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19p13.12 microdeletions



Sources

The information in this guide is drawn from four sources: the medical literature, the chromosome database Decipher (www.decipher.sanger.ac.uk), the Unique members' database and a survey of Unique members. For the published medical literature, the first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. This guide draws mainly on information from the medical literature (Engels 2007; Jensen 2009; Bonaglia 2010; Van der Aa 2010; Kosaki 2011; Gallant 2011; Dale 2012). Seven people (four female, three male) are described, ranging in age from a newborn to 31 years.

19p13.12 microdeletions

A 19p13.12 microdeletion is a very rare genetic condition, in which there is a tiny piece of one of the 46 chromosomes missing. In this case, it is from the region known as p13.12, on chromosome 19 (see diagram on page 3). The missing piece of chromosome is very small (less than 5Mb) and is called a microdeletion.

The information in this guide is new as this is an emerging syndrome. There is likely to be a range of effects from mild to more severe.

Genes and chromosomes

The human body is 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, which carry the genetic material, or DNA, that makes up our genes.

Chromosomes usually come in pairs: one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from the largest to the smallest. Each chromosome has a short (p) arm (from the French for small, petit) and a long (q) arm (see diagram on 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 achievement, is influenced by both the genetic material he or she has, and the environment in which he or she lives.

Looking at chromosome 19p13.12

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram of chromosome 19 (see page 3). Each band of each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.

Notes:

Genetic Report

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken in your child. With a 19p13.12 microdeletion, the results are likely to read something like the following example:

arr[hg19] 19p13.12 (14,661,584-15,655,570)x1 dn

arr The analysis was by array (arr) comparative genomic hybridisation (cgh)

hg19 Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new 'builds' of the genome are made and the base pair numbers may be adjusted

19p13.12 The chromosome involved is 19 and the position of the deletion is in band p13.2

14,661,584-15,655,570

The base pairs between 14,661,584 and 15,655,570 have been shown to be deleted. Take the first long number from the second and you get 993,986 (0.994Mb or 993kb). This is the number of base pairs that are deleted

x1 means there is one copy of these base pairs, not two – one on each chromosome 19 – as you would normally expect

dn means *de novo*. The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 2p16.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child.

mat means that the deletion has been inherited from the mother;

pat means that it has been inherited from the father.

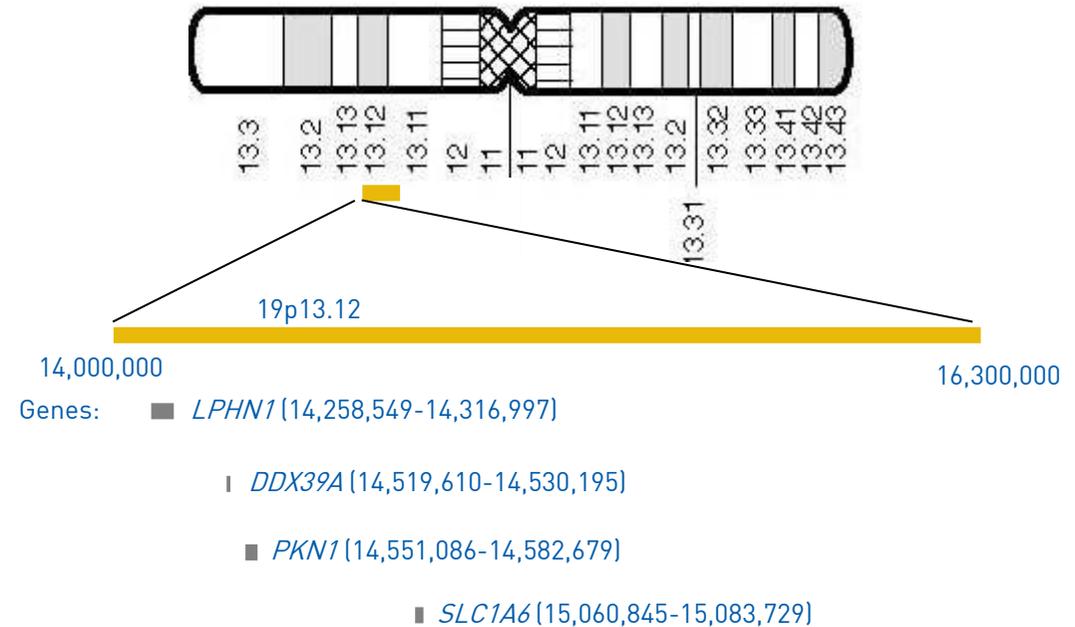
Emerging phenotype: what to expect

Chromosome changes involving chromosome 19 are very rare and microdeletions are rarely reported. Only two Unique members have a 19p13.12 microdeletion.

Recently, seven people with deletions of 19p13.12 were published in the medical literature (Engels 2007; Jensen 2009; Bonaglia 2010; Van der Aa 2010; Kosaki 2011; Gallant 2011; Dale 2012). The Decipher database

(www.decipher.sanger.ac.uk) also lists six people with a 19p13.12 microdeletion. As the number of affected individuals is so small, it is not certain what the full range of possible effects of the microdeletion are. The information presented here is derived mainly from the medical literature. The most consistent features are:

- **Newborn** – children with a 19p13.12 microdeletion are frequently small at birth. Other detectable signs may include: a small head, facial features (such



The numbers in this diagram refer to the human genome build 19 (hg19; see page 4 for more details). Your child's report may refer to a different human genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Why did this happen?

A blood test to check both parents' chromosomes allows parents to find out how the 19p13.12 microdeletion occurred. The child may have inherited the microdeletion from their mother or their father. However, where both parents have been tested and have normal chromosomes, the microdeletion occurred in the child for the first time and was not inherited. Geneticists call this '*de novo*' which means 'new'. *De novo* 19p13.12 microdeletions are caused by a change that occurred when the parents' sperm or egg cells formed, or possibly during formation and copying of the early embryonic cells.

All documented 19p13.12 microdeletions are *de novo*, with the exception of one girl (Dale 2012), where the microdeletion was inherited from her mother who had learning difficulties (Engels 2007; Jensen 2009; Bonaglia 2010; Van der Aa 2010; Kosaki 2011; Gallant 2011; Decipher).

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

Puberty and Fertility

There may be a tendency for puberty to start early in children with a 19p13.12 microdeletion.

One girl started her periods at aged nine years and had heavy menstrual bleeding (Jensen 2009). The normal age range in girls unaffected by a chromosome disorder is 9-16 years old, with an average age of onset of 13 years old. Two boys were diagnosed with precocious puberty (sexual development before the aged of eight in girls and ten in boys) (Van der Aa 2010; Bonaglia 2010). Puberty is defined as sexual development before the age of eight in girls, and age 10 in boys.

Although there are no well-documented cases of children born to someone with a 19p13.12 microdeletion, one five year old girl in the medical literature had inherited a 0.41Mb 19p13.12 microdeletion from her mother (Dale 2012). The mother had a learning disability and mildly different facial features but no other marked features. One person on the Decipher database had inherited a 0.1Mb 19p13.12 microdeletion from a normal parent.

Ongoing research: candidate genes

The 19p13.12 region is located between 14.0Mb and 16.3Mb on chromosome 19 (hg19). The variation in size of the microdeletions (0.16Mb to 2.52Mb) within this region can mean anything from approximately 5-64 genes missing (see diagram below). Candidate genes that might play a part in the features associated with a 19p13.12 microdeletion include:

- *DDX39A* – DEAD-box RNA helicase. This is highly expressed in the developing central nervous system and plays a role in regulating the development of the brain.
- *LPHN1* may be partially responsible for language delay, learning disabilities and/or behavioural problems.
- *PKN1* is implicated in a variety of functions in nerve cells and a deficiency in this gene may have an effect on language and mental development.
- *SLC1A6* is also involved in the formation of the brain and has also been implicated in language delay and learning disabilities.

As 19p13.12 is a gene-dense region, there are likely to be a number of different genes involved; the precise size and location of the deletion (within the 14.0-16.3Mb region of 19p13.12) will govern which genes are deleted. It is also important to remember that, whilst identifying the gene(s) responsible for certain features of 19p13.12 microdeletions is valuable and may help guide future research, it does not lead directly to immediate improved treatment. In addition, even if a gene is missing, it does not always mean that the associated feature(s) will be evident or that there is a direct relationship between an absent gene and a particular feature. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

as a flat-shaped head, almond-shaped eyes or low set ears with skin tags), hypotonia and difficulty breathing.

- **Growth** – Children have low birth weights at birth; as older children and adults, the rate of growth may be slow, sometimes resulting in short stature as an adult. Scoliosis (a curved spine) is common.
- **Development: sitting, moving, walking (gross motor skills):** There is likely to be a degree of delay, sometimes significant, in acquiring gross motor skills; hypotonia (low muscle tone and reduced strength) may affect gross motor skills.
- **Development: hand-eye coordination, dexterity and self-care (fine motor skills):** As with gross motor skills, children with a 19p13.12 microdeletion may be behind their peers in some fine motor skills. The medical literature reports a broad range of global developmental delay from mild to severe but provides no further information on fine motor skills. Washing, dressing and toilet training will be influenced by the level of fine motor skills.
- **Speech and language development:** Communication problems are frequently reported; children often have significantly delayed speech development. In some people, speech may be minimal and there may be a reliance on sign language.
- **Behaviour:** Children with a 19p13.12 microdeletion are often happy, engaging and sociable individuals; some may have hyperactive, anxious or aggressive tendencies.
- **Learning:** Learning disabilities occur in children with a 19p13.12 microdeletion, although the level of impairment may vary. Communication difficulties are likely to affect children's ability to learn.
- **Eyesight:** Some people with a 19p13.12 microdeletion may have one or more eye problems, including squints and short or long sightedness.
- **Hearing:** Hearing problems occur in most people with a 19p13.12 microdeletion.
- **Heart:** Around half of children with a 19p13.12 microdeletion have a hole in the heart: some close spontaneously, other require surgical intervention.
- **Feet and hands:** Approximately 70 per cent of people with a 19p13.12 microdeletion have hands and feet that appear different in appearance to unaffected individuals; some of these changes may impede movement and flexibility.
- **Puberty:** There may be a tendency for puberty to start early in children with a 19p13.12 microdeletion.

These features are discussed below, although detailed information is not always available on all the known cases.

Pregnancy and birth

Some children with a 19p13.12 microdeletion were born at term after uneventful pregnancies; others were delivered early by caesarean with slow growth *in utero* (before birth) regularly reported.

One pregnancy was initially uneventful but after week 21 the baby's slow growth was observed on ultrasound examination and intrauterine growth restriction (IUGR) recorded. IUGR occurs when an unborn baby is smaller than it should be because it is not growing at a normal rate inside the womb. The baby was delivered at 32 weeks by caesarean (Engels 2007). Another pregnancy was also complicated by slow growth, noted one month prior to delivery, and polyhydramnios (excess amniotic fluid). Two other babies were also delivered by caesarean, one at 36 weeks (Bonaglia 2010) and one due to decreased movement, in a pregnancy that had been complicated by reduced amniotic fluid (Jensen 2009). One child was born at 35 weeks after severe IUGR (Unique). Approximately 40 percent (3/8) were delivered spontaneously at 40-41 weeks, after an uneventful pregnancy (Bonaglia 2010; Van der Aa 2010; Kosaki 2011).

Newborn

Children with a 19p13.12 microdeletion are often born small and may have signs at birth, for example, a small head, hypotonia or difficulty breathing.

Children with a 19p13.12 deletion are often small at birth. Birth weights are known for seven children and were in the range 1.29kg – 2.74kg (2lb 14oz – 6lb 1oz), with an average birth weight of 2.25kg (4lb 15oz) (Jensen 2009; Bonaglia 2010; Van der Aa 2010; Kosaki 2011; Gallant 2011; Dale 2012; Unique).

Small babies may spend some of their early life in a special care baby unit (SCBU). This is a neonatal intensive care unit specialising in the care of ill or premature newborn infants. One Unique member came home after 13 weeks in a SCBU on oxygen and on NG feeds. A nasogastric (NG) tube is passed through the nose down into the stomach to allow feeding and administration of medicine. Another child also had supplementary oxygen for the first few days of life (Jensen 2010). One baby was in a SCBU with apnoea (temporary cessation of breathing) and bradycardia (a slow heart rate) (Bonaglia 2010) and another had difficulty breathing soon after birth (Dale 2012).

A newborn's physical condition is evaluated using the Apgar scoring system which monitors heart rate, breathing, muscle tone, response to stimuli and skin colour. Measurements are made at one, five and ten minutes after birth; ten is the ideal maximum score. One child with a 19p13.12 microdeletion had low initial scores, for example, 3 at one minute, rising to 9 at 5 minutes after birth (Jensen 2010). One child had a score of 6 at one minute and 8 at five minutes (Gallant 2011). In two other children, where Apgar scores were noted, these were both 9 at one minute and 10 at five minutes (Bonaglia 2010; Kosaki 2011). Apart from a low birth weight, other features of a 19p13.12 microdeletion may be evident at birth. Unusual facial/head features may be noted, such as a small

Occupational therapy (OT): Occupational therapists work with children to increase their ability to cope with the tasks presented by everyday life. Their work not only covers areas like dressing but also less obvious ones like writing skills and difficulties with perception. Occupational therapy improves fine motor skills, self-care skills and can also help deal with sensory processing disorder and attention span issues. It can be beneficial into the teenage years.

Physiotherapy: Physiotherapists use exercises to help people gain and keep the best possible use of their bodies. Unique members have reported that physiotherapy has improved gross motor skills and, for example, balance.

Routine medical appointments that form part of the life of a family member with a 19p13.13 or a 19p13.12 microdeletion might include some of the following medical specialists:

- **a cardiologist** – a specialist in the structure and function and disorders of the heart
- **an endocrinologist** – a specialist in treating conditions that are caused by hormone imbalances in the body
- **a gastroenterologist** – a specialist who treats diseases of the digestive system
- **a nephrologist** – a specialist who treats kidney diseases
- **a neurologist** – a specialist in treating conditions that affect the nervous system, which is made up of the brain, nerves and spinal cord
- **an ophthalmologist** – a specialist in treating eye problems
- **a paediatrician** – a specialist in treating children
- **a urologist** – a specialist in treating conditions that affect the urinary system

Other routine appointments might include:

- **a continence adviser** – a nurse specialising in bladder and bowel problems
- **an educational psychologist** – to help children and teenagers having trouble progressing with their education, for example, due to a learning disability
- **a geneticist** – a doctor who specialises in genetics
- **a genetic counsellor** – a health professional with specialized training and experience in the areas of medical genetics and counselling
- **a health visitor** – a qualified nurse with extra training who helps families with babies and young children
- **a social worker** – to give advice about practical issues such as benefits, housing and day care

What is the outlook?

We can't be sure yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan. Many children who have learning and developmental disabilities do not appear to have major health problems.

(Bonaglia 2010).

One girl has supernumerary abdominal nipples, a relatively common finding where more than one set of nipples develops (Jensen 2010). Two men (aged 15 and 31 years) have **hypertrichosis**, an abnormal amount of hair growth over the body (Bonaglia 2010; Van der Aa 2010).

The medical literature does not detail childhood infections or general wellbeing although one teenager suffered from recurrent lower respiratory tract infections and asthma as a young child (Van der Aa 2010).

What were the first signs of a 19p13.12 microdeletion?

Children with a 19p13.12 microdeletion are often born small (see 'newborn', p. 6) and may have detectable signs at birth, for example, a small head or unusual facial features, hypotonia (low muscle tone, resulting in floppiness) or difficulty breathing.

Shortly after birth, one child had a tooth that grew in the first month of life; although this is rare, it may not have been associated with a 19p13.12 microdeletion. He also has an preauricular skin tag (see 'facial features', p. 13). Within the first few weeks of life, his weight and length dropped below the 3rd percentile (see 'growth', p. 7) (Engels 2007). The age of diagnosis is not given in the medical literature but the first indications of a chromosome problem may lead to further investigations, for example, brain and heart scans. One child was referred to geneticists at seven months old (Kosaki 2011).

Therapy/routine medical appointments

Regular therapy appointments are highly beneficial with ongoing work to develop skills in all environments

A program of regular therapy can be very helpful in coping with the different features of a 19p13.12 microdeletion. Some of these are mentioned in the relevant section above but outlined below are some examples of the most common with their aims and benefits. Parents often comment on the importance of collaboration between therapists, parents and other adults caring for their children and therefore the continuing development of skills in all settings – home and school.

The comments below are provided by Unique members with a 19p13.13 microdeletion but some are likely to be relevant to 19p13.12 microdeletions too.

Speech and language therapy (SALT): Speech and language therapists work with any child with a communication problem. Eating involves similar mouth and tongue control to speaking and so speech therapy also helps if there are feeding issues. Speech therapy can be started as young as three months and is commonly used by Unique members.

head or malformed ears. Babies may also be hypotonic, a loss of muscle tone, resulting in floppiness.

Feeding/digestion

The medical literature does not describe feeding and/or digestion in any detail. The only medical information available is a report of gastrointestinal reflux (acid coming up from the stomach into the oesophagus) in one child (Engels 2007) and some intestinal findings (including a midgut malrotation - a twisted gut) in a child who died at six weeks old (Gallant 2011). One Unique member also had GERD (gastroesophageal reflux disease) which was treated by a surgical procedure called a Nissen fundoplication repair. This enabled normal oral feeding (as opposed to a feeding tube) from nine months old. Another Unique member was incontinent at seven years old. This was due to a neuropathic bowel, where nerve damage alters the ability to control bowel movements.

“ He is sensitive to textures in his mouth. He is receiving feeding therapy. We have used many tools and exercises from the therapist to help him improve in this area, although there is still a long way to go. He also doesn't like his clothing changed or his face wiped. With occupational therapy we are working with brushing techniques to help him ” – 2 years

Growth

Children have low birth weights at birth; as older children and adults, the rate of growth may be slow, sometimes resulting in short stature as an adult. Scoliosis (a curved spine) is common.

Growth and height measurements can be plotted on a graph to show the normal range; the average is on the 50th centile (percentile). Measurements in people with a 19p13.12 microdeletion may reflect the range seen in the general population (Engels 2007; Bonaglia 2010; Van der Aa 2010; Unique). Weights may be proportionate to their height or, as in the case of two short individuals (aged 15 and 31 years), they can be overweight (Bonaglia 2010; Van der Aa 2010).

A common finding is low birth weight. One Unique member had a very low birth weight when she was born at 35 weeks (1.290 kg/2lb 14oz) and was still small for her age at 34 months old. One child had short stature at 18 months old, with height, weight and head circumference all below the 3rd percentile. However, by eight years old, these measurements were within the normal range (Engels 2007).

Scoliosis (a curved spine) was reported in three people in the medical literature (Jensen 2009; Bonaglia 2010). One child has spina bifida (a congenital defect of the spine, present at birth, in which part of the spinal cord is exposed through a gap in the backbone. It often causes paralysis of the lower limbs, and sometimes learning difficulties) (see 'Skeletal', p 12) (Unique).

A small head is commonly observed with five children reported in the medical literature having a head circumference smaller than the 10th centile (Engels 2007; Bonaglia 2010; Kosaki 2010; Van der Aa 2010; Gallant 2011).

Development: sitting, moving, walking (gross motor skills)

There is likely to be a degree of delay, sometimes significant, in acquiring gross motor skills; hypotonia (low muscle tone and reduced strength) may affect gross motor skills.

The medical literature does not describe gross motor skills in detail but there are reports of a delay in, for example, holding the head up, crawling or walking. Typically-developing babies who don't have a chromosome disorder, generally hold their head steady at 4-6 months, sit unaided at around 7 months and walk on average at 13 months (age range 9-18 months).

Head control may be delayed with one child holding his head up at two years old (Bonaglia 2010). One child had a moderate delay in their development of gross motor skills, sitting unaided at 15 months old and making their first attempts to crawl at 16 months old (Engels 2007). Learning to walk ranges from a normal time scale to a severe delay, with three children started to walk at one (Kosaki 2011), two (Van der Aa 2010) or three years old (Bonaglia 2010) respectively. A Unique member walked from two years old. One adult was described as walking with small steps at 31 years old (Bonaglia 2010).

Developmental delay may be more pronounced in some children than others. Hypotonia (low muscle tone and therefore reduced strength) can be an issue, with hypotonia evident at birth and persisting in some individuals (Bonaglia 2010).

Development: hand-eye coordination, dexterity and self-care (fine motor skills)

As with gross motor skills, children with a 19p13.12 microdeletion may be behind their peers in some fine motor skills. The medical literature reports a broad range of global developmental delay from mild to severe but provides no further information on fine motor skills. Washing, dressing and toilet training will be influenced by the level of fine motor skills.

In general, when Unique parents see that their child finds everyday activities difficult, for example, dressing, holding a pencil or feeding themselves, occupational therapy and physiotherapy are reported as beneficial, often from a young age.

Speech and language development

Communication problems are frequently reported; children often have significantly delayed speech development. In some people, speech may be minimal and there may be a reliance on sign language. Speech and occupational therapy are beneficial.

Children may start talking significantly later than their unaffected peers with a wide range of ability from mild to severe language delay (Engels 2007; Jensen 2009; Bonaglia 2010; Van der Aa 2010; Kosaki 2011; Gallant 2011; Dale 2012; Unique).

This is a condition in which, instead of being level with the ribs, the breastbone (sternum) is 'sunken' so that the middle of the chest looks 'caved in'. In the UK, pectus excavatum affects approximately one in every 250 children and is more common in boys than girls.

■ Feet and hands

Approximately 70 per cent of people with a 19p13.12 microdeletion have hands and feet that appear different in appearance to unaffected individuals; some of these changes may impede movement and flexibility.

Four have brachydactyly (short fingers and toes) (Jensen 2009; Bonaglia 2010; Kosaki 2011). In contrast, another has long slender fingers with broad big toes (Gallant 2011). One has syndactyly of some fingers and toes (Bonaglia 2010). This is a condition that occurs when two or more fingers or toes are fused together by skin, resulting in a webbed appearance. Another has clinodactyly, where the fingers are bent or curved (Bonaglia 2010).

Facial features

Children with a 19p13.12 microdeletion may look slightly or markedly different from other family members.

Unusual features may include: a flat-shaped head, eyebrows that meet in the middle, almond-shaped eyes, a long philtrum (the midline groove in the upper lip that runs from the top of the lip to the nose) a small lower jaw or mouth and small and/or low set ears.

Ears may have several unusual features. Three children have ear pits which are dents or dimples in the cheek near the ear (Engels 2007; Jensen 2009). One of these children also has preauricular skin tags (Gallant 2011), an extra piece of skin that forms near the ear. Another child also had skin tags which were surgically removed at 12 months old (Kosaki 2011). Babies born with preauricular skin tags or ear pits are at increased risk for hearing loss.

One child had a high palate (Van der Aa 2010) and others may have missing or irregular teeth (Engels 2007; Jensen 2009; Bonaglia 2010; Van der Aa 2010). An eight year old had two of the front teeth missing in her upper jaw (Engels 2007), another had two front teeth missing in her lower jaw (Kosaki 2011) and a third had prominent incisors (four teeth at the front of each of the lower and upper jaws (Van der Aa 2010).

Other medical concerns

Other medical concerns are described rarely, or occur quite commonly in the general population, and may not be related to a 19p13.13 microdeletion. One two-year old had **hypospadias** (Bonaglia 2010). This is a relatively common birth defect, affecting between 1 in 125 and 1 in 300 male babies in the UK. It occurs when the hole through which urine and semen leave the body is not located at the tip of the penis. In this case, it was repaired surgically at nine months old (Unique). Another boy had cryptorchidism (undescended testicles)

■ Heart

Holes in the heart occur in approximately 40 per cent of children with a 19p13.12 microdeletion: some close spontaneously, other require surgical intervention.

Children may have a routine cardiology appointment to check for heart defects. About one in 250 babies born without a chromosome disorder will have a problem with their heart or major blood vessels. These problems appear to be more common in children with a 19p13.12 microdeletion, occurring in three of the seven people in the medical literature. The problems depend on the size and nature of the defect. Some cause few or no symptoms or the doctor may notice a murmur. One Unique member has a small muscular ventricular septal defect (VSD): this is a hole in the wall (septum) that separates the two lower chambers (ventricles) of the heart. A muscular VSD is a hole in the lower, muscular part of the ventricular septum and is the most common type of VSD. Another child had several similar small holes in the heart, all of which closed spontaneously by three months old (Jensen 2009). Larger holes may require surgery.

One child had bradycardia (a slow heart rate) as a newborn and a persisting ductus Botalli. This is a blood vessel that links the heart and lung circulation in the fetus. As the baby breathes at birth, it empties and becomes a connective-tissue cord (ligament). In rare cases, when the ductus Botalli remains open, a surgical operation is necessary. This child's persisting ductus Botalli was successfully treated by surgery. In addition, he had a foramen ovale (another form of hole in the heart) in early childhood which had spontaneously resolved by the age of eight years old (Engels 2007; Bonaglia 2010). Another child also had two holes in the heart (Gallant 2011).

■ Skeletal

One Unique member was born prematurely and had metabolic bone disease of prematurity (characterised by a reduction in bone mineral content). This is not uncommon in pre-term infants born with a low birth weight and results in bones with a low bone mass that are brittle and prone to fractures.

Another Unique member has spina bifida. Spina bifida is a fault in the development of the spine and spinal cord which leaves a gap in the spine. There is a wide range of severity with symptoms including mobility difficulties and bladder/bowel incontinence. About one baby in 1,000 is born with myelomeningocele, the most serious form of spina bifida.

Scoliosis (a curved spine) was reported in three people in the medical literature aged 8, 10 and 31 years old (Jensen 2009; Bonaglia 2010). In children and teenagers, scoliosis often does not have any noticeable symptoms. The curved spine is not painful and, if it is mild, it can go unnoticed. As teenagers approach adulthood, if the curvature is significant, physiotherapy to strengthen the back muscles, a back brace and/or surgery may be necessary. In the UK, scoliosis affects approximately one in every 250 children.

One of these people with scoliosis also has pectus excavatum (Bonaglia 2010).

Expressive language involves being able to put thoughts into words whilst receptive language is the ability to understand spoken or written words. One girl can't talk at 34 months but her receptive language is good; she understands two languages. Others report: meaningful words at 12 months old and two word sentences at 31 months old (Kosaki 2011), no speech at 18 months (Engels 2007), or a moderate or severe language delay (Bonaglia 2010). Although speech has now improved (at 15 years old), one boy had poor communication skills in early childhood due to an expressive language delay (Van der Aa 2010). Speech and occupational therapy will encourage communication using a variety of methods. Sign language can be learnt from an early age, for example 14 months. One Unique member is learning Makaton [signs and symbols which help people communicate]; at 34 months old she is slowly picking it up. PECS (picture exchange communication system, a picture-based method) may also aid communication.

Behaviour

Children with a 19p13.12 microdeletion are often happy, engaging and sociable individuals; some may have hyperactive, anxious or aggressive tendencies.

At 34 months, one child is very happy and active. She is sociable and fascinated by everything (Unique). Another child is described as having difficult behaviour at eight years old (Unique). Hyperactive behaviour is mentioned in several reports (Engels 2007; Bonaglia 2010; Dale 2012). One five year old has been diagnosed with ADHD (attention deficit hyperactivity disorder) (Dale 2012).

Behaviour may change with age. As a toddler one boy was happy and sociable; at 15 years old, he is very shy, extremely insecure and anxious (Van der Aa 2010).

Another child's behaviour deteriorated during adolescence: repetitive questioning and limited interests developed alongside aggression, particularly in response to minimal environmental changes. As an adult (aged 31 years), drug therapy has led to a progressive improvement in behaviour (Bonaglia 2010).

Anxiety or aggression may be an issue in some children although with the small numbers of known affected individuals, many of whom are still young, it is unclear how pervasive or long-lasting an issue these may be. Some anxiety may be related to difficulties in communication. Information on behaviour is not generally available in the medical literature.

Learning

Learning disabilities occur in children with a 19p13.12 microdeletion, although the level of impairment may vary. Communication difficulties are likely to affect children's ability to learn.

A mild to moderate learning disability is reported in most children with a 19p13.12 microdeletion (Bonaglia 2010; Van der Aa 2010; Kosaki 2011; Dale 2012).

Detailed information on learning and schooling is not available in the medical literature although measurements of intelligence are recorded in some people.

Intelligence quotient, or IQ, is an assessment of someone's ability to think and reason. A score of 100 means that, compared to people of the same age, you have an average intelligence. Learning disabilities can be mild (an IQ of 50-70), moderate (an IQ of 35-50) or severe (an IQ of 20-35). One child had an IQ of 63 at five years old, consistent with a mild learning disability (Jensen 2009). Four others have moderate learning disabilities (Bonaglia 2010; Van der Aa 2010; Kosaki 2011).

Medical concerns

Some of these features may occur more frequently than in the general population, such as the eyesight and hearing problems. Others may not be associated with the 19p13.12 microdeletion. Some medical concerns may not have been identified as there are such small numbers of affected individuals and some of them are still quite young.

■ Eyesight

Some people with a 19p13.12 microdeletion may have one or more eye problems, including squints and short or long sightedness.

Approximately half the people described in the medical literature have eye problems. One child had a normal eye examination at eleven months; at eight years she was found to have hyperopia (long sightedness) and astigmatism (Engels 2007). Another child has strabismus (a squint) and blocked tear ducts (Jensen 2009). One adult (31 years old) has nystagmus (uncontrolled movement of the eyes) and myopia (short sightedness) (Bonaglia 2010). A fourth individual has amblyopia in their right eye: a decrease in vision with no apparent cause (Van der Aa 2010).

■ Hearing

Hearing problems occur in the majority of people with a 19p13.12 microdeletion.

A range of hearing losses occur in people with a 19p13.12 microdeletion and children may need a hearing aid (Jensen 2009; Bonaglia 2010). One child failed the newborn hearing test (Gallant 2011). Three children have conductive hearing loss and three have sensorineural hearing loss (Engels 2007; Jensen 2009; Bonaglia 2010; Kosaki 2011; Gallant 2011).

There are two main types of hearing loss – conductive and sensorineural. It is possible to have both types of hearing loss, as is the case with one person (Jensen 2009).

Conductive hearing loss is the result of sounds not being able to pass freely to the inner ear. This usually results from a blockage in the outer or middle ear, such as a build-up of excess ear wax or fluid from an ear infection (especially common in children). It can also happen as a result of an abnormality in the structure of the outer ear, ear canal or middle ear – or be due to a ruptured eardrum. Depending on its cause, a conductive hearing loss can either be temporary or permanent.

Sensorineural hearing loss is a permanent hearing loss resulting from damage to the hair cells within the cochlea (tiny snail shell-like structure in the inner ear) or the hearing nerve (or both).

■ Seizures

Seizures, of various types, occur in about 40 per cent of people with a 19p13.12 microdeletion.

A newborn baby had seizures at about five weeks old (Gallant 2011).

One seven-year old child had seizures at five years old. Anti-epileptic treatment was not started as the seizures happened rarely. Electroencephalography was used to record the brain's electrical activity, producing an electroencephalogram (EEG) reading. The EEG showed traces of electrical activity associated with epilepsy (Bonaglia 2010).

Clonic seizures cause repeated jerking movements of muscles in the arms and/or the legs. Sometime on both sides, sometimes on one side or only in an arm or leg. An adult had several generalised clonic seizures with falls, at 24 years old, which were associated with an increase in his medication for behavioural problems. This is a known side effect of this particular drug and, as it was felt that anti-psychotic therapy could not be reduced, anti-epileptic treatment was initiated. Complete seizure control was achieved with a follow up period of eight years and EEG recording showed slowing of epilepsy-associated activity (Bonaglia 2010).

■ Brain

Brain imaging (MRI – magnetic resonance imaging) may be performed, especially if neurological symptoms are present. This is a highly sensitive imaging technique which provides detailed information about the structure of the brain. It's not always clear how any observed abnormalities relate to a child's development (they may not affect it at all) but regular analysis allows any abnormalities to be monitored and potentially treated.

Two children had normal MRI scans (Engels 2007; Bonaglia 2010). One of these had a cyst and a brain haemorrhage detected at three days old: at two and five years old, the MRI scans were normal (Bonaglia 2010).

Three people had an absent or thinned corpus callosum (the structure that connects the right and left sides of the brain) (Jensen 2009; Van der Aa 2010; Gallant 2011). Defects in this region of the brain can be associated with features such as seizures and developmental delays in motor skills and speech development. One of these individuals had a narrow brainstem but otherwise the MRI scan was normal (Van der Aa 2010). The brain stem is at the base of the brain and connects the brain to the spinal cord. The brainstem controls and regulates vital body functions, such as breathing and the regulation of the heartbeat. Two children had other findings on MRI, for example, an underdeveloped cerebellar vermis (an area of the brain that deals with coordination and movement) (Jensen 2009; Gallant 2011).