first faeces (Chien 2010).

Birth weights at Unique range from 1.6kg (3lb 9oz) in a baby at 37 weeks to 3.86kg (8lb 8oz) in a full term baby. There is no clear link between deletion size and birth weight: the smallest and largest babies share a very similar large deletion. Aside from feeding, babies were generally well at birth. Two had mild jaundice; some were floppy; and one born with the cord wound three times round her neck did not cry or suck for the first 3 hours.



## Feeding

Some babies and children with a chromosomal abnormality have difficulties sucking and swallowing. These feeding difficulties can partly be caused by low muscle tone (hypotonia). Hypotonia is described in 16 babies, children and adults with a 9q interstitial deletion including 9q33 (Kulharya 2008; Saitsu 2008; Tohyama 2008; Campbell 2012; Barcia 2014; Ehret 2015; Nambot 2015; Nicita 2015; Serati 2015). Some people show both low muscle tone and high muscle tone (hypertonia or spasticity); others show primarily hypertonia (Saitsu 2012; Serati 2015). One boy was tube fed as a result of his developmental delay and hypotonia (Matsumoto 2014).

Hypotonia can also contribute to gastro-oesophageal reflux (GERD/GORD). In GERD contents from the stomach pass back up into the oesophagus (food passage). Reflux has been described in 4 babies and children with a 9q interstitial deletion including 9q33 (Campbell 2012; Harrison 2013; Matsumoto 2014; Nambot 2015). Reflux can usually be controlled by feeding the child slowly, in an upright position and if necessary tilting the bed slightly up at the head end.

Three people had a high and/or narrow palate (Park 1991; Schlaubitz 2007; Kulharya 2008). Three children had a cleft lip and/or palate (Chien 2010; Saitsu 2012; Nicita 2015). This can sometimes cause problems with sucking and swallowing, although it does not necessarily do so. Two children suffered frequently from constipation (Ehret 2015; Nambot 2015). Two children had

pyloric stenosis, in which the passage from the stomach to the intestines is narrowed.

Contents of the stomach cannot pass properly to the intestine and this can cause vomiting (van Silfhout 2009; Serati 2015).

Another child had oesophageal inflammation



“ She fed OK, but was so weak that she couldn’t breastfeed. So we fed her with a syringe. It was a joy to get 10cc into her. Then she’d burp up the second syringe. ”  
Here she is 16.

## Vision

Some children have strabismus (a squint). A 28-year-old man had a drooping eyelid (ptosis) (Park 1991). One boy had an abnormal shape of the iris (Marini 2013). Two children had an astigmatism, an abnormally shaped front of the eye (Nambot 2015). In one of these children the eyes were sunken into their sockets (enophthalmia). A 5-year-old boy had nystagmus, where the eyes move to and fro without control (Matsumoto 2014). A 5½-year-old girl had small eyes, and damage to her retina as a result of her premature birth (Ehret 2015).

Most children have perfect sight, especially those with only a 9q33 deletion. One girl has an astigmatism, a common curve of the eyeball that affects focus; another wears glasses for reading. Four/8 children with a deletion of part of 9q34.1 have a sight problem. One was born with apparent cataracts; another has a deteriorating astigmatism; a third has cortical visual impairment (CVI), where her brain does not process visual information properly. At 5 years she can track well but only sees in big colourful blurs. A fourth child of 8 has a squint (strabismus), short sight and an astigmatism, as well as the involuntary eye movements known as nystagmus. She always wears glasses.



## Hearing

Hearing problems do not appear to be very common in children with a 9q interstitial deletion including 9q33. Two children have been reported with hearing loss in the medical literature (Chien 2010; Nicita 2015). Two other children had recurrent ear infections which required ear tube (grommet) surgery (Ehret 2015).

Six/20 Unique families report hearing loss, most often caused by glue ear, a fluctuating deafness very common in young children. In one child the eardrum remains a problem at 12 years, with bleeding daily. Problems are more common (3/8) in those with a 9q34.1 deletion; in 2 children the ear canals are unusually narrow.

“ Excellent hearing: loves music.” - 5 years



## Genitals and puberty

A number of children have been reported in the medical literature who had abnormalities of their genitalia. Five children had ambiguous genitalia. These children had a male chromosomal pattern, but their external genitalia appeared to be female or unclear (e.g. they had an enlarged clitoris) (Schlaubitz 2007; van Silfhout 2009; Alfonsi 2013; Brandt 2013; Harrison 2013). In two children the nipples were widely spaced and underdeveloped. In two children nipples were absent (Schlaubitz 2007; Alfonsi 2013). Studies have shown that these abnormalities are related to the deletion of the NR5A1 gene in 9q33.3. The NR5A1 gene is important for the development of male genitalia. In females, the NR5A1 gene is important for the development of the ovaries and fallopian tubes. In one of the children mentioned above, the NR5A1 gene was missing. This boy

At Unique, only one/12 children with a deletion only involving 9q33 has had proven seizures but at least 5/8 children with a deletion involving 9q34 have had proven epilepsy. The girl with a 9q33 deletion had absences around 11 which developed into a full seizure. A 24-hour EEG showed nothing significant; after taking medication for 2½ years, she has now been seizure-free for 3 years. Among those with a 9q34.1 deletion, the seizure course varied a lot. One baby had daily clusters of hard-to-treat seizures; another had 2 years of weekly seizures, then 3 seizure-free years. Seizures started in one baby at around 3 months. Her arms and legs would fly out as if startled. By 3 she had Lennox-Gastaut syndrome. Her seizures are hard to control despite many medications, the hormone treatment ACTH, cannabis extracts and the ketogenic diet. Only one child with a 9q33 deletion has had a brain scan showing abnormalities. These include an irregular blood vessel arrangement; and features suggesting possible neurological changes. This child does not have epilepsy. Four/8 children with a 9q34.1 deletion have an unusual head size. Two have a very big head, and one has hydrocephalus (fluid on the brain). In 2 others, the head is small, but not microcephalic. Of these two, one (without epilepsy) had late maturing of the insulating nerve sheaths (myelination). The other (with very severe epilepsy) has a normal brain, albeit with a thin corpus callosum (the band of nerve fibres linking the brain's hemispheres).



#### ■ Heart

Most children with a 9q interstitial deletion including 9q33 have no heart problems. Eight children with heart problems have been described in the medical literature. Two children had a patent ductus arteriosus (PDA) which required surgery (van Silfhout 2009, Ehret 2015). The ductus arteriosus is a channel between the pulmonary artery and the aorta which normally closes after birth. Two children had a hole between the lower pumping chambers of the heart (ventricular septal defect or VSD) (Saitou 2012; Sellitto 2013). Another child had a patent foramen ovale. The foramen ovale is a hole between the two upper chambers of the heart that normally closes after birth (Nicita 2015). Multiple cardiac anomalies were seen on a pregnancy ultrasound in one unborn child. These included a VSD and an abnormal position of the large blood vessels leading to and from the heart (Alfonsi 2013). A boy had an abnormal conduction of the electrical current of his heart and a mild thickening of the right lower chamber of his heart (Marini 2013). Finally, one girl had a prolapse (collapse, allowing blood to flow back) of one of her heart valves (mitral valve prolapse) (Chien 2010).

Five/20 Unique babies were born with a heart problem. Three had a small hole between each side of the heart. Two had a common condition called PDA, an open channel between blood vessels leading from the heart that usually closes naturally just after birth. One child was found at 3½ to have a heart murmur that varies as he breathes.



(Nambot 2015). Finally, another child had ulcerations in the stomach and oesophagus which made her cough up blood periodically (Chien 2010).

Eight/9 Unique families have had difficulty feeding their baby or child. Some babies sucked very weakly at first, or had swallowing difficulties putting them at risk of inhaling part of their feeds. Breastfeeding was not possible, but some babies were fed expressed milk and formula. One baby was initially fed by syringe, and two needed tube feeding. One baby with a misshapen epiglottis was fed via a nasogastric tube up the nose to the stomach. A child with problems coordinating feeding and swallowing had a gastrostomy tube inserted and at 5 years uses the tube for liquids and medications, but eats purées and mashed food by mouth. Seven babies and children have had significant reflux (see above), in one baby so milk flowed out of her nose. Two children of 3½ and 7 years are very fussy eaters, and one has a dairy intolerance, needing hydrolysed formula as a baby. But there is good news: reflux does generally improve, and most children are having a varied diet by early childhood.

Low muscle tone plays a role in feeding difficulties, and is common in all babies with a chromosome anomaly. Only one baby had a cleft palate, hidden behind the lining of the top of the mouth, and one baby had a high palate; neither had particular feeding difficulties.

Constipation is also very common in children with chromosome disorders, and is a significant problem for 5/7 Unique children. One girl dribbles when she needs a bowel movement. One child of 12 is in constant pain unless medicated, and another, diagnosed with a neurogenic (the nerves do not function properly) bladder and bowel, will probably need a colostomy to bypass her non-functioning bowel.

*“ She eats well now and manages food with small lumps. She coughs and splutters occasionally during feeds but is able to clear herself easily by coughing. She loves sucking chocolate thickshakes and smoothies through a straw.” - 8 years*



#### Growth

Thirteen people with a 9q interstitial deletion including 9q33 are known to have growth retardation or short stature (Park 1991; Schlaubitz 2007; Kulharya 2008; Saitou 2008; Tohyama 2008; Chien 2010; Marini 2010; Saitou 2010; Ehret 2015; Nambot 2015; Serati 2015).

Nearly all children at Unique who we know about are short for their age, although only one is so short that she is off the growth charts. One child is the right height and weight for her age: she is 5. Most children had difficulty gaining weight, especially as babies, and a boy of 12 is described as anorexic. Two children were overweight until they stopped or changed their anti-epilepsy medication.

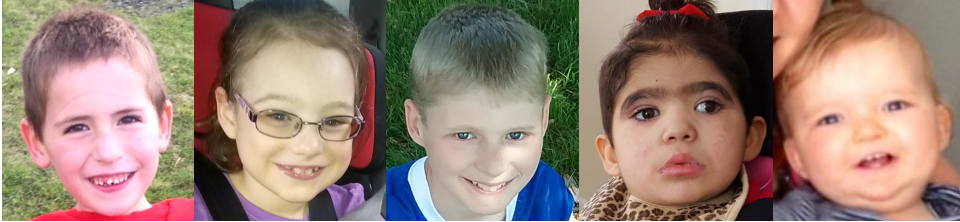
*“ Small but she grew.” - 16 years*



## Appearance

Facial features among children with a 9q interstitial deletion including 9q33 are variable.

A number of facial features have been reported more frequently in children with the deletion. Features reported in more than 5 children in the medical literature are: a small head circumference, strabismus (a squint), low set and/or abnormally shaped ears, thin lips, a broad or bulbous nose (however, 4 children had a small or short nose) and a round face.



## Hands and feet

Some people with the deletion have somewhat unusually shaped hands and feet. Three had slightly tapering fingers. One child had long, thin fingers. In one child, fingers overlapped (Park 1991; Chien 2010; Saitsu 2012; Ehret 2015). A man had short metacarpal bones (in the hand) (Park 1991). One boy had a single palm crease (Turleau 1978; Nambot 2015). Two people had unusually bent fingers (Kulharya 2008; Ehret 2015). Club feet, talipes equinovarus, flat feet and an abnormal position of the ankle have been reported in ten individuals (Schlaubitz 2007; Marini 2010; Ehret 2015; Nambot 2015; Serati 2015). In one child the toes were partially webbed (Kulharya 2008).

Eight/11 Unique children had something unusual about their hands: curved 5th fingers (4); a single palm crease on one or both hands (2); short, broad and triangular middle bones in 5th fingers (1); small hands (2); tapered fingers (2); abnormal distribution of fat pads (1); and excess skin on the palms. One baby's hands were clenched, but gradually uncurled with neoprene opening gloves. Six/11 babies were born with unusual feet, but only one baby needed intervention to correct the abnormal position of both feet at birth. He spent months in a plaster cast, followed by a fixed bar similar to those used for children with club foot. Other more minor problems include small feet (2), one with heightened tone and curled toes; overlapping toes (2); partly joined toes (1); and excess skin on the soles (1).



## Nail patella syndrome

Nail anomalies have been reported in 9 people with a 9q deletion including 9q33 (Schlaubitz 2007; Marini 2010; Mignot 2011; Nambot 2015; Ehret 2015). Nails may be short or ribbed. Nail rim anomalies can occur and nails may be absent. Researchers think that these anomalies are caused in some people by the deletion of the LMX1B gene in 9q33.3 (see page 19). Mutations or deletions of



immaturity; temper tantrums; anxiety; and in a father and son with the same deletion, obsessive compulsive disorder. One child has been in hospital three times with very severe behavioural problems and aggression.

**“ Wouldn't change him for the world.” - 7 years**

Five children, 4 of them with a 9q33 deletion, have a diagnosis of autism, or autistic traits such as making odd noises or arm flapping. The diagnosis was reached in two children at the age of 2½.

Two children have some level of sensory disorder.

**“ She loves to rub her head from side to side when lying or sitting, so much so that it wears her hair away. She scratches material that provides her either with sound or tactile feedback, such as squeaky material, carpet or the tray on her feeding chair.” - 8 years**



## Medical concerns

### ■ Head, brain and seizures

A number of children with a 9q interstitial deletion including 9q33 have epilepsy. In many of the 15 children (Serati 2005; Saitsu 2008; Tohyama 2008; Saitsu 2010; Mignot 2011; Campbell 2012; Saitsu 2012; Barcia 2014; Matsumoto 2014; Ehret 2015; Nambot 2015; Nicita 2015) the deletion not only encompassed band 9q33 but also band q34.11. Band q34.11 includes the STXBP1 gene. Doctors think that the epilepsy in these individuals is related to the deletion of this gene. A separate leaflet on the STXBP1 gene is available from Unique.

Nonetheless, there are also children in whom the STXBP1 gene is deleted, but who do not show epilepsy (Campbell 2012; Ehret 2015). Furthermore, one child had epilepsy, but no deletion of the STXBP1 gene (Ehret 2015). It is therefore likely that other factors are involved in causing epilepsy.

Four children with ataxia are described in the medical literature. Someone with ataxia has difficulties in maintaining balance and co-ordinating movements (Campbell 2012; Ehret 2015). One of these children also had a tremor (Campbell 2012). One girl had spasticity of her legs (Mignot 2011).

In 20 children brain imaging, mostly by MRI, was performed (Sellitto 2008; Kulharya 2008; Saitsu 2008; Tohyama 2008; Saitsu 2010; Marini 2010; Mignot 2011; Campbell 2012; Saitsu 2012; Barcia 2014; Matsumoto 2014; Ehret 2015; Nambot 2015; Nicita 2015). In four children this showed no abnormalities, but in a number of children it did. Some of the abnormalities reported are: underdevelopment of the corpus callosum (the brain structure connecting the left and right sides of the brain), underdevelopment of the cortex (outer layer of nerve tissue) of the brain, underdevelopment of the cerebellum (part of the brain involved in balance), delayed myelinisation (insulation of nerve fibres) and a Chiari I malformation (in which the cerebellum partially descended into the base of the skull).



## Speech

“ Our daughter communicates well. She can speak in beautiful sentences and she is able to tell us clearly her feelings, thoughts and opinions. She used to have speech therapy for her pronunciation. But nowadays her pronunciation is fine. ”

Unique children do show speech delay, but the severity varies and children with little speech can still communicate well. Two families said their child started talking at 18 months. At 3, a child uses signing and about 10 words. At almost 4, one boy's understanding is seen as normal, but his talking is delayed: he is using 4-word sentences, and making good progress with therapy. At 4-5, one girl gets very tired after speech therapy: her family suspect that talking tires her. She also has a short tongue, and difficulties placing it. At 5½, a girl is not yet speaking fluently but is starting to babble and recently said 2-3 word sentences; she understands nearly everything. A boy of 12 years has a language, communication, speech and articulation disorder. Active speech lets a 16-year-old girl down. Her immediate family can understand, but speech seems to be a great effort. 'It's as if every word she says comes from the depths of her being.'

“ At 18 months she was saying 'bubba' and 'mmmm' with a few gurgles and lots of squeals. Six years on, she has a very good and apt shake of the head for 'no' and an occasional nod for 'yes'. She squeals loudly when excited, babbles, and says 'Mum', 'Dad' and sometimes 'Nan'. She has lots of individual sounds, and sometimes likes to 'tell us a story'. ” - 8 years



## Behaviour

Two children described in the medical literature are specifically reported to be very happy, upbeat and obedient (Ehret 2015). But a number of children with behavioural problems have been described (Park 1991; Campbell 2012; Brandt 2013; Harrison 2013; Ehret 2015; Nambot 2015).

Six people show autistic traits and/or stereotypic behaviour (e.g. flapping hands). An 18-year old woman also put objects in her mouth and showed other behaviour typical of autism. One girl was anxious. Two children had sleeping problems. Two others showed hyperactive behaviour and/or ADHD (attention deficit hyperactivity disorder). Two people have bipolar disorder. A mother developed obsessive compulsive behaviour after the birth of her son (Serati 2015). A man of 28 is described who is a paranoid schizophrenic. (Park 1991).

“ Our daughter is very sweet and compassionate to other people. ” - 8 years

Parents of Unique babies and young children describe their behaviour positively, using words like happy, kind, bright, content, loving, sweet, and mellow. By school age, difficulties with attention become a problem in some children, with attention deficit hyperactivity disorder (ADHD) suspected or diagnosed in 4/12.

One child responded very well to treatment with methylphenidate (Ritalin). Other problems are only seen in individual children. They include: moodiness;



this gene can result in nail patella syndrome (NPS). Besides nail anomalies, abnormalities of the knee cap can also occur in this syndrome.

Abnormalities of the patella have been reported in 7 people with a 9q deletion including 9q33 (Schlaubitz 2007; Jiang 2014; Ehret 2015; Nambot 2015). NPS can also result in elbow problems. Movement in the elbows may be limited. In some people the bones in the lower arm may also be involved. Elbow involvement has been reported in 5 individuals with the deletion (Schlaubitz 2007; Marini 2010; Ehret 2015; Nambot 2015).

Thirty to fifty per cent (3-5 in ten) of people with NPS have kidney problems. Five people with the deletion have kidney anomalies (Sellitto 2008; Campbell 2012; Matsumoto 2014; Nambot 2015; Nicita 2015). Anomalies included: small kidneys, calcium deposits in the kidney (nephrocalcinosis), an underdeveloped right kidney and slight enlargement of the pyelum, the area where the tube to the bladder leaves the kidney. However, these specific anomalies are not typical of NPS. Also, the LMX1B gene was not part of the deletion in all these people.

Only 3/6 Unique children have anything unusual about their nails. The toe nails are missing in one child, and finger and toe nails are fast growing in two others. No Unique family has reported any abnormalities of their child's elbows or kneecaps. One child has kidney involvement, with slight scarring of both kidneys due to repeated hard-to-diagnose urine infections.



## Psychomotor development

Most children with a 9q interstitial deletion including 9q33 who have been reported in the medical literature have developmental delay and/or intellectual disability. The degree of delay or disability can be moderate to severe. One girl, aged 6½, is described as follows: she developed normally until she was 2½ years old. After that she lost her speech and language abilities. She had made some progress again by the age of 6½ (Brandt 2013). Another article reports similar findings in another girl. She developed normally until she was 5 months old, but thereafter regressed (Mignot 2011).



The developmental delay may be related to epilepsy in some children. Epilepsy may be difficult to control using medication (e.g. Ehret 2015).

Motor development can also be delayed in children with a 9q interstitial deletion including 9q33. For instance, children can be slower in learning to roll over, sit or walk. Some children do not learn to walk. Out of 9 children, 6 could not walk at ages between 3 and 11 years (Matsumoto 2014; Ehret 2015; Nambot 2015). Three children did walk at the ages of 22 months, 24 months and 3½ years (Schlaubitz 2007; Ehret 2015; Nambot 2015).

All Unique members have reported some degree of developmental delay, but its course and severity differs between children. Most children are late to meet all their baby milestones and this is usually the reason for the tests leading to the 9q33 deletion diagnosis. One child developed very slowly until physiotherapy at 1 year 'flicked a switch'. Severity varies: at the mild end, one child has a slight delay, while another child of 5 years is at the level of a 4-6-month-old baby.

Epilepsy affected some children's development. One child made progress until he developed epilepsy at 2. Another progressed more steadily once seizures stopped. No Unique family said that their child's development went backwards because of seizures.

**" At 12 months, she could stay sitting but she didn't sit up on her own, roll or crawl, and she didn't cry or laugh, but could look straight through you. After just one week of physiotherapy and learning to roll over, her development was transformed. We had a completely different child. She started looking at you, laughing and crying. It was as if she woke up."**

Babies are late to hold their heads steady and to sit: 8 children learned to sit without support between 7 months and 3 years, but getting into a sitting position typically came much later and some children are not sitting yet at 3. Mobility is also late, and can be very late. There is great variety and some babies roll before they crawl. One baby crawled at 12 months, walked at 19 and could jump with both feet off the ground at 4 years, while a girl of 8 years cannot yet stand without support or crawl. Among the children who do walk, balance, coordination and motor planning are common problems, and some children need leg supports, gait trainers and walkers.

Not walking is no bar to enjoying being mobile, however:

**" She can weight bear and stand for minutes holding on to something, with her right leg bent. She loves to go swimming. She has full control of her breathing; wearing goggles she loves to look underwater. With lower body support she will lower her trunk and head into the water, look around for longer than Mum and Dad can believe, raise her head out of the water for a breath and return underwater, repeating for as long as we will let her! She loves to swim a very energetic sort of butterfly stroke. Floating quietly on the top of the water is much too boring for her. She also loves to ride on her trike. Sometimes she will refuse to hold the handlebars, other times forcing them to go where she wants to go!"** - 8 years

Low or varying (low and raised) muscle tone is one factor in the late mobility. Six families report low tone or mixed tone in their child. Low tone generally improves with age, therapy and practice, but it can persist.



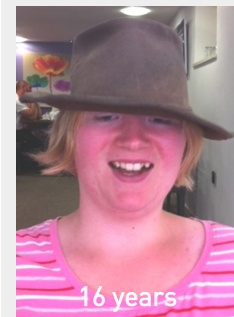
## Intellectual development

Many children show intellectual disability. Speech and language development can also be delayed. A number of children do not speak, but communicate using other means. One 28-year-old man with intellectual disability and speech and language delay had an IQ of 75 (Park 1991).

A number of people with a small 9q33 deletion show normal intellectual development (van Silfhout 2009; Harrison 2013; Jiang 2014; Serati 2015). One woman with the deletion had a mild intellectual disability and poor speech and language development. Her 6-year-old daughter had developmental delay and epilepsy (Ehret 2015).

**" Her level of development is that of a 7 year old girl. She did the first year of kindergarten twice and now she keeps up well with 'the others'."** - 8 years

All Unique children have some difficulty with learning, but it can be very mild - or more profound. Speech delay (see below) can make any intellectual difficulty hard to assess. A short attention span impinges on some children's learning. Behaviour difficulties (see pages 12-13) can make learning at school harder for some children. Some children go to a mainstream school, others a special school. A boy of almost 4 needs a little extra time to learn new concepts. A girl of 5½ knows two-thirds of the alphabet, while another girl of 8 is at kindergarten level with the alphabet. At 9, a girl is beginning to recognise letters and words. A



boy of 12 with an IQ of 65 is 'extremely good at computers and maths', but has a 'poor' memory. A girl of 16 reads books for 7-8-year-olds, and can write a short message or her name with letters of different sizes.

**" She is very visually inclined and can remember by heart a complicated route in detail that she has walked only once a year before. She can cycle quite well and learned her cycling route to work after only 1 or 2 times. She also looked out properly for traffic, so we might be able to let her make the journey by herself."**



**" She gets the giggles quite often, rubbing Dad's beard with her hands, tickles, dancing or being thrown around. She loves her swing, it is a very easy way to cheer her up. She loves to give and receive cuddles. She is an absolute joy."**  
- 8 years

**" Always has a smile and cuddle for everyone. He has taught us all about determination and perseverance."**  
- Almost 4 years

**" He loves to love and give hugs."** - 12 years