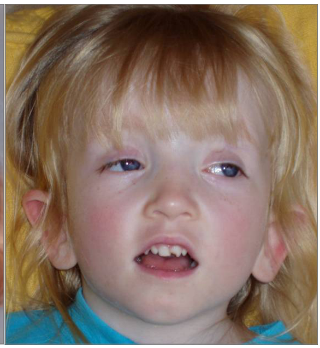
Understanding chromosome disorders

Unique

18p deletions



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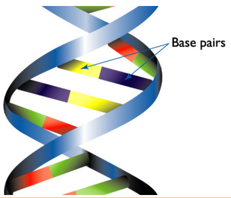
18p deletions

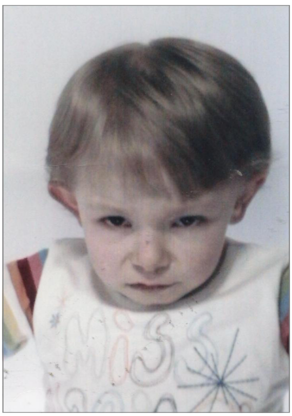
A deletion of 18p means that the cells of the body have a small but variable amount of genetic material missing from one of their 46 chromosomes – chromosome 18.
For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Like most other chromosome disorders, 18p deletions increase the risk of birth defects, developmental delay and learning difficulties. However, the problems vary and depend very much on what genetic material is missing.

Chromosomes are made up mostly of DNA and are the structures in the nucleus of the body's cells that carry genetic information (known as genes), telling the body how to develop, grow and function. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. Chromosomes usually come in pairs, one chromosome from each parent. Of these 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 in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm (shown at the top in the diagram on the facing page) and a long (q) arm (the bottom part of the chromosome). People with an 18p deletion have one intact chromosome 18, but the other is missing a smaller or larger piece from the short arm and this can affect their learning and physical development. Most of the clinical difficulties are probably caused by the presence of only one copy (instead of the usual two) of a number of genes. However, a child's other genes and personality also help to determine future development, needs and achievements.



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

About 1 in 50,000 babies is born with a deletion of 18p. Although there is a great deal of variability between those with an 18p deletion, there are enough similarities to define the loss of part of chromosome 18p as a syndrome, hence the term 18p- syndrome or 18p-. The first case was reported in 1963 and there have since been more than 150 published cases. Most reports suggest that 18p deletions affect girls more often than boys – around 60 per cent of reported cases are girls. Unique families support this: 59 per cent of the children with 18p- are girls. The reasons for this are, as yet, not known (de Grouchy 1963 and for a review see Turleau 2008).



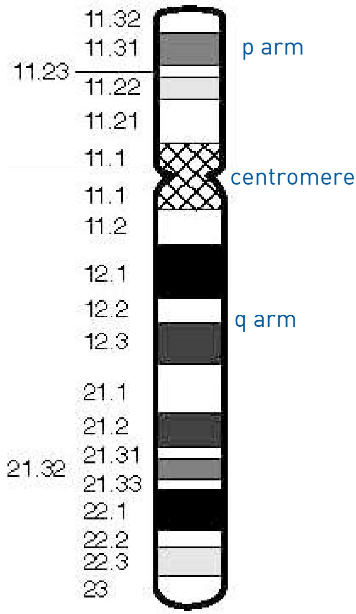
5 years

Looking at 18p

Chromosomes can't be seen with the naked eye but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands. By looking at your child's chromosomes in this way, it is possible to see the point (or points) where the chromosome has broken and to see what material is missing.

In 18p-, part of the short (p) arm of chromosome 18 is missing. All deletions of 18p reported to date are terminal; this means that the tip of the short arm is included in the deletion.

In the diagram of chromosome 18 on the right the bands are numbered outwards starting from where the short and long arms meet (the centromere).
A low number, as in p11.1 in the short arm, is close to the centromere. Regions closer to the centromere are called proximal. A higher number, as in p11.32, is closer to the end of the chromosome. Regions closer to the end of the chromosome are called distal.



Sources

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from a survey of members of Unique conducted in winter 2007/2008, referenced Unique. When this leaflet was written Unique had 51 members with a pure 18p deletion without loss or gain of material from any other chromosome. These members range in age from babies to an adult aged 40.

Many more people, described in the medical literature and members of Unique, have a loss or gain of material from another chromosome arm as well as an 18p deletion, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a 'pure' deletion, they are not considered in this leaflet. Unique holds a list of these cases in the medical literature and the karyotypes of those in Unique; this is available on request.

Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point where the chromosome has broken in your child. You will almost certainly be given a karyotype which is shorthand notation for their chromosome make-up. With an 18p deletion, the results are likely to read something like the following example:

46, XY, del(18)(p11.2)

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(18)	The deletion is from chromosome 18
(p11.2)	The chromosome has one breakpoint in band 18p11.2, and material from this position to the end of the chromosome is missing

In addition to, or instead of a karyotype you may be given the results of molecular analysis such as cytogenetic fluorescent in situ hybridisation (FISH) or microarrays (array -CGH) for your child. In this case the results are likely to read something like the following example:

46,XX.ish del(18)(p11.3)(D18S552-)de novo

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
.ish	The analysis was by FISH (fluorescent *in situ* hybridisation)
del	A deletion, or material is missing
(18)	The deletion is from chromosome 18
(p11.3)	The chromosome has one breakpoint in band 18p11.3, and material from this position to the end of the chromosome is missing.
(D18S552-)	The deleted part of chromosome 18 includes a stretch of DNA termed D18S552
de novo	The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 18p11.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

arr[hg19] 18p11.32p11.21(2,120-15,227,370)x1

arr	The analysis was by array-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
18p11.32p11.21	Chromosome 18 has two breakpoints, one in the band 18p11.32, and one in band 18p11.21
(2,120-15,227,370)	The base pairs between 2,120 and 15,227,370 have been shown to be deleted. Take the first long number from the second and you get 15,225,250 (15.2Mb). 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 18 – as you would normally expect

Are there people with an 18p deletion who are healthy, have no major medical problems or birth defects and have developed normally?

Yes. In a few people, a deletion appears to have only a mild effect. A Unique mother with an 18p deletion has no problems due to the deletion, while her baby who inherited the deletion was severely affected and died. There are also reports in the literature of individuals who are only mildly affected. One reports a 26-year-old woman with borderline learning difficulties who is small (below the 25th centile for height and weight) but has no major medical concerns. Another describes a mother who had two children who also had 18p-. This mother was small and had some of the facial features of 18p- (high palate, misaligned teeth, a small mouth with a receding chin) but was otherwise little affected. A 34-year-old man is described as having normal growth and psychomotor development. He had ptosis (drooping of the upper eyelids) which was surgically corrected as a child; he also has severe tooth decay and clinodactyly of the fifth finger. Developmental testing at age 6 revealed no problems and he attended normal school and lives independently, working in a factory. All of these individuals are thought to have a non-mosaic deletion of 18p, that is, the 18p deletion is present in all the cells. A mosaic deletion of 18p is where the deletion is only present in some, not all, of the cells (Tonk and Krishna 1997, Rigola 2001, Maranda 2006, Unique).

What is the outlook?

The outlook for any baby or child depends on how the deletion has disrupted early development in the womb. The most significant medical concern that can affect lifespan is holoprosencephaly, a brain defect that is sometimes seen in individuals with 18p-. For those not affected in this way, life expectancy is normal and there are many healthy older teenagers and adults with deletions of 18p (see Adults with 18p-).

> “ She leads a relatively normal life and is a happy confident girl with a bright future. ”
> *10½ years*

Growing up with an 18p deletion:

1 year

3 years

6 years

Most likely features

Every person with 18p- is unique and so each person will have different medical and developmental concerns. Additionally, no one person will have all of the features listed in this leaflet. The most common form of the disorder can be non-specific and hence is often not obvious at birth. However, the features of 18p- vary widely and others may be more severely affected. In spite of this, a number of common features have emerged:

- Short stature
- Hypotonia (low muscle tone or floppiness)
- Children may need support with learning. The amount of support needed by each child will vary
- Feeding problems
- Tooth decay
- Ptosis (drooping of the upper eyelids)
- Communication difficulties

Pregnancy

The majority of mothers carrying babies with a deletion of 18p experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. Of the 17 families who participated in the Unique survey and have told us about their pregnancy experiences, three babies showed reduced fetal movement and three were premature, arriving between 33 and 35 weeks. One case of preterm delivery was associated with polyhydramnios (an unusually high volume of amniotic fluid). Polyhydramnios can result in a premature delivery due to overdistension of the uterus (Unique).

One Unique baby had an increased nuchal translucency at the 12 week ultrasound scan. There has also been a published case of 18p- associated with increased nuchal translucency. In this case chorionic villus sampling revealed an 18p deletion and the parents chose not to continue with the pregnancy. There are several other examples in the medical literature of prenatal diagnosis of 18p- by amniocentesis performed for advanced maternal age or after fetal anomalies, such as craniofacial abnormalities, were detected on prenatal ultrasounds. In three cases, the parents chose not to continue with the pregnancy. In the fourth case the pregnancy was continued and a baby boy was born at 39 weeks; unfortunately there is no further information available on the child (Wang 1997, Chen 2001, McGhee 2001, Kim 2004, Unique).

Feeding and Growth

Around four out of five of those with 18p deletions are of short stature, although some children are of average height and very few are extremely short. The majority of birth weights recorded at Unique were within the normal range, with an average of 3.02 kilos (6lb 11oz), suggesting that for most the growth delay does not start in all babies before birth. However, three out of 25 babies reported in the literature had a low birth weight (below 2.6 kilos) at term (Brenck 2006, Unique).

Range of birth weights at Unique (at or near term):

1.5 kilos (3lb 5oz) to 4.082 kilos (9lb)

After birth, babies tend to grow more slowly than their peers, with a small minority of babies described as "failure to thrive". This term is used to describe a baby who has poor weight gain and physical growth failure over a period of time. Feeding problems in babies can also be a problem. The hypotonia that is common in babies with 18p- can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a high palate can also find the action of sucking and swallowing difficult. Ten of the 17 mothers surveyed by Unique breastfed their babies. A few had difficulties and moved to bottle feeding after a few weeks but many had no trouble at all and breastfed their babies up until weaning onto solid foods. Two of the 17 babies surveyed by Unique benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat) and one had a gastrostomy tube placed (a G-tube, feeding direct into the stomach). The floppiness can also affect their food passage and contribute to gastro-oesophageal reflux (in which feeds return readily up the food passage). In the Unique survey, around 20 per cent of babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head end of the bed for sleeping. If these measures are not enough, feed thickeners and prescribed medicines to inhibit gastric acid may control reflux but some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Unique).

Many children are described as picky or slow eaters. Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems (Unique).

" He is a very picky eater; any new foods can cause severe diarrhoea. " *5 years*

" All food has to be blended. Even now! " *6 years*

" He now eats perfectly. " *7 years*

" He breastfed on demand with no problems. " *now 9 years*

" He was fine with liquid feeds (he was breastfed until 6 months) and fine with first soft foods, but found food that needed chewing difficult to swallow and would regurgitate it. " *now 17 years*

Some people with 18p- and short stature have been found to have growth hormone deficiency which may warrant growth hormone treatment to help normalise growth. Almost 20 per cent of Unique children have a deficiency of growth hormone and a number have, or had in the past, growth hormone treatment with generally positive experiences (Artman 1992, Unique).

" She was very small for her age, particularly in the first seven years. She has poor muscle tone in her stomach so she has a very pronounced 'pot belly'. She wears age 7 -8 years clothes. " *10½ years*

Learning

Learning difficulties are common in children with 18p-. Most children have mild to moderate learning difficulties. However, a few children have no problems at all while a small minority have severe or profound learning disabilities and intellectual disabilities. The evidence from Unique reflects this variability. Around half of Unique children attend a special educational needs school. The remainder go to mainstream schools, some having 1:1 help in the classroom or the benefits of a special needs unit attached to the school (Unique).

Many, but not all, Unique children have mastered reading to some degree: some can recognise their name and some basic words; others love to read. Writing and drawing has also been achieved by the majority of children. The hypotonia and problems with fine motor skills can make writing difficult and many children find using a keyboard to write easier than a pencil or pen (Unique).

“ The developmental psychologist at her 2-year assessment estimated that she is at least at her own age-level. ” *2 years*

“ Although he cannot speak he can spell out 50+ words; knows his numbers up to 100 and above and can add simple numbers. ” *5 years*

“ He can recognise his name, Mummy, Daddy and other names. He can recognise and count to 20 and attempts the alphabet but cannot read a simple book. ” *6 years*

“ She's always been a bright little button and has no learning difficulties aside from speech problems. Her memory is absolutely brilliant. ” *6½ years*

“ He can write his first and last name and the names of some friends and family. He can draw people and animals, although they are not always recognisable! ” *9 years*

“ She has a borderline learning disability and learned to read at 5 years and is now reading Oxford Tree Reading scheme level 10. ” *10½ years*

“ He is good at reading, spelling, science and maths. He is very good on a computer. He loves reading factual books. ” *11 years*

“ She is better with numbers than written English. She reads children's books and has a reading age of 8-10 years. Even at 30 she still enjoys learning! ” *30 years*

This level of achievement will not be possible for all. A number of adults known to Unique do not read or write. There is variability in other skills as well. Many children, but not all, have an excellent memory and are good at retaining information.

Many children have a reasonable attention span, whereas others have poor concentration and struggle to stay focused. For many children a lot of encouragement, praise, repetition and well-ordered routines are helpful for the learning process.

Many parents report that it is important to make learning fun, visual and interactive. Most children seem to flourish when in a calm environment, in small groups and with 1:1 help (Unique).

“ He is not reading yet but can match letters and numbers. He will attempt to draw circles and straight lines if encouraged. ” *6½ years*

“ He does not read yet but likes to draw buildings. ” *17 years*

Speech and communication

Speech appears to be more affected than non-verbal skills in children with 18p- and language skills may be delayed. Unique has seen that most children begin speaking between 15 months and 4 years old, with most mastering speech around the age of 3 years. Some have speech and language that is completely fluent and age-appropriate. However, for others mastering clear speech and multiple syllables is a challenge.

A number of children known to Unique have age-appropriate comprehension but speech that lags behind their peers. Commonly, receptive language is markedly better than expressive language skills - many children understand far more than they are able to express. A picture exchange communication system (PECs) and/or sign language can help children communicate their needs. Many Unique children utilise these methods and make good, steady progress. For some, as speech develops they find they no longer have any need for sign language. A number of children have difficulties making particular sounds of speech. Speech therapy can be enormously beneficial, enabling some children whose speech is initially delayed to master clear speech with good vocabulary and sentences. However, a small minority of children do not talk (Wester 2006, Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which as well as causing insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with certain sounds (Unique).

“ He has a few words (5-20), points, gestures, babbles and will pat a chair if he wants to sit down. He communicates well. He is not that consistent with sounds but the glue ear doesn’t help. He’s average but mother’s instinct tells me we may have a few challenges and will need to give him extra help. ” *16 months*

“ She uses over 50 signs. She can sign 2-3 word phrases, like ‘Mummy eats bread’. ” *2 years*

“ He makes sounds but has no speech. He uses PECs, ASL or writes what he wants. ” *5 years*

“ He communicates mainly with speech, which although not brilliant is improving all the time. For a while he would learn a new word, we would hear it all the time for a week and then we’d never hear it again – it was almost as if he didn’t retain it. Now, thankfully, he does remember words and can form sentences up to about 6 words. Sometimes his words are crystal clear, other times he is very hard to understand. He has developed ways of being understood by gesturing; he has some signing and by showing us what he wants. One of our biggest issues is that he gets very frustrated if he is not understood and trying to keep him calm is important. ” *6 years*

“ Speech has now largely taken over from signing, though she still uses signs to reinforce the odd phrase. She uses cued articulation gestures to help remind herself how to pronounce sounds correctly. Her receptive language is way ahead of speech – it is in the normal range, whereas speech is delayed by around 2-3 years. ” *6½ years*

“ He uses gestures and a few single words to make his needs known. He understands a lot more than he expresses and will readily follow instructions or answer ‘yes’ or ‘no’ to a question. ” *6½ years*

“ She talks well but with reduced clarity. ” *8 years*

“ He has speech but his sounds are poor. He cannot make a ‘g’ sound and forgets to use the end sounds of words. His speech deteriorates when he’s upset. ” 9 years

“ Speech and language are her main problem, but she has made very good progress. ” *10½ years*

“ He learnt sign language at 3 years old. It was the best thing we ever did! He had very few words at age 3 and made very slow progress until 7 years. He talks in sentences now and never shuts up! It’s brilliant! He finds it very difficult to make consonant sounds: he really has to think hard in order to make the right mouth shape and when closing his lips together. ” *11 years*

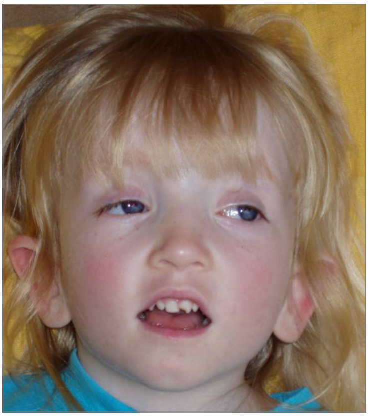
“ She has no formal communication skills – no speech or signing. She vocalises and intonates well and uses smiles and cries to express happiness, displeasure or pain. She has quite expressive facial gestures. ” *18 years*

“ She was slow to develop spoken language, but now OK. Her comprehension has always been better than her speech. Even as an adult she can still struggle to make herself understood if she is stressed. ” *30 years*

Facial appearance

In addition to short stature, children with 18p- sometimes have facial features in common. They may have a short neck and a round face. The nasal bridge can be flat and broad. They may have drooping eyelids (ptosis), their eyes may be set unusually far apart (hypertelorism) or there may be an extra fold of skin covering the inner corner of the eye (epicanthal folds). The ears may be set lower than usual, be large and protruding or look slightly different from a typical ear. Their chin or lower jaw may be small and slightly receding.

The corners of the mouth are often down-turned. Sometimes the hair line at the back of the neck can be particularly low. These facial features are often not at all obvious at birth but may become more apparent as toddlers enter childhood (around the age of 3 years).



2½ years

However, many children look little different to other children and closely resemble their siblings or parents (Unique).

“ His head size is a little bigger than others; eyes are more droopy and he is a mouth breather so his mouth is open a lot! But he is SO beautiful! ” *5 years*

Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Hypotonia can affect fine motor skills in children with 18p- and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and having food cut up have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard can often be easier. Many children have occupational therapy in order to improve these skills. Threading, jigsaws, dot-to-dot pictures, peg boards and shape-sorters can all be helpful (Unique).

As a result of these difficulties, children may continue to need help with dressing and undressing. They may also require assistance in tasks such as brushing teeth and washing. Nonetheless, some older children and adults achieve at least a reasonable independence in self-care. Toilet training may also be delayed in some children. Data from Unique suggests that although a minority of children achieve bladder and bowel control at the usual age, many take a little longer. The range of ages for toilet training is between 15 months and 7 years. For a small minority, control may not be consistently or ever possible (Unique).

“ He needs help in all aspects of personal care although this is improving and he tries to do more things for himself. He can undress himself so long as there are no buttons and he manages his clothes when he goes to the toilet. In the last two weeks he's managed to get one sock on a couple of times. He attempts to brush his teeth but really just wants to suck the toothpaste! ” *6 years*

“ She can put on knickers and trousers and will have a go at socks (but needs help); she can't manage the feet of tights or pull tights up very well by herself; can pull vests and loose tops over her head but can't manage front-opening blouses, cardigans or coats alone; can undo, but not do up buttons and zips. Needs quite a lot of help but it has to be offered tactfully as she wants to do everything for herself. ” *6½ years*

“ Her handwriting is delayed compared to her reading skills. ” *8½ years*

“ She has poor fine motor skills and still has problems with buttons, scissors etc. ” *10½ years*

“ He was delayed in holding a bottle and has still not managed to use a knife to cut up food. He is very good now with a fork and spoon. ” *11 years*

“ He was unable to use a knife and fork until about 9 years. He still has problems cutting food. He has to use an electric shaver and toothbrush due to his poor dexterity. ” *17 years*

“ She has small weak hands which can make opening bottles/jars a problem. Also struggles to use a knife to cut 'hard' foods. No help needed with her personal care. ” *30 years*

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


9 years

Often gross motor skills are in the normal range and some children have no problems at all with mobility and gross motor skills. However, many children with 18p- show slowness in action and motion. For others the hypotonia that is a common feature of 18p- means that it may take a little longer for them to roll over, sit, crawl and walk. From Unique's experience, most children sat unaided between the ages of four months and two and a half years, with an average of around ten months. Walking was mastered by most between nine months and five and a half years, at an average age of two years. Not all babies crawled: some shuffled on their bottoms. Balance and co-ordination problems affect some children. Nonetheless most children learn to run, skip and jump. Swimming is particularly popular. Other activities that children enjoy include horse-riding, gymnastics, dance classes, trampolining and riding bikes and scooters. However, some children will need considerable support while learning to walk but eventually most walk independently, although this is not possible for all (Wester 2006, Unique).

“ He was slow to reach all his milestones, but now manages everything normally. He enjoys swimming and while he'll never make the Olympics, he's come on brilliantly in the last year and a half. He can spend hours jumping on the trampoline and adores playing chasing games with his sister and friends. ” *6 years*

“ She could not roll unaided until nearly a year, didn't sit unaided until over a year, didn't walk without support until 2½ years. She never crawled – her arms and shoulders weren't strong enough to support the weight of her body and especially her head. Instead, once she learnt to sit up, she bottom-shuffled with her left leg stuck out in front, using her right leg to hook herself along. Later, she had a little ride-on car that she used to scoot herself about. She now goes horse-riding and would happily stay there all day if she could! She enjoys riding her bike (with stabilisers) and her three-wheeler scooter. ” *6½ years*

“ She walks like a toddler would and cannot walk far. She can climb stairs with help, but cannot climb down (even with help). ” *6½ years*

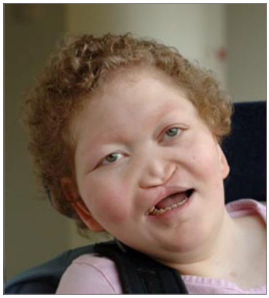
“ He is able to walk, run and jump. His balance is not great due to core stability and pelvic weakness. He gets tired easily. He is unable to ride a bike without stabilisers and finds riding a tricycle hard work. He is able to climb stairs one foot per step using the handrail. ” *9 years*

“ He walks well although he is slow on uneven surfaces. He has a rather ungainly running style. ” *11 years*

“ He moves around in a normal manner. He tires more easily and tends to slouch at his desk and lean on things. He sometimes uses a special seat at school. ” *11 years*

Medical concerns

Brain



17 years

A handful of people with 18p- (around 10 per cent) have brain malformations as part of the holoprosencephaly (HPE) spectrum. This is a developmental defect that occurs when the brain and face are forming. The forebrain (the front section of the brain) does not grow forward and divide into two separate halves (hemispheres) as it is supposed to do. There is a wide range in severity. In some babies, the forebrain fails to divide at all, resulting in a single frontal brain mass (whole prosencephalon). This form (alobar) is so severe that these babies do not survive in the womb or they may die shortly after birth. In less severe cases (semi-lobar or lobar), the brain has divided but there may be some fused structures. HPE can also result in changes in midline facial features that may affect the eyes, nose and upper lip. These can include a cleft lip and palate, hypotelorism (eyes that are unusually close together), a flat nasal bridge or a single central incisor (upper front tooth) located in the midline of the mouth. In more severe cases which are not usually compatible with life there may be a single central eye (cyclopia). HPE may result in a number of different health concerns, including developmental delay, learning disabilities and, less frequently, seizures. One of those who took part in the Unique survey has HPE accompanied by seizures. Neurological problems that are unrelated to holoprosencephaly are frequently seen in 18p-. A Unique child, who does not have a diagnosis of HPE, has low myelination. Myelin is the substance that covers nerve cells (much like the plastic coating covering the wire in an electric cable). Myelination, the formation of myelin, is an ongoing process that starts in the womb and continues after birth and into middle age (Overhauser 1995, Taine 1997, Kantaputra 2006, Portnoi 2007, Unique).

A recent study showed that 24 of 54 people with a 18p deletion had white matter abnormalities. Besides a delay in myelinisation these included other white matter abnormalities like an ususual signal on the MRI and features occuring after lack of oxygen of the brain (Hasi-Zogaj 2015). It is important all children with a 18p deletion have an MRI scan of the brain.

Teeth

In general, children with chromosome disorders appear to have more dental problems than others. Some children have a single central incisor, associated with the HPE that can be part of 18p-. In addition, there are many reports in the medical literature of teeth that are often of poor quality resulting in cavities or tooth decay. However, one study on tooth decay in those with 18p- suggested that the risk of dental caries is about the same as those without an 18p deletion.

Nonetheless, the Unique survey revealed that around one in three children have one or more teeth missing; almost half have teeth that are irregular and misaligned and 20 per cent are described as having excessive cavities. One child's upper front-left incisor delaminated at 15 months. She had fluoride paste applied to help strengthen the broken surfaces and no further action was required. A number of children's permanent (adult) teeth arrived before losing the deciduous (baby) teeth. Due to all of these issues, regular and high quality dental care is important (Hermesch 2000, Brenck 2007, Naudi 2007, Unique).

Eyelids and vision

Vision problems are common in 18p-, with around 80 per cent of Unique children surveyed affected in one way or another. The most common feature was a squint (strabismus) affecting almost half of children. Another common problem is long sight which affects around a third of all children. Short sight has also been reported. Both long and short sight can be corrected with glasses (Unique).

A number of children have an inability to open the eyelids fully (ptosis). Both eyes are often affected and this is evident at birth and does not develop later. This can cause problems with vision with the eyelid covering the eye and reducing vision.
If necessary, ptosis can be corrected by a surgical procedure. Several children known to Unique have undergone surgical correction for ptosis, all with positive outcomes.
One girl has double elevator palsy: her eyeballs cannot roll upwards (Turleau 2008, Unique).
Also a number of children with this deletion has congenital cataract. In a recent study it was present in 5 out of 90 people. Six percent may have hypoplasia of the optic nerve (Hasi-Zogaj 2015). It is important children with a 18p deletion frequently have an eye examination.

Ears

Babies and children with 18p– may have more frequent ear infections than other children. These can sometimes lead to a build up of fluid in the middle ear, called glue ear, which affected forty per cent of those surveyed by Unique. Glue ear usually resolves as children get older and the ear tubes widen and become more vertical resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum (Unique).
A recent study showed that 7 in 83 people had sensorineural hearing loss (Hasi-Zojag 2015). It is recommended to frequently check the hearing of a child with a 18p deletion.

15 years

Feet

The feet of babies with 18p- are sometimes not perfectly formed. Almost half of those who took part in the Unique survey had some sort of foot anomaly. Feet may be small, with overlapping toes or a wide gap between the 1st and 2nd toe. A small minority of babies are born with club foot (talipes equinovarus) where the foot is at an unusual angle. Other children have flat feet. Some children will need special, supportive special footwear or, more rarely, surgery and the difficulties may delay the age at which children learn to walk (Unique).

Hands

Hands can also be affected in children with 18p-. Many of these features are not specific to babies or children with an 18p deletion but are also found in other chromosome disorders. Fingers may be short and tapering, sometimes with an incurving 5th finger (clinodactyly). Hands may be wide and short. In general, the hand anomalies do not greatly affect the function of the hands, although they can lead to problems with fine motor skills (Maranda 2006, Unique).

Skeleton

Various skeletal problems can occur in those people with 18p-. Some people develop curvature of the spine (scoliosis). Two of those who took part in the Unique survey had spinal problems. One had kyphosis and wore a back brace for support. The second developed severe scoliosis which necessitated surgery. Dislocation of the hip can occur and is reported to affect 10 per cent of individuals. Two of those who took part in the Unique survey had a hip dislocation. One was born with a congenital hip dislocation (dysplasia). The other had an acquired hip dislocation at age 6 due to persistent 'windsweeping', where both legs are positioned to one side (Urban 1987, Kantaputra 2006, Unique).

Breathing

Breathing problems can be a feature of 18p-. Around 20 per cent of those who took part in the Unique survey suffer from asthma, often only mildly and frequently improving as children grow up. One child had obstructive sleep apnoea (pauses in breathing) which resolved after removal of tonsils and adenoids. Another suffers from occasional obstructive apnoea when she has a bad cold. Parents report that a number of children snore noisily when asleep. One toddler has recurrent respiratory distress when he gets a cold or an infection. He uses an inhaler and has on occasion needed hospital administration of steroids and a nebuliser (Unique).

Infections

Some children with 18p- have decreased resistance to infections. One explanation for this is that low levels of an infection-fighting antibody, IgA (immunoglobulin A), are found in some people with 18p-. IgA plays an important role in defending the body against infection that invades the body through the mucous membranes, such as the nose, eyes, lungs and intestines. Therefore, people with low IgA are more susceptible to infections and colds. Almost 20 per cent of children who took part in the Unique survey have been diagnosed as having low IgA. In most cases, this is managed by treating infections promptly (Gul 1994, Unique).

Thyroid

Thyroid problems can affect people with 18p-. The thyroid hormones regulate a number of functions in the body, including how fast your heart beats and how quickly you burn calories. Thyroid problems can arise at any time in life, so many people will have regular thyroid screening. Around 10 per cent of those in Unique have an underactive thyroid (hypothyroidism) which can be treated by taking a thyroid hormone supplement, thyroxine. One girl had an overactive thyroid (hyperthyroidism) which became so serious she had her thyroid removed (thyroidectomy) and now takes daily thyroxine (Dharmaraj 2006, Unique).

Heart problems

Heart conditions are relatively uncommon, having been observed in around 10 per cent of babies with 18p-. Several different types of heart defects have been diagnosed in babies with 18p-, with no one defect appearing to be particularly associated with 18p-. One Unique girl has very mild tricuspid regurgitation which involves the backward flow of blood across the tricuspid valve which separates the right ventricle (lower heart chamber) from the right atrium (upper heart chamber). Another Unique girl has patent foramen ovale (PFO), where the opening between the two upper chambers of the heart that is open during pregnancy does not close soon after birth as expected. Although she does not experience any symptoms due to the PFO, the defect is due to be surgically corrected when she reaches two years. The most common heart defect reported in the literature is patent ductus arteriosus (PDA) where the ductus arteriosus (channel between the aorta and the pulmonary artery that takes blood to the lungs during pregnancy) fails to close. It is important all children are examined by a paediatric cardiologist (Digilio 2000, Xie 2008, Unique).

Seizures

Seizures have been reported in a small number of children with 18p-. Children with HPE are more likely to have seizures. Only one of those who took part in the Unique survey was affected by seizures; this child also had holoprosencephaly (see Brain).
Two of those who took part had a single febrile convulsion (a seizure brought on by a high temperature), in both cases before the age of three years (Grosso 2005, Unique).
A report showed that 6 out of 90 people had epilepsy. Three had grand mal attacks, two absences and one partial complex seizures. The epilepsy started at a mean age of 11 years (Hasi-Zogaj 2015).

Palate

Cleft lip and palate (the roof of the mouth) have been reported to be relatively common in babies with 18p-. Sometimes the palate does not form correctly during development. This results in an opening in the roof of the mouth. A cleft lip occurs when the tissue that forms the upper lip does not fuse during prenatal development. Only one baby out of the 17 who participated in the Unique survey was born with a cleft palate.
More common was a high arched palate, which was seen in around 20 per cent of surveyed children. Both cleft and high palates can contribute to the early feeding difficulties seen in children, A high palate can make latching on and sucking more difficult and a breastfeeding counsellor or, if bottle-fed, a variable-flow teat can help. Palate anomalies may also make speech and making the sounds of speech more difficult (Unique).

Minor genital abnormalities

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. These include cryptorchidism (undescended testes) or hypospadias, where the hole usually sited at the end of the penis is on the underside instead. In some cases, surgery may be needed to correct these concerns.
Micropenis (a small penis) has also been described and one boy is described as having a tight foreskin which may need an operation in the future (Unique).

The genitalia are usually less often affected in girls and in this group there is only one report of a minor anomaly: enlarged labia majora which did not need treatment (Unique).

Tonsils

The Unique survey revealed that a number of children (around 30 per cent) have unusually large tonsils. In most, but not all, cases this has necessitated their removal. For one child the enlarged tonsils were obstructing her airway and so were removed (Unique).

Digestion

Babies and children with 18p- may have some problems with digestion.

One problem is chronic constipation. Other children suffer from diarrhoea or frequent loose bowels. Many children have had stool and blood tests and even colonoscopies in an attempt to discover the cause but most of those known to Unique have not been able to obtain any conclusive results and the cause remains unknown. Dietary changes and/or medication can help to manage the problem (Unique).

Other concerns

Juvenile arthritis affects two of the 17 who took part in the Unique and has also been reported in the medical literature. Commonly it is the hands that are affected; more rarely it affects the elbows and/or knees (Finley 1972, Horsley 1998, Unique). Absence of the PTPN2 gene may play a role in the development of juvenile arthritis. Changes in the gene have previously been linked to other autoimmune diseases such as bowel diseases. But these have not been reported in people with this deletion until now. However, diabetes and for example thyroid problems have been described (Hasi-Zagoj 2015).

5 years

A number of hair problems have been reported in the medical literature, including hypotrichosis simplex (sparse hair), alopecia totalis (total baldness) or alopecia areata (patches of hair loss anywhere on the body), although none are known to have affected any of those known to Unique (Uchida 1965, Kantaputra 2006, Unique).

Children and adults with 18p- often have a broad chest with widely spaced nipples. Pectus excavatum (a sunken or funnel chest) has also been reported and affects one child known to Unique. Pectus excavatum is usually considered cosmetic, however it can affect cardiac and respiratory function, and cause pain in the chest and back. In severe cases it can be corrected surgically. One of those that participated in the Unique survey had Harrison's sulcus (an indentation of the chest) as an infant, which affected her respiratory function, but with age she outgrew the problem (Horsley 1998, Unique).

Dystonia is a movement disorder caused by involuntary contraction of muscles and has been reported in a small number of people with 18p-. It is characterised by involuntary twisting or repetitive movements; because the muscles cannot relax, people with dystonia may have changes in their posture. It may start at a young age and/or present later on in life but most commonly starts in late childhood or adolescence. However, none of those known to Unique are affected in this way, although one girl is described as having ataxic-like (uncontrolled muscle) movements and apparent involuntary contractions (Klein 1999, Nasir 2006, Unique).

The ataxia is probably caused by absence of the AFG3L2-gene. Changes in this gene may result in spinocerebellar ataxia type 28. This condition is characterised by progressive ataxia starting in early adolescence. Other features are speech difficulty (dysarthria),

hyperreflexia and eye problems like nystagmus and ptosis (Hasi-Zagoi 2015).
The medical literature reports that absence of the SMCHD1-gene results in an increased risk of facioscapulohumeral muscular dystrophy. Symptoms of this muscle disease are mostly diminishing muscle strength and ultimately its loss. It starts with the muscles in the face, shoulders and upper arms, followed by the muscles of the abdomen and legs. The order in which muscles are affected may be different. According to the authors of the article, absence of this gene would cause the disease in 1 in 8 persons with a 18p deletion (Lemmers 2015). But in another study none of 21 persons with this deletion had facioscapulohumeral muscular dystrophy. But they may have been too young to show it (Hasi-Zajog 2015).

Behaviour

There is little information in the medical literature but information at Unique suggests that children and adults with 18p- are frequently placid, affectionate and sociable. However, behavioural issues can occur. These include temper tantrums and aggressive behaviours such as biting, pinching and scratching (directed both at themselves and others).

Some may not show challenging behaviour but may be sensitive and shy and have trouble making friends. Conversely, a number of children and adults demonstrate inappropriate friendliness to strangers. There are also reports of emotional immaturity. Some, however, are sociable, happy and have many friends. Parents often remark on their child's caring nature and willingness to help and good sense of humour (Wester 2006, Unique).

A number of children are restless with boundless energy. They may lose attention easily and can find concentrating on tasks difficult. Sleep problems are not uncommon and a number take melatonin (Unique).

Two of the 17 surveyed by Unique have been diagnosed with autism or an autistic spectrum disorder. One boy with autism has extreme fears of everyday things such as the toilet and animals which can make his behaviour especially challenging. Another child, diagnosed with autistic spectrum disorder at the age of 22 months, still struggles to interact with other children but has become an easier child now he has reached the age of 5½ years (Unique).

In one study, 8 out of 21 children with a 18p deletion near the centromere (area on the chromosome where the p arm and q arm meet, also called 'proximal') may have autism. So maybe 19-38% could develop autism (Hasi-Zagoj 2015).

❝ He is a happy, feisty, gorgeous little charmer who takes every infection without much complaint. ❞ *16 months*

❝ She is like any other 2-year-old girl happy and playful. ❞

❝ She bites herself and pulls her hair out. She can break out into screams and tantrums for no reason at all and then she can laugh in the next minute. ❞ *6 years*

❝ His behaviour is of major concern to us mainly due to issues of restlessness and not listening to us or doing what we ask. He has masses of energy and likes to be on the go and sometimes this is difficult to deal with. He has beautiful manners with minimal prompting and can be very affectionate. ❞ *6 years*

❝ It can be difficult to get him to concentrate as he is easily distracted and likes to be physically active. ❞ *6½ years*

“ She is very sociable and funny! She can be hesitant in new situations and gets scared easily (for example films or TV). She is an incredibly caring girl and is desperate to please! ” *8 years*

“ He is liked by everyone who meets him. He is very funny and can be loving when he wants to be. Toby doesn’t need much sleep and will get up early or be difficult to settle. ” *9 years*

“ She has determination to achieve the things she wants to. She is our angel. ” *10½ years*

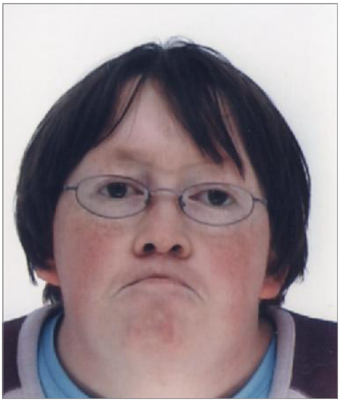
“ He has a lovely nature and is very loving and usually well-behaved. However, if something isn’t right, it is the end of the world and he will shout and cry and get really anxious until the problem is solved. This could be something really simple like losing his hat! As he gets older it is getting a bit easier to reason with him. ” *11 years*

“ She needs to stick to her routines. She tends to be very slow in all she does and screams and stamps her feet when we try and hurry her up. She is well-behaved and well -liked at school and has a good sense of humour. ” *11½ years*

“ He is always patient and empathetic towards others. He is a joy to be with! ” *17 years*

“ She loves other people – she is very sociable – and has her distinct favourite adults and peers. She loves music of any kind and loves being taken out and about and going into shops and supermarkets where there’s lots of colour, variety and activity.
She loves a good gossip and will join in conversations with her intonations and vocalisations! ” *18 years*

“ Her behaviour can be challenging. Over the years we have realised that aggressive behaviour is usually due to some underlying unhappiness she is unable or unwilling to discuss; often she wants to give up a particular activity but does not say this. ” *30 years*



29 years

Puberty and Fertility

From the limited information that is available, puberty generally appears to occur at the normal time and to proceed as expected. An 18-year old girl, however, with HPE and pituitary (a gland involved in the control and production of many hormones) dysfunction, has not fully reached puberty – she has no breast development, no evidence of menstruation and scant under-arm and pubic hair. A recent study using an MRI scan showed that 6 out of 53 persons had problems in the development of the thyroid. This caused dysfunction of the thyroid (Hasi-Zagoj 2015).
In another girl, puberty at the age of 12 years was accompanied by weight gain and mood swings. She now takes a daily dose of a combined oral contraceptive pill in order to regulate her mood swings (Unique).

Transmission of an 18p deletion from mothers to their child(ren) has been reported in at least seven cases. Therefore affected women clearly can be fertile and should be offered genetic counselling. Two Unique mothers have passed on a deletion of 18p to their children. However, to date there are no reports, in the literature or known to Unique, of paternal transmission of an 18p deletion (Uchida 1965, Velagaleti 1996, Tonk and Krishna 1997, Rigola 2001, Tsukahara 2001, Maranda 2006, Portnoi 2007, Unique).

Adults with an 18p deletion

Except for those with severe brain problems, life expectancy is normal and Unique has a number of adult members. A small number of adults have also been reported in the published medical literature, one of whom is a mother with two daughters also carrying the 18p deletion. The mother has moderate learning difficulties but leads an active and independent life. One of her daughters also has moderate learning difficulties, whereas the second has mild or borderline learning difficulties. Two adult males of 42 and 62 years of age are also described in the medical literature. The 42-year-old man is in good physical shape. His short neck has become more obvious and he has extensive dental caries. He has mild kyphosis and pectus excavatum and has hypothyroidism. He is described as being a happy, charming person who copes well with most basic daily activities although his behaviour can sometimes be aggressive. The 62-year-old man has developed Parkinson-type signs, although this may be unrelated to 18p- since this is the only reported case (de Ravel 2005, Maranda 2006).

Unique has eight members over the age of 18 years. One cannot cook for herself but can make a cup of tea or coffee. She attends a day centre three days per week. Another graduated from high school, has a driving licence and he drives 10 miles to his work in a workshop every day. One 30-year-old woman lives independently with a small amount of support from social services. She manages her own finances (with a little help from her mother), and shops and travels by bus alone. She lives an active life with drama, art, keep fit and lunch clubs every week as well as doing voluntary work for the Red Cross (Unique).

“ I am very proud of her independence. ” *mother of a 30-year-old*

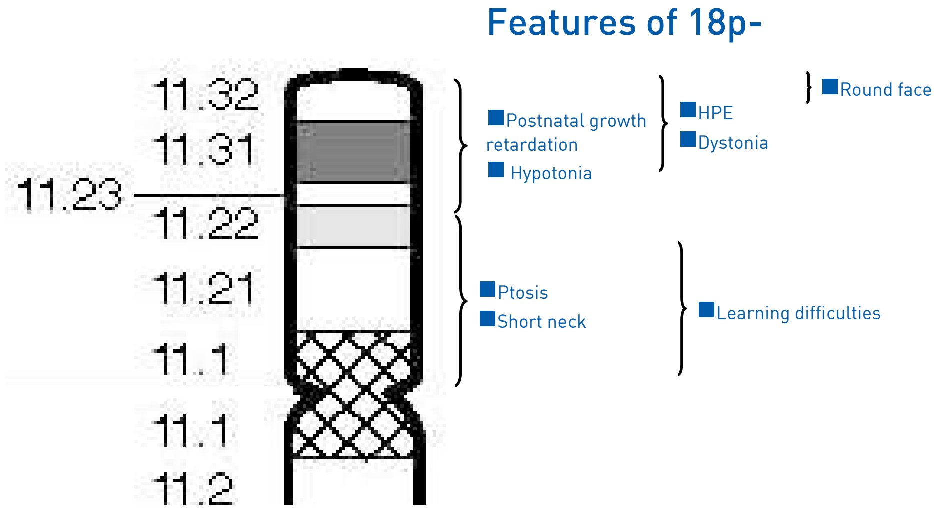
Potential genes involved in 18p-

Chromosome 18 represents about 2.5 per cent of the total DNA in cells and has been estimated to contain between 300 and 500 genes, around 100 of which are located on 18p (the rest are located on 18q). The features of 18p- are likely to be a result of the loss of a number of different genes.

One study has identified a preferential breakpoint or “hotspot” on 18p. This hotspot is located close to the centromere and within region 18p11.1. In this study 72 per cent of the 25 individuals assessed had breakpoints within this band. Data from Unique do not appear to corroborate this: only 44 per cent of those with known breakpoints (35 individuals) had a break in 18p11.1 (Schaub 2002, Unique).

Determining the exact size of the deletion is necessary for identifying critical regions and candidate genes that may contribute to the features of 18p- syndrome and, with the increasing use of molecular techniques such as array-CGH, SNP array and FISH, the deleted region will be more accurately defined and will lead to a more accurate delineation of 18p- syndrome. Indeed, a number of recent studies have attempted to correlate the clinical features in people with 18p- with the part of the chromosome they have missing in order to define a critical region of 18p that is responsible for the features of 18p- syndrome, and to help to narrow down the genes responsible.

Correlation between the breakpoints and the degree of learning difficulties suggests a critical region between p11.1 and p11.21, since three patients with a deletion distal to this point have normal intelligence or only very mild learning difficulties. Mapping of other 18p- traits has also been attempted. The round face seen in some children has been mapped to the distal region of 18p. Post-natal growth retardation and seizures have also been attributed to the distal half of 18p. Ptosis and short neck have been mapped to the proximal half of 18p (Wester 2006, Brenk 2007, Portnoi 2007).



A critical region for holoprosencephaly (HPE) has been defined in the most distal segment of 18p. Mutations in *TGIF* gene located on 18p11.31 have been shown to cause holoprosencephaly. However since not all of those with deletions of this region of 18p have features of holoprosencephaly, other genetic and/or environmental factors must play a role (Overhauser 1995, Gripp 2000).

The dystonia that affects a handful of those with 18p- syndrome has been mapped to the region which harbours the gene *DYT7* (Klein 1999).

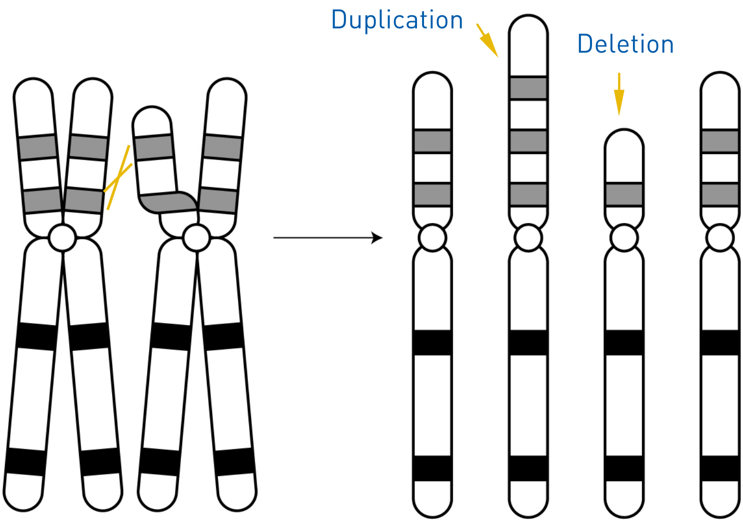
While identifying the responsible gene(s) is interesting, it does not lead directly to improved treatment. Additionally, even if the supposedly responsible gene is missing it does not mean that the feature will necessarily be present. Other genetic and environmental factors may have a role in determining the presence or absence of a particular feature.

Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 18p deletion occurred. In 85-89 per cent of published cases the 18p deletions occur when both parents have normal chromosomes (Hasi-Zagoj 2015). The term that geneticists use for this is *de novo* (dn). *De novo* 18p deletions are thought to be caused by a change that occurred when the parents' sperm or egg cells were formed or shortly after fertilisation.

A study which included 56 persons with a de novo deletion showed that in 25 persons the deletion occurred in the chromosome inherited from father (Hasi-Zagoj 2015).

Some 18p deletions are accompanied by a gain of material from another chromosome and are the result of a rearrangement in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation, in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers. Whether the deletion is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 18p deletion and nothing you could have done would have prevented it occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. It is no-one's fault.



One way that a deletion and a duplication could theoretically arise during the formation of egg or sperm cells. On the left are two matching chromosomes, each split to the centromere and ready to pair and exchange segments. The shaded bars show similar sequences of DNA in the chromosome that enable correct pairing. But just above the centromere mispairing has occurred. When the chromosomes separate (right), the mispairing has given rise to two normal and two abnormal chromosomes, one with a deletion and one with a duplication.

Can it happen again?

The possibility of having another pregnancy with an 18p deletion depends on the parents' chromosomes. If both parents have normal chromosomes, the deletion is very unlikely to happen again. If either parent has a chromosome rearrangement involving 18p, the possibility is greatly increased of having other affected pregnancies. If they wish, parents should have the opportunity to meet a genetic counsellor to discuss the specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). 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. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

6 years

Inform Network Support

Understanding chromosome disorders

Unique

Rare Chromosome Disorder Support Group
G1, The Stables, Station Rd West, Oxted, Surrey. RH8 9EE
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

The Chromosome 18 Research & Registry Society
7155 Oakridge Drive, San Antonio, Texas 78229, USA
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This guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by Unique and reviewed by Professor Albert Schinzel, Institute of Medical Genetics, Switzerland, Courtney Sebold, Genetic Counsellor, Chromosome 18 Clinical Research Center, USA and by Professor Maj Hulten BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, UK

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