

## Inform Network Support



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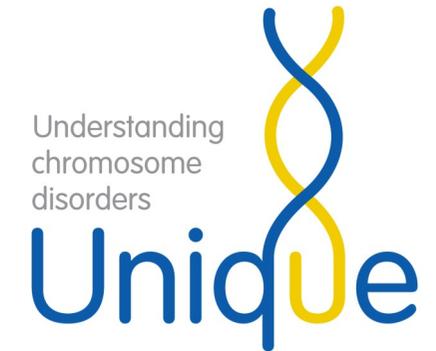
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# 18q deletions from 18q11.2 to 18q21.2

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## Proximal deletions of 18q: from q11.2 to q21.2

A proximal 18q deletion is a rare disorder in which some of the genetic material that makes up one of the body's 46 chromosomes is missing. Although the other chromosomes are intact, this small missing piece does increase the possibility of developmental delay, learning difficulties and behaviour problems. However, the problems can vary and depend very much on what genetic material is missing.

Chromosomes are made up 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 and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from the largest to the smallest. In addition to these 44 chromosomes, each person has another pair of chromosomes, called the sex chromosomes. Girls have two Xs (XX), whereas boys have an X and a Y chromosome (XY). Each chromosome has a short (p) arm (shown at the top in the diagram below) and a long (q) arm (the bottom part of the chromosome).

For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. People with proximal 18q deletions have one intact chromosome 18, but the other is missing a variably-sized piece which 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.

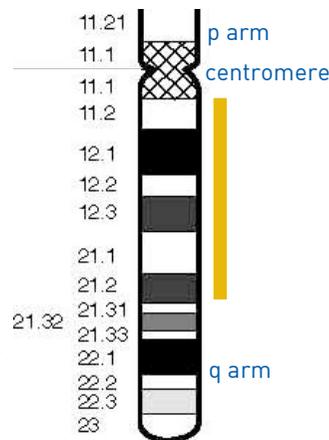
## Looking at 18q

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.

A **proximal** deletion of 18q is when part of the long arm (q) of chromosome 18 is missing. Proximal deletions of 18q are **interstitial**. This is where a piece of the long arm of chromosome 18 is missing, but the tip is still present.

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 q11 in the long arm, is close to the centromere. Regions closer to the centromere are called **proximal**. A higher number, as in q23, is closer to the end of the chromosome. Regions closer to the end of the chromosome are called **distal**. About 1 in 40,000 babies is born with a deletion of chromosome 18q.

The majority of deletions of 18q are distal deletions of 18q (those with a breakpoint between band 18q21.1 and the end of the chromosome). However, although there are far fewer cases of proximal deletions, it has recently become clear that these deletions result in a separate but recognisable set of features. It is these deletions that are covered in this guide and the region is marked by the red bar on the diagram on the right. Distal deletions of 18q are covered in separate guide available from *Unique*.



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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.

It is thought that proximal 18q deletions may be an underappreciated syndrome due to the lack of both significant major birth defects and other typical anomalies that would lead to a chromosome test. Additionally, smaller interstitial deletions are much harder to pick up by conventional cytogenetic analysis. With the increasing use of molecular techniques such as array-CGH and FISH in diagnosing proximal 18q deletions, the deleted region will be more accurately defined, and there will almost certainly be an increase in the number of people diagnosed. This will also lead to a more accurate delineation of the features of proximal 18q deletions.

## Why did it happen?

The majority of proximal 18q deletions occur out of the blue as a sporadic event when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn). One possibility is that *de novo* proximal 18q deletions are caused by a change that occurred when the parents' sperm or egg cells were formed. However, less commonly a proximal 18q deletion may be the result of a rearrangement in one parent's chromosomes (Chudley 1974).

A blood test to check both parents' chromosomes will confirm what the situation is. In either case, no environmental, dietary or lifestyle factors are known to cause these chromosome changes. So there is nothing that either parent did before or during pregnancy that caused the deletion to occur and equally nothing could have been done to prevent it.

## Can it happen again?

If both parents have normal chromosomes, the deletion is very unlikely to happen again.

If either parent has a chromosome rearrangement involving the proximal region of 18q, the possibility of having another affected child is higher. 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 very accurate, although not all of these tests are available in all parts of the world.

## Sources

The information in this guide is drawn partly from the published medical literature. To date there have been 27 published cases of proximal deletions of 18q. In addition, this guide draws on information from a survey of members of *Unique* conducted in winter 2007/2008, referenced *Unique*. When this guide was written *Unique* had ten members with a proximal 18q deletion ranging in age from 4 years to 27 years. 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*.

## Results of the genetic test

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

### 46,XY,del(18)(q12.3q12.3)

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  
(q12.2q21.1) The chromosome has two breakpoints, both in the band 18q12.3 indicating a small deletion

In addition to, or instead of a karyotype, you may be given the results of molecular analysis such array-CGH for your child. In this case the results are likely to read something like the following example:

### arr[hg19] 18q12.3q21.1(39703953-45137422)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  
18q12.3q21.1 Chromosome 18 has two breakpoints, one is band q12.3 and one in band q21.1  
39703953-45137422 The base pairs between 39703953 and 45137422 have been shown to be deleted. Take the first long number from the second and you get 5,433,470bp (5.43Mb or 5433kb). 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  
dn means *de novo*. The parents' chromosomes have been checked and no deletion or other chromosome change has been found at ?. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child.  
mat means that the deletion has been inherited from the mother;  
pat means that it has been inherited from the father.

## Most likely features

Every person with a proximal 18q deletion is different and so each person will have different medical and developmental concerns. Additionally, no one person will have all of the features listed in this guide. However, a number of common features have emerged:

- Lack of major birth defects
- Hypotonia (low muscle tone or floppiness)
- Children may need support with learning. The amount of support needed by each child will vary
- Speech and language delay
- Obesity
- Behavioural problems
- In some, short stature

## Feeding and Growth

Around a third of those with proximal 18q deletions are of short stature, although many children are of average height. Birth weights recorded at *Unique* were within the normal range suggesting that this growth delay does not seem to start in babies before birth.

### Range of birth weights at or near term:

3.146 kilos (6lb 15oz) to 4.025 kilos (8lb 14oz)

Feeding problems in babies are very common and are often attributed to the hypotonia that is common in these children. Many children have a poor sucking reflex. Babies and children with a high palate can also find the action of sucking and swallowing difficult. The floppiness can also affect their food pipe and contribute to gastro-oesophageal reflux (in which feeds return readily up the food passage).

A number of children at *Unique* are described as plump and around 20 per cent of those in the literature have obesity. Obesity can be seen in children as young as three (Wilson 1989; Buysse 2008; *Unique*).

“ He was breastfed for 6 weeks. However, his weight gain was minimal so he was put onto bottles ” – 14 years

## How might a proximal 18q deletion alter a child’s ability to learn?

Published medical literature states that learning difficulties for those with proximal 18q deletions are commonly in the moderate to severe range, and the evidence from *Unique* appears to back this up. Three *Unique* children attend a mainstream school, with the remainder benefiting from a specialist education environment. Many children suffer from poor concentration or a low attention span that can make learning especially challenging. However, the evidence from *Unique* suggests that reading and writing, to some degree, is possible for some children (Cody 2007; Bouquillon 2011; *Unique*).

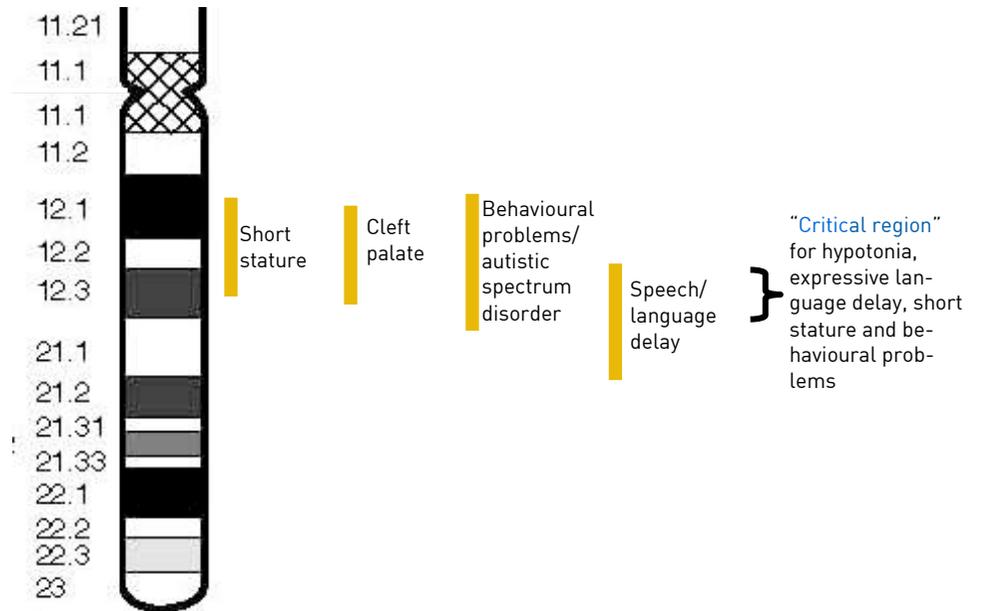
“ She has moderate learning difficulties but seems a bright little girl ” – 6 years

“ Play helps him to learn. He finds it hard to concentrate on trying to read or write ” – 15 years

## Potential genes involved in proximal 18q deletions

Research to identify the genes that are responsible for the features of proximal 18q deletions is ongoing. The increasing use of molecular techniques such as array-CGH and FISH in diagnosing these deletions will more accurately define the deleted region and will lead to a more precise delineation of the features of a proximal 18q deletion.

In fact, a number of recent studies have attempted to correlate the clinical features in people with a proximal 18q deletion with the part of the chromosome they have missing in order to define a critical region (a region responsible for the features seen in proximal 18q deletions) on chromosome 18q for individual features and to help to narrow down the genes responsible (see diagram below).



One report noted that the majority of people who took part in the study had expressive speech delay which was more severely affected than their receptive language abilities. This has led to the hypothesis that there are genes in this region of chromosome 18 that are involved in the development of speech. A recent study has proposed that the gene *SETBP1* located on 18q12.3 may be responsible for this expressive language delay (Cody 2007; Filges 2011).

Two reports have identified a region on 18q12 that may be responsible for the autism and/or some of the behavioural problems seen in some children with proximal 18q deletions (McEntagart 2001; Gilling 2008).

Another recent study attempting to correlate the features seen in deletions of 18q with the region of the chromosome that is missing identified a proximal region that is responsible for the short stature that is sometimes seen in those with a proximal 18q deletion. The researchers have also identified a region that may be responsible for the cleft palate that affects a small minority (Feenstra 2007).

## Behaviour

In general, children with a proximal 18q deletion are placid and affectionate. However, they are as vulnerable to frustration as other children with a communication difficulty and temper tantrums and aggression can present carers with challenges. Behavioural problems have been reported in as many as 50 per cent of children and the evidence from *Unique* seems to agree with this figure (Buysse 2008, Bouquillon 2011; *Unique*).

Behavioural problems tend to emerge in childhood. These can include hyperactivity, poor concentration, distractibility, restlessness (attention deficit hyperactivity disorder; ADHD) and aggression, as well as autistic-like features including social withdrawal and self-stimulation (repetitive body movements or repetitive movement of objects). A 4-year-old reported in the medical literature was described as kind and social but had difficulty concentrating and no sense of pain or danger. A 20-year-old was restless with continuous movement and gesticulation. Many parents report that children with challenging behaviour have responded well to standard discipline techniques such as ignoring unwanted behaviour and rewarding them with cuddles and attention when they stop. Two of the four *Unique* boys have ADHD for which medication has been effective, particularly in helping concentration and learning in school. An information leaflet on behaviour difficulties is available from *Unique* (Wilson 1979; Schinzel 1991; Poissonnier 1992; Tinkle 2003; Kotzot 2005; Filges 2011; Bouquillon 2011; *Unique*).

“ She gets angry and frustrated and finds it difficult to express her feelings or thoughts ” – 6 years

“ He has ADHD. He is great at home, it is when we go out sometimes that there are problems. When we go to a restaurant he can get very restless. He can't sit easily and moves things on the table around. He will talk to anyone and everyone and says Hello to people he doesn't know! He is affectionate and never in bad humour ” – 15 years

## What is the outlook?

The experience at *Unique* suggests that many children learn to wash and dress themselves, although some will need directions and encouragement to do so. For the most part, toilet training can be achieved, although often somewhat later than their peers, and some continue to need nappies and/or protective clothing during the night. The lack of any major or life-threatening anomalies would suggest a normal life expectancy (*Unique*).

“ He can wash and dress himself, but has to be told when to get out of the shower – he would never decide for himself! ” – 15 years

“ He can dress himself but frequently puts shirts/jumpers on back to front. He uses the toilet well during the day, but is doubly incontinent during the night and therefore wears nappies ” – 16 years

## Adults with a proximal 18q deletion

Very few adults have been described in the published medical literature and *Unique* has only one member over the age of 18. A 20-year-old is reported in the medical literature. He has some moderate learning difficulties and limited speech. There is also a report of a 67-year-old woman. She has spent much of her life living in a group home, but now participates in a sheltered workshop programme (Tinkle 2003).

## How might a proximal 18q deletion affect my child's ability to communicate?

Problems with language development are a recurrent feature of proximal 18q deletions. Almost half of those in the published literature had speech delay. The data from *Unique* appear to support this. Sign language can help children communicate their needs. For some, as speech develops they find they no longer have any need for sign language. 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 (Cody 2007; Buysse 2008; *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 insufficient sucking, can also affect the development of speech. Those with a high palate may also have specific difficulty with certain sounds (*Unique*).

Experience at *Unique* suggests that for some children receptive language is markedly better than their expressive language skills – they understand far more than they are able to express. This is backed up by recent reports that noted that five out of the six people showed a striking discrepancy between expressive and receptive language skills, with expressive speech development being much more severely affected. In the published literature a 7-year-old speaks only a few words. A 4-year-old has no expressive speech but his receptive language is intact and he actively communicates using gestures illustrating ideas and demands. A 10-year-old had delayed speech and used signs until the age of 4. She struggled to understand sentences and had problems with articulation but had a desire to communicate and a normal level of vocabulary. A 20-year-old has 30 mono- or disyllabic words, he signs and can obey simple instructions (Cody 2007; Buysse 2008; Bouquillon 2011; Filges 2011; *Unique*).

“ She has severe expressive speech delay but receptive language put at 1 to 2 years advanced ” – 7 years

“ Although he has no speech, he has a very good understanding of spoken language, as long as short sentences are used. He is very quick to pick things up, and has often started a task before the sentence is finished ” – 14 years

“ Aaron talks quite well ” – 15 years

“ When younger she supplemented her speech with sign language but no longer uses it. She uses 3 to 5 word sentences and is good at getting her point across ” – 24 years

## How can a proximal 18q deletion affect a child's development and mobility?

Hypotonia, low muscle tone (floppiness), is also common and has been seen in over half of those described in the medical literature. This can result in delays in reaching milestones such as sitting independently, crawling and walking. The evidence in the literature and from *Unique* is that children walk independently between the ages of 18 months and 4 years 9 months, at an average age of around 2½ years. However, some children maintain a clumsy gait into adulthood. Early intervention with physiotherapy and occupational therapy is important (Bouquillon 2011; Filges 2011; *Unique*).

Mobility can be an issue due to the behavioural problems that affect some children with

proximal 18q deletions (see section on [Behaviour](#)). Some children suffer from hyperactivity and may feel the need to run everywhere. Other parents describe their children as struggling with depth perception which can also lead to clumsiness and difficulties negotiating uneven surfaces, such as steps (*Unique*).

“ He walks very clumsily. In fact he tends to run everywhere which means that he is a constant danger to himself and others. He has no fear or understanding of danger which is a constant worry ” – 14 years

“ He has no mobility problems ” – 15 years

## Hand-eye co-ordination and dexterity (fine motor skills)

Fine motor skills seem to be affected in children with proximal 18q deletions, often attributed to the hypotonia that is common in these children. 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 a great deal of children. Many children have occupational therapy and go on to achieve good fine motor skills and pincer grip (*Unique*).

“ He is a very messy eater! ” – 14 years

“ He had poor muscle tone until around one year, which then sorted itself out. He still doesn't hold a pen very well ” – 15 years

## Appearance

In addition to short stature, children with proximal 18q deletions sometimes have facial features in common. Their eyes may be deepset with droopy eyelids (ptosis). Sometimes there are tiny skin folds across the inner corner of the eye (epicanthic folds). They may have a high or prominent forehead. However, many children look little different to other children and closely resemble their siblings or parents (*Unique*).

## What are the medical concerns?

### ■ Lack of major birth defects

In general, a proximal deletion of 18q does not lead to any major birth defects, and children and adults are generally in good health.

### ■ Vision problems

A squint (strabismus) is common, occurring in around half of all those with a proximal 18q deletion. Treatments for strabismus are most effective in young children and include wearing a patch on the good eye to encourage the eye with the squint to work harder or wearing glasses to correct the refractive error. If these are not successful surgery can be performed to realign the muscles that hold the eye in place.

Other vision problems that have been described are short sight, long sight and astigmatism. It is likely that these do not occur any more frequently than in the general population. Although very few adults have been described in the literature, all but one had cataracts (cloudy patches in the lens inside the eye) in mid-life, which may suggest that this is a later onset feature of proximal 18q deletions, although again, this is a common finding in the general population. Treatment for cataracts depends on how much the eyesight is affected. Early cataracts may be dealt with by wearing stronger glasses. If the loss of vision is more serious, the cataracts can be treated with an

operation to remove the cloudy lens of the eye and replace it with a plastic lens (Tinkle 2003; Buysse 2008; Bouquillon 2011; Filges 2011; *Unique*).

### ■ Seizures

Seizures have been reported in around two thirds of people described in the medical literature, but in only around half of *Unique* members. The seizures tend to occur early in childhood (around the age of one year) and seem to be easy to control with medication. Some children have outgrown them (Cody 2007; Feenstra 2007; Bouquillon 2011; Filges 2011; *Unique*).

“ She had a febrile seizure at 12 months old. Seizures following this could not be controlled at first. She was on anti-convulsants for 5 years after which she was weaned off with no re-occurrence of seizures ” – 24 years

### ■ Ears and Hearing

Although hearing problems do not seem to be a common feature of proximal 18q deletions, a number of children seem to suffer from frequent ear infections that can result in some mild or moderate hearing loss and require the insertion of grommets (a small ventilation tube). These grommets are temporary and children grow out of the ear infections. However, the treatment of the temporary hearing loss is especially important for these children because of their expressive language delay (*Unique*).

### ■ Minor genital anomalies

Although major birth defects are uncommon in people with a proximal 18q deletion, minor anomalies of the genitals are often seen in babies with a chromosome disorder, especially boys. The most common problem for those with a proximal 18q deletion is undescended testes. If one or both of the testes remain undescended, a decision will be taken whether to bring them down surgically. Hypospadias, where the hole usually sited at the end of the penis is on the underside instead, has also been reported. Depending on how mild this is, it may need no treatment or require corrective surgery to re-site the hole (Cody 2007; *Unique*).

### ■ Brain

Some people with proximal 18q deletions have changes in the structure of their brain that can only be detected with an MRI (magnetic resonance imaging). For example, two people have been identified with a thin corpus callosum. The corpus callosum is the bundle of nerves that connect the right and left sides of the brain. Other people have been diagnosed with enlarged lateral ventricles which means that the fluid-filled spaces in the brain are larger than expected (Bouquillon 2011).

### ■ Palate

Cleft lip and palate (the roof of the mouth) have been reported to be more common in babies with a proximal 18q deletion. 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. However, none of the *Unique* children have been affected in this way.

A high arched palate has also been reported, but again is not present in any of the *Unique* children. Both cleft and high palates can contribute to the early feeding difficulties seen in children. A high or cleft palate may make speech and making the sounds of speech more difficult (Feenstra 2007; Bouquillon 2011; *Unique*).