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19p13.13 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 on information from a survey of three members of Unique in 2013, referenced Unique, and the medical literature. When this guide was written (Autumn 2013), Unique had six members (two female, four male) with a 19p13.13 microdeletion. The six Unique members range in age from 2-21 years old with only one member older than 7 years old. There are seven people (five female, two male) described in the medical literature (Auvin 2009; Dolan 2010; Nimmakayalu 2013) ranging in age from 3-16 years old.

19p13.13 microdeletion

A 19p13.13 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 p13.13, 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

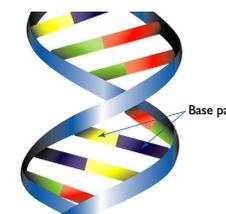
The human body is made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; this genetic information tells the body how to develop, grow and function. Genes are carried on structures called chromosomes, which carry the genetic material, or DNA, that makes up our 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 19p13.13

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a

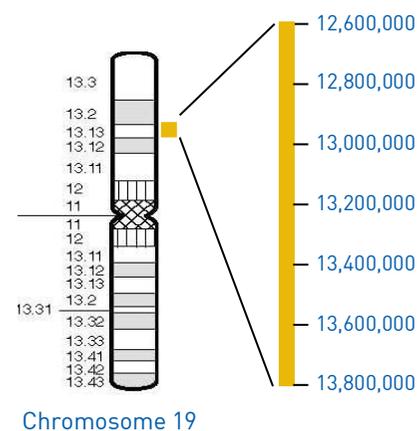
Notes:

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 diagram below). 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.



People with a microdeletion of band 19p13.13 have between 0.16Mb to 2.39Mb deleted.

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



Note: the numbers in this diagram refer to the human genome build 38 (hg38; see page 4 for more details). Your child's report may refer to a different genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Genetic testing

Microdeletions of chromosome 19 are too small to be seen down even the highest powered microscope. Molecular DNA technology gives a more precise understanding of the size and position of the microdeletion. This is important as scientists identify genes and pinpoint their location on chromosomes.

Genetic testing

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.

A microarray will tell you the size of the deletion:

arr [hg38] 19p13.13 (13155005-13554043)x1 dn

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

hg 38 Human Genome build 38. 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.

**19p13.13
13016005 – 13415043** The chromosome involved is 19, band 13.13 of the short p arm

The region from base pair 13155005-13554043 has been lost. By taking the first number from the second, you get 399,038 (approximately 0.4Mb). This is the number of base pairs that are missing

x1 One copy of the segment of band 19p13.13, not two – one on each chromosome 19 – as you would normally expect.

dn de novo – Latin for anew, meaning that the microdeletion has arisen for the first time in that individual and is not inherited from either parent. **pat** means inherited from the father; **mat** means inherited from the mother).

Emerging phenotype: what to expect

Chromosome changes involving chromosome 19 are uncommon and microdeletions are rarely reported. Only six Unique members) have a 19p13.13 microdeletion.

Recently, seven people with deletions of 19p13.13 were published in the medical literature (Auvin 2009; Dolan 2010; Nimmakayalu 2013). Another person was described with a deletion which includes part of the 19p13.13 region but mainly covers the 19p13.2 region and is detailed in the Unique's 19p13.2 microdeletion information guide (<http://www.rarechromo.org/information/Chromosome%2019/19p13.2%20microdeletions%20FTNW.pdf>) (Lysy 2009).

This is an emerging syndrome.

The most consistent features are:

- **Feeding/Digestion** - Some children with a 19p13.13 may have difficulties with feeding and digestion, with reports of constipation and abdominal pain in some cases. It may also be difficult to introduce solid food.
- **Growth** - Children may be tall with a large head.
- **Sitting, moving, walking (gross motor skills):** Delay in learning to sit, move and walk is likely; walking may be unsteady and hypotonia (low muscle tone) is common.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 19p13.13 microdeletion or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 19p13.13 microdeletion. This is called **germline mosaicism** and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the deletion. This is what is thought to have happened with the two affected sisters described in one paper in the medical literature, as both parents tested negative for the 19p13.13 microdeletion (Nimmakayalu 2013).

In families where the 19p13.13 microdeletion has been inherited from a parent, the possibility of having another child – either a girl or a boy – with the 19p13.13 microdeletion rises to 50% in each pregnancy. However, the effect of the microdeletion on the child's development, health and behaviour cannot be reliably predicted. The parent's ability to look after a child is very likely to be related to their own degree of learning ability.

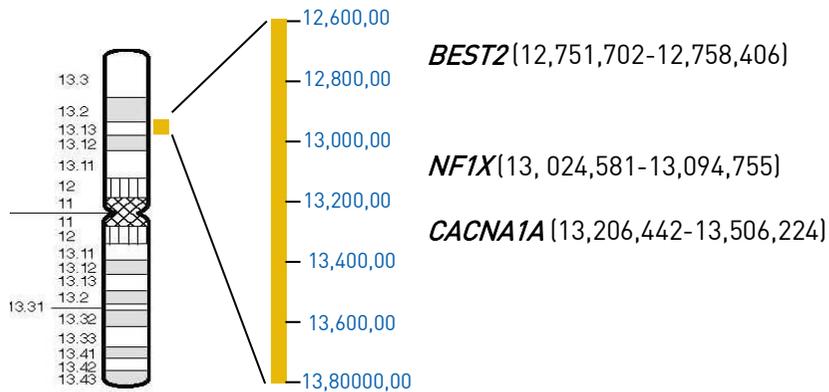
Your genetics centre should be able to offer counselling before you have another pregnancy.

References

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Nimmakayalu M, Horton VK, Darbro B, Shivanand RP, Alsayouf H, Keppler-Noreruil K and Shchelochkov OA. 2013. Apparent germline mosaicism for a novel 19p13.13 deletion disrupting NFIX and CACNA1A. *American Journal of Medical Genetics*: 1105-1109.



Chromosome 19

Note: the numbers in this diagram refer to the human genome build 38 (hg38; see page 4 for more details). Your child's report may refer to a different 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 19p13.13 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* 19p13.13 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 reported cases of 19p13.13 microdeletions, except one, are *de novo*, or of unknown genetic origin (Auvin 2009; Dolan 2010; Nimmakayalu 2013; Decipher; Unique).

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.

- **Hand-eye coordination, dexterity and self-care (fine motor skills):** Delay is likely. Children might need extra support with toilet training.
- **Speech and language:** Communication problems are frequently reported; children often have significantly delayed speech development. In some people, speech may be minimal and sign language may be helpful.
- **Learning:** Learning (intellectual) disabilities occur in children with a 19p13.13 microdeletion. Children are likely to need support with their learning. The amount of support needed varies. Communication difficulties are likely to affect children's ability to learn.
- **Eyesight:** Eye problems are common and children may need glasses at a young age. An underdeveloped optic nerve (optic nerve hypoplasia) is present in some children and squints (strabismus) in over half of children
- **Seizures:** Seizures occur in approximately half of children

Pregnancy and birth

Most children were born at term after an uneventful pregnancy.

Mothers do not generally report significant problems in pregnancy. Birth weights are known for nine children and were in the range 2.1kg – 4.1kg (4lb 11oz – 9lb) (Dolan 2010; Nimmakayalu 2013; Unique), with an average birth weight of 3.28kg (7lb 3oz).

Newborn

Children often do not have obvious signs at birth.

Unique members and individuals in the medical literature did not show any features of a 19p13.13 microdeletion at birth, other than characteristics that occur quite commonly in newborn babies, for example, jaundice. No Unique members had low Apgar scores (measure of baby's wellbeing at birth).

“ She was very healthy at birth ”

One child was born prematurely:

“ He was born at 35 weeks, 5 days and went straight into the special care baby unit as he was grunting when he was born and couldn't catch his breath. He stayed in there until he was able to feed, which was 2 weeks ”

In the medical literature one new baby had difficulty feeding due to a tongue-tie. This occurs when the thin piece of skin under the baby's tongue is very short and restricts the movement of the tongue. The skin can be snipped painlessly in young babies, but older babies usually have an anaesthetic (Dolan 2010). Another newborn had hypotonia and severe constipation (Auvin 2009).

Feeding/digestion

Some children may have difficulties with feeding and digestion, particularly when solid food is introduced.

Unique members do not describe any particular issues with breastfeeding or bottle-feeding but weaning to solid food can be problematic (Decipher; Unique). Two children found eating solid foods difficult; one was only eating 6-7 month stage baby food at 17 months old and the other was prone to choking due to oral hypotonia (low muscle tone around the mouth) and lack of coordination (Unique). Two children were sensitive to the texture of solid food (see sensory issues under 'Behaviour', page 11).

“ She was breastfed and did great with it. She had minor trouble learning to latch correctly, but once that was figured out she did great. She was breastfed until 11 months old ”

“ He breastfed as a newborn and until he was 15 months old, with no problems. We tried introducing baby food and cereal at six months and there have been significant feeding issues to date. He has many issues with textures and vomits when anything other than stage 1 or stage 2 baby food is in his mouth. He's been in feeding therapy since 10½ months and has made very slow progress. He was very underweight due to our inability to increase his consumption of baby food. Also, when ill with any virus, he vomits profusely due to gagging on any mucus in his throat. He has recently increased in weight with added calories through oils in baby food and higher calorie formula from the GI specialist ” – 2 years

Constipation is regularly reported, with medicines such as a stool softener sometimes prescribed. Adding fibre or oil to the diet also helped (Auvin 2009; Unique). Two children in the medical literature had abdominal pain and vomiting. In one who had difficulties with solid food the symptoms started at 17 months old (Dolan 2010). The other person was diagnosed with coeliac disease, having shown signs of this from between 7-9 months, and is now on a gluten-free diet (Dolan 2010). One six year old girl had chronic diarrhoea, of unknown cause, for the first four years of her life (Dolan 2010).

Growth

Children may be tall with a large head.

Children with a 19p13.13 microdeletion are usually a normal height, although half (6/13) are taller than average (Dolan 2010; Nimmakayalu 2013; Unique). Weight is usually proportionate to height. One child is overweight (Dolan 2010) and three underweight (Dolan 2010; Unique).

“ She is very tall for her age; her weight is normal for her height ”
– 7 years

“ He is a big sturdy boy and very strong ” – 5 years

“ When she was first diagnosed, we wanted to know what the future would hold for her. This still applies. How can we help her? Support groups and other families with affected children were the most helpful. When she was first diagnosed, we wish we'd realised that she is just the way she should be and her future is full of possibilities ”

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.

Puberty and Fertility

Based on age alone, only three individuals covered in this booklet have been through puberty and no information is available on the process. There are no reported cases of children born to someone with a 19p13.13 microdeletion.

Ongoing research: candidate genes

The 19p13.13 region is located between 12.6Mb and 13.8Mb (hg38). Candidate genes that might play a part in the features associated with a 19p13.13 microdeletion include:

- *BEST2* (bestrophin 2) is expressed in the colon and may be related to constipation
- *CALR* is another gene that codes for a protein found in the intestine and may also play a role in any gastrointestinal symptoms
- *CACNA1A* has been associated with epilepsy and also ataxia (a lack of voluntary coordination of muscle movements which can affect all parts of the body – walking, balance, swallowing, speaking)
- *NFIX* (nuclear factor 1) is essential for normal brain and skeletal development (and is implicated in corpus callosum defects in the brain)

As the 19p13.13 region is gene-dense, there are likely to be a number of different genes involved; the precise size and location of the deletion will govern which genes are deleted. It is also important to remember that, whilst identifying the gene(s) responsible for certain features of a 19p13.13 microdeletion 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.

Routine medical appointments that form part of the life of a family member with a 19p13.13 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

Helping other parents

Parents of people with a 19p13.13 have provided comments, concerns and advice that helped them, particularly when their child was first diagnosed:

“ When he was first diagnosed [as a baby], I wanted to know if he would look different and was mostly concerned about intellect and speech. These are still my biggest concerns; particularly at what age do any problems become clear. I wish I had known when he was first diagnosed that he would be a happy, interactive and loving 15 month-old. I was so worried he wouldn't connect with us like he has ”

A large head is common in children with a 19p13.13 microdeletion with all seven children reported in the medical literature having a head circumference above the 97th percentile (Auvin 2009; Dolan 2010; Nimmakayalu 2013). Head size is not particularly noted by Unique members but some report facial features which may relate to a large head (see 'Facial features' page 15).



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

There is likely to be some delay in learning to sit and walk. Walking may be unsteady and hypotonia (low muscle tone) is common. Developmental delay may be more obvious in some children than others.

Most parents report a delay in learning to walk. Typically-developing babies, who don't have a chromosome disorder, generally sit unaided at around 7 months and walk between 9 and 18 months. At 9 months old, one Unique member was nearly able to sit. At 12 months, another Unique member's gross motor skills were delayed by about 6 months. He sat at 11 months and crawled/cruised between 12-15 months. Of the four Unique members who mention crawling, the average age was around 16 months (age range 13 months – 22 months). Walking was achieved at around 2 years 4 months old (age range 22 months – 3 years) (Unique) . One child was just lifting her head at 17 months old (Unique). Another child reached her developmental milestones but 12-18 months behind her peers (Unique). Hypotonia (low muscle tone) can be an issue, with a resulting lack of coordination, and can be persistent (Auvin 2009; Dolan 2010; Nimmakayalu 2013; Decipher; Unique).

“ He has hypotonia; he was very floppy and is still unstable in the trunk at 15 months old. He didn't sit up until 11 months. A bathing chair was necessary at bathtime ”

“ He's had developmental delay since birth; he sat at 11 months and walked at nearly 2½ years old. He was prescribed Pedro boots [designed for children with disabilities and/or children who require extra arch or ankle support] when he was tiny and they helped him to walk. His walking is fine although he is unsteady when negotiating pavements and kerbs. If he is unwell or tired, he is very unsteady. He climbs the stairs by himself although he holds on to the rails. He is just starting to run although slowly. ”

“ He has a major buggy if he gets really weak and his bike has been altered by a charity into a stationary bike to help with his muscle tone ” – *6 years*

“ She took her first steps at 37 months and at 3½ years was still learning to master walking. She used a reverse walker [designed to make walking less energy-consuming, improve posture and maximize the potential for walking] from aged 3 to just before her sixth birthday. This was extremely helpful with teaching her to walk and helping her to be comfortable with walking, so that she walked well on her own by 6 years old. She can walk well on her own indoors and outdoors. She climbs stairs with the assistance of a handrail. She loves playing tag or chases. Her favourite part of school is PE. She has hypotonia in her trunk: this has improved by 7 years old and her muscle tone is near normal. The hypertonia (an increase in muscle tension and a reduced ability of a muscle to stretch) in her extremities has also improved with age ” – *7 years*

In the medical literature, developmental delay is common with, for example, a child of 2 years sitting independently and starting to pull himself up to stand (Auvin 2009). Another child walked at 2-3 years (Dolan 2010; Nimmakayalu 2013).

One child has many dyspraxic (a coordination disorder affecting both gross and fine motor skills) traits with hypotonia and poor proprioception (a sense of how your limbs are coordinated in space); she is clumsy, falling several times each day (Unique). One adult Unique member does walk but her ability to walk is deteriorating; she is unsteady and she has to use a wheelchair for longer distances. An 11 year old girl had an unsteady gait which had started when she was 9 years old; she also had dizzy spells (Nimmakayalu 2013). Ataxia (a lack of voluntary coordination of muscles) may be a feature of a 19p13.13 microdeletion and may affect speech as well as coordination and balance.

Five of the seven people presented in the medical literature have hypotonia (Auvin 2009; Dolan 2010; Nimmakayalu 2013).

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 19p13.13 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.

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.

“ He is starting speech therapy at 16 months. We are aiming to develop first words and purposeful speech ”

Specific feeding therapy is also useful to some Unique members:

“ He's been having feeding therapy from 10 months to help him move beyond baby food and ensure adequate intake. He has come a long way but has a long way to go. This is probably the hardest area for us thus far ” – *2 years*

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.

“ He is having occupational therapy which aims to improve his spatial awareness and dexterity ” – *2 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.

“ He has had physiotherapy from six months old for mobility ” – *2 years*

minor genital anomaly, where the hole usually at the tip of the penis is on the underside instead. In this case, it was repaired surgically at nine months old (Unique).

Two children have asthma which is treated with an inhaler (Unique). General wellbeing was good in most Unique members, although they may be more prone to infections. A child, a twin, gets more colds and chest infections (requiring antibiotics) than his unaffected twin. One child had pneumonia and two ear infections in his first year. Another child is healthy apart from a few ear infections and an occasional cold. She is allergic to ibuprofen and the antibiotic penicillin (Unique).

Renal ultrasounds (kidney scans) were performed in three people and one person had an extra renal pelvis (a protruding part of the kidney that can occur in individuals unaffected by a chromosome disorder) and has remained stable. As extra renal pelvis generally has no effect on kidney function although it may predispose some people to kidney infections (Dolan 2010).

What were the first signs of a 19p13.13 microdeletion?

Most children do not have obvious signs of a 19p13.13 microdeletion when they are born. Parents often noticed there was something different in the first year, although a formal diagnosis may not be made until later (Unique). A delay in developing gross motor skills, particularly with obvious hypotonia, was the most common feature that parents observed (Dolan 2010; Unique).

“ At six months, we started to worry about her, mostly because her motor development was behind. She was not rolling or sitting up at six months ” – subsequently diagnosed at 2½ years old.

“ He wasn’t sitting up until he was 11 months old or rolling over. He was very behind in his milestones in every respect ” – subsequently diagnosed at 5 years old.

In affected individuals, the age of diagnosis ranges from six months to five years old, with an average of approximately two years old (Auvin 2009; Dolan 2010; Nimmakayalu 2013; Unique).

In the medical literature, developmental delay and tall stature or a large head were often the first signs (Auvin 2009; Dolan 2010; Nimmakayalu 2013). Parents had concerns regarding the development of one girl at the age of three months, in particular delays in acquiring gross motor skills and speech. These became more apparent as she grew older. Two children had significant eye problems at a young age (six months and two years old) (Dolan 2010).

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

Children are likely to be behind their peers in some fine motor skills.

Children may need extra support with toilet training.

A delay in using their hands is universal in Unique members and the medical literature (Auvin 2009; Dolan 2010; Nimmakayalu 2013). Occupational therapy and physiotherapy, often from a young age, help although one parent says that progress is slow. At two years old their child’s pincer grasp is not well-developed but is coming along. He tends to throw things instead of purposely placing, for example, a ball into a box, but this skill is improving (Unique) (see ‘Therapy’ page 17). A five year old was struggling with his fine motor skills; he had just started scribbling on paper but was unable to pedal a bike or use a scooter.

“ He finger feeds himself fine and is trying with a spoon although this is messy ” – 6 years

“ She can feed herself most foods. Some foods, like soup, can be a little messy. She can drink from a cup on her own ” – 7 years

Parents sometimes comment on useful aids, such as the iPad.

“ She can navigate a ‘touch screen’ (like an iPad) very well on her own; it helps with hand-eye coordination and her fine motor skills ” – 7 years

Self care may be challenging for some children with a 19p13.13 microdeletion (see ‘Therapy’ page 17) and is directly linked to their fine motor skill ability.

“ She needs moderate help getting dressed, but can undress by herself. She needs moderate assistance bathing and brushing her teeth. She can wash her hands all by herself ” – 6 years

“ He cannot wash himself but does try and clean his teeth with his battery-operated toothbrush although he has to be assisted. He cannot dress himself ” – 6 years

Children are likely to be toilet trained later than their peers. One child was toilet-trained during the day at five years old but still had regular accidents; at six years old she was still wet at night.

“ She is not yet potty-trained. She will occasionally remember to use the toilet but often forgets, or doesn’t notice, so she wears nappies [diapers] at all times ” – 6 years

“ He was toilet trained at four years old but he is still in nappies at night time ” – 6 years

Speech and language

Communication problems are frequently reported; children often have significantly delayed speech development. Some may use little speech and rely on signing. Speech and occupational therapy help.

Children may start talking significantly later than their peers (Auvin 2009; Dolan 2010; Nimmakayalu 2013; Decipher; Unique). One boy was about 2½ years behind; he started talking at four years old and at five was beginning to speak in sentences. A girl was just starting to say words such as 'no' and 'go' purposefully at 3½ years old, with sign language her main means of communication. Speech was very limited at this age but gradually improved. At six years old she was using verbal approximations for some 20 words and knew about 10 signs. Speech therapy in school is ongoing and her speech has improved significantly since starting school.

The medical literature also describes marked and often quite severe speech delay. One child had delayed speech development; by 9½ years old she had a markedly expanded vocabulary (Dolan 2010). Two children were essentially non-verbal, except for a few words, a girl of 11 years old (Nimmakayalu 2013) and a boy of 14½ years old (Dolan 2010).

“ She uses vocal noises to get your attention or show emotions and is able to wave. She's not properly pointing yet but is learning a few signs (more, all done); we are working every day on signing ” – 2 years

“ He uses 3-4 word sentences although these are very babyish. Some words and sounds are extremely clear. Others like 'F' are hard to understand ” – 6 years

“ She says approximately 50 words and will imitate most words. Since starting school and speech therapy she is much more effective at expressing wants and needs. She has a few 2-3 word phrases, like 'got to go' but she mostly uses one word to express herself. She does lots of signs and words together, for example, she will say and sign 'more' at the same time. She does not link signs. She is using words more and more. Signing has been very helpful for Ella. We have not tried any other communication devices because her speech has improved so much since starting school ” – 7 years

Sign language can be learnt from an early age, for example 14 months, and is used by at least four Unique members. A non-verbal adult is using Makaton [signs and symbols which help people communicate] to communicate at 18 years old (Unique). Others have successfully used PECS (picture exchange communication system, a picture-based method) to aid communication. Parents also comment that it helped to support the work done at nursery/school/therapy at home, where possible.

“ He used PECS at his nursery; from 1½ years, he went to a special needs

brain had been pushed downwards towards the spinal cord; it was surgically treated at five years old (Auvin 2009; Dolan 2010).

Three people had a missing or thinned corpus callosum (the structure that connects the right and left sides of the brain) (Nimmakayalu 2013; Dolan 2010; Decipher). This may have a variety of effects including: hypotonia, poor coordination, learning difficulties, delayed toilet training, hearing difficulties and reflux.

■ Heart

Children may have a heart check. One Unique member commented that heart investigations were forthcoming but at 15 months they had not had any evident problems. Four children had normal findings on investigation (Dolan 2010; Unique). One child had a mildly dilated blood vessel (the aortic root) in the heart, which will require close monitoring.

■ Bones

No Unique members have told us that their child had any problem with their bones. One person in the medical literature had an advanced bone age: at 15 months this was equivalent to that of a three year old child (Auvin 2009). Another had severe pectus excavatum, also known as funnel chest. This is a condition in which the breastbone (sternum) is 'sunken' so that, instead of it being level with the ribs, the middle of the chest looks 'caved in'. It can be so mild as to be cosmetic, or so severe that it affects breathing, but if need be can be corrected surgically (Nimmakayalu 2013).

■ Feet and hands

No Unique members comment on any features of the hands and feet. In the medical literature, two children were reported to have long fingers; one also had long toes and some deeper creases on the soles of her feet and one has large hands. Two people have large flat feet (Dolan 2010; Nimmakayalu 2013).

■ Facial features

Children with a 19p13.13 microdeletion do not look markedly different from other children or other family members. Some have slightly unusual features, such as a prominent or large forehead (10/13), low set ears, an upturned nose or almond-shaped eyes (Auvin 2009; Dolan 2010; Nimmakayalu 2013; Unique). Seven children have a large head, with a circumference larger than the 97th percentile (Auvin 2009; Dolan 2010; Nimmakayalu 2013). One child has a relatively high-arched palate and another child has a high palate and a small mouth with crowded teeth (Dolan 2010).

■ Other medical concerns

Other medical concerns are rarely reported, or occur quite commonly in the general population, and may not be related to a 19p13.13 microdeletion. One two year old had hypospadias (Unique). This is a relatively common

children had surgery to correct a squint; in two cases these involved two operations (Dolan 2010; Nimmakayalu 2013). One of these also had an upper lid retraction (upper eye lid is pulled upwards) corrected surgically (Dolan 2010).

Two children have nystagmus (uncontrolled movement of the eyes) (Dolan 2010).

■ Seizures

Seizures occur in about 50 per cent

One Unique child had febrile seizures at 4½ years old but nothing since; she is now 7 years old. A febrile seizure is a fit that occurs when a child has a fever. Five of the seven people in the medical literature are described as having had at least one seizure. One child had a febrile seizure at five years old, while another had a rare type of epilepsy that usually begins with visual hallucinations, rapid eye blinking or other eye-related symptoms (occipital lobe epilepsy) (Nimmakayalu 2013). One child had mild epilepsy, which was diagnosed after several clusters of spasms at about one year of age. He was on medication for two years, and at 4½ years, 18 months after medication was stopped, he was seizure-free (Auvin 2009). Another child developed epilepsy at four years old, also controlled medically (Dolan 2010).

A fifth child had myoclonic jerks. These are sudden, brief, involuntary muscle contractions which may be mild and affect only part of the body, or be strong enough to throw the child abruptly to the floor. They can be a normal phenomenon or suggest a condition that requires medical investigation. This child had a prolonged seizure at the age of nine years but no epilepsy was diagnosed (Dolan 2010).

■ Brain

Brain imaging (MRI – magnetic resonance imaging) may be performed. 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 anomalies relate to a child's development, and they may not affect it at all. All the same, regular screening/ imaging allows any anomalies to be monitored and if need be treated.

One adult Unique member has cerebral atrophy (in which brain cells are lost or the connections between them are damaged) and associated enlarged ventricles (spaces). In the medical literature, one person had a normal MRI scan and two had mildly underdeveloped sections of the optic nerve pathway (see optic nerve hypoplasia under Eyesight on page 13). Another had mild atrophy of the frontal lobes of the brain. These are involved in reasoning, planning, speech, movement, emotions, and problem-solving.

One child had a normal MRI scan at five months but a repeat scan at four years showed a Chiari I formation. This means that the lower parts of the

nursery and they were superb with signing and PECS with him. They even sent me on a course to help him; we did PECS at home as well” – 6 years

Behaviour

Children with a 19p13.13 microdeletion are frequently described as happy, engaging and sociable, although there may be some anxious and/or aggressive behaviour and/or sensory issues.

Anxiety or aggression may be an issue in some children although with the small numbers, many still young, it is unclear how pervasive or long-lasting these may be. Some anxiety may be related to difficulties in communication. The information on behaviour comes from Unique.

“ I find it difficult that I do not understand what he vocalises lots of the time. Sometimes when asked to do something new, once he does it and receives praise, he falls apart and gets so sad and cries. We aren't sure why and so we try not to praise loudly when it's something he hasn't quite mastered” – 2 years

Affected children do not generally appear to have severe behavioural problems. One child was described as having severe behavioural problems at a young age but at five years he was starting to get easier as his mother could now reason with him (Unique). He can however still have outbursts for what seems to be no reason:

“ He is aggressive if he is stressed or doesn't understand. Sometimes I find it hard to understand and don't know why he has these outbursts. If he is hungry, he gets nasty. Aggressive behaviour consists of ripping his clothes, biting his skin and head-banging. It can be hard work and can have a big effect on the whole family but we just get on with it! He is restless when he is not happy where he is” – 6 years.

“ She is more difficult for her mum and dad than other people. She can throw fits for us when things don't go her way. She does not do this at school. Her teacher says she is surprised to hear she gets mad at home because they don't see any sign of that at school” – 7 years

Children with a 19p13.13 microdeletion enjoy a range of activities including: books, watching films, singing, drawing, playing with animal/people figures, Lego^R, swimming and playing outdoors. Play is often sociable, involving their peers or siblings.

“ He loves playing chase with his brother or mummy” – 2 years

“ She is a very social child and loves it a lot when she is clapped and cheered for achieving things” – 2 years

“ He is very sociable...he loves people and just goes up and tries to chat with them” – 6 years

Four of the six Unique members report sensory issues, in two cases an aversion to food textures. Loud noises may also be disturbing.

“ He hates loud noises and fireworks. We just try to calm him down when he starts shaking ” – 6 years

“ She has tactile sensitivity. We used the Wilbarger Brushing protocol (a brushing therapy, used several times a day, to reduce sensory or tactile defensiveness) and it worked very well. She is very anxious on doctors'/ dentists' visits and loud places ” – 7 years

Parents often comment on how easy going and sociable their children are, with both their peers and adults:

“ He is a happy, sweet and smiling boy. He has the happiest smile and is the most easy-going soul on earth. Everyone comments on it; he lights up a room ” – 2 years

“ He is a lovely boy; he is so loving and what he cannot do academically, he makes up for as he is a funny, happy, little boy and everyone who meets him loves him immediately and just to hear his laugh makes me happy ” – 6 years

“ Where to begin...! She is always so happy. She brings so much joy to those around her. Someone once said she has the gift of brightening someone's day with just a smile ” – 7 years

Learning

Learning disabilities occur in children with a 19p13.13 microdeletion. Children are likely to need support with their learning. The amount of support needed varies. Communication difficulties are likely to affect children's ability to learn.

Among the three Unique members who are of school age (and all three are only in an early stage at schooling) some level of learning (intellectual) disability is reported, usually moderate. One seven year old child is in a mainstream school with 20 hours help per week but may move to a special school. Another child has started mainstream kindergarten in school with special support (Unique):

“ She is doing better than expected at school and is learning letters and numbers. She is still behind her peers; however, she is making great progress. She has an IEP [individual education plan]. She has done remarkably well in kindergarten. Half way through the school year she knows the entire alphabet, can count to 10 easily, recognises some words and can write her own name (although it is a little sloppy). She has a learning difficulty but we are not sure of its severity: her great progress in school has us all surprised. She loves music. She seems to have a great memory; school tests show she retains what she learns and does not

regress during breaks. She is a hard worker and is very easy-going and pleasant to work with. She learns best in quiet places and places that are not visually distracting. She has a 1:1 aide with her at all times, which is very helpful. She learns well watching her peers; she imitates them ” – 7 years

“ He is delayed about two years in learning. He has a statement and has been on the SEN [special educational needs] register from 1½ years old. He has a good memory. He's not reading yet but started scribbling at five years old. He's in mainstream school with 25 hours a week 1:1. He likes learning if it is fun and he loves his 1:1. He learns least well when he is hungry ” – 6 years

Learning aids, some computer-based, can help:

“ She writes with a pen/pencil. The iPad has also been helpful with learning letters etc. She seems to pay better attention to the iPad and we have wondered if the backlit screen is easier for her to see and focus on ” – 7 years

Detailed information on learning and schooling is not available in the medical literature although some measurements of intelligence are recorded. 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. Two children had an IQ of 43 and 49, consistent with moderate learning disabilities (Dolan 2010; Nimmakayalu 2013).

Medical concerns

As information on this microdeletion is so new, we do not know yet whether these features are typical or not.

■ Eyesight

Eye problems are common in children with a 19p13.13 microdeletion and children may be wearing glasses from a young age.

Three Unique members have eye problems, two needing glasses. Two have strabismus (a squint) and one has optic nerve hypoplasia. This occurs when the optic nerve (the part of the eye that carries visual information from the eye to the brain) is under-developed or absent. The impact of optic nerve hypoplasia ranges from blindness, with no light perception, to good vision; it may affect one or both eyes. Most children with optic nerve hypoplasia experience some improvement in their vision during their early childhood.

Five of the seven people in the medical literature have eye problems. Three have optic nerve hypoplasia. In one child, this developed between 8-11 years of age (Dolan 2010). Two children had delayed maturation of vision that improved over time. Four children have esotropia, which is a type of squint (strabismus) where one or both eyes turn inwards (Dolan 2010). Four