Inform Network Support

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18q deletions: from 18q21 and beyond

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18q distal deletions breakpoints in band q21 and beyond)

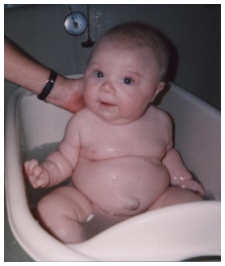
A chromosome 18q deletion is a disorder in which some of the genetic material that makes up one of the body's 46 chromosomes is missing. Like most other chromosome disorders, this increases the risk of birth defects, developmental delay and learning difficulties. However, the problems can vary and depend very much on what genetic material is missing.

Chromosomes are made up of DNA and are the structure in the nucleus of the body's cells that carry genetic information (known as genes), telling the body how to develop and function. In total each one of us normally has 46 chromosomes. Of these, 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. One chromosome from each pair is inherited from the mother while the other is inherited from the father. Each chromosome has a short (p) arm (shown at the top in the diagram on the next page) 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 an 18q deletion have one intact chromosome 18, but the other is missing a smaller or larger piece 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 determine future development, needs and achievements.

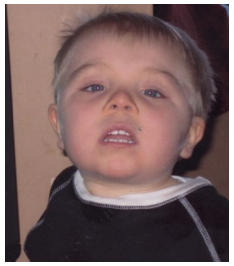
About 1 in 40,000 babies is born with a deletion of chromosome 18q. Although there is a great deal of variability between those with an 18q deletion, there are enough similarities to define the loss of part of chromosome 18q as a syndrome, hence the term 18q- syndrome. 18q- syndrome is also sometimes called 18q-, de Grouchy, monosomy 18q or 18q deletion syndrome, and was first described in 1964 (de Grouchy 1964). There have since been many published cases (for a review see Cody 1999).

Growing up with 18q-:



4½ months

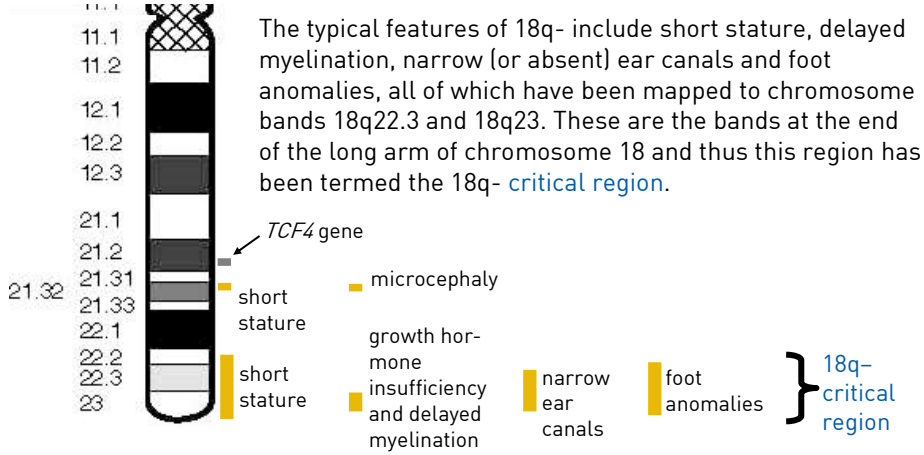
10 months



2½ years

5 years

facial features (including a large, beaked nose, wide mouth and fleshy lips) and breathing problems (Zweier, 2008).



The typical features of 18q- include short stature, delayed myelination, narrow (or absent) ear canals and foot anomalies, all of which have been mapped to chromosome bands 18q22.3 and 18q23. These are the bands at the end of the long arm of chromosome 18 and thus this region has been termed the 18q- critical region.

Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 18q deletion occurred. Most 18q deletions occur when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn). *De novo* 18q deletions are caused by a change that occurred when the parents' sperm or egg cells were formed. Some 18q deletions are accompanied by an addition of material from another chromosome. This is usually referred to as an unbalanced translocation. If a child has an unbalanced translocation, there is a significant possibility that one of the parents has a balanced translocation. In a balanced translocation, no chromosome material has been lost or gained. Therefore, 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*, it is certain that, as a parent, there is nothing you did to cause the 18q deletion and nothing you could have done which would have prevented it. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. It is no one's fault.

Can it happen again?

The possibility of having another pregnancy with an 18q 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 18q or has a 18q deletion him- or herself, 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 very accurate, although not all of these tests are available in all parts of the world.

Ongoing research involved in 18q-

An intact 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. The features of 18q- are likely to be a result of the loss of a number of different genes.

In two studies of more than 50 people all the 18q deletions were shown to be different indicating that there is no common breakpoint or breakpoint "hotspot" involved in 18q deletions. Therefore, most people with 18q- are missing a different, but often overlapping, portion of chromosome 18. This would mean that each individual with 18q- would be missing a different set of genes. This may explain some of the variability, although it also seems that the features can be highly variable even between first degree relatives with the same deletion (Strathdee 1995, Linnankivi 2006, Feenstra 2007, *Unique*).

Nonetheless, the increasing use of molecular techniques such as array-CGH and FISH in the research laboratory enables more accurate definition of the breakpoints. This, in turn, enables researchers to study which parts of the chromosome correlate with the different clinical features of the condition. Indeed, a number of recent studies have attempted to correlate the clinical features in people with 18q- with the part of the chromosome they have missing in order to define a critical region of 18q that is responsible for the features of 18q-, and to help to narrow down the genes responsible. In one study looking at 29 people, the study team have then been able to produce a kind of map of chromosome 18q that indicates which region of the chromosome is responsible for a number of particular features (Feenstra 2007, see diagram on the following page).

This study confirms a previous one that demonstrated a critical region for the short stature that is often seen in 18q-. It is thought that the decreased growth may be due to a growth hormone deficiency. This region contains the genes myelin basic protein (*MBP*) and the galanin receptor which are both candidates for the growth hormone insufficiency. The galanin receptor is involved in growth hormone response and is therefore a good candidate for the growth hormone insufficiency (Cody 1997, Ghidoni 1997, Feenstra 2007).

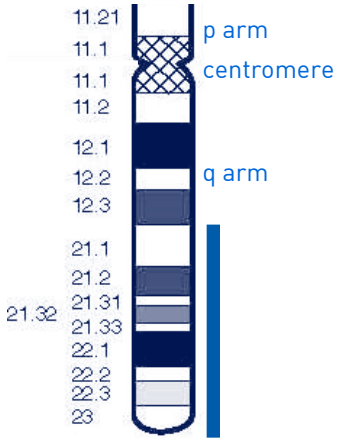
Interestingly, this region is almost identical to the region that has been identified to be responsible for the myelination problems. Thus, the gene or genes responsible for these two features are either the same gene or two tightly-linked genes. Up until now, all people who have been shown to have dysmyelination also have a growth hormone deficiency, so it has not yet been possible to uncouple these two features. As MBP is present exclusively in the cells of the nervous system that produce myelin and plays an important role in the formation and maintenance of myelin in the central nervous system, the *MBP* gene has been proposed as the primary candidate gene for the delayed myelination (Mahr 1996, Gay 1997, Feenstra 2007).

The common finding of narrow ear canals in 18q- has been linked, by three studies, to the loss of part of the region 18q22.3 (Veltman 2003, Dostal 2006, Feenstra 2007).

A critical region for the microcephaly (small head) that is often present in 18q- has been shown to be located to band 18q21.33 (Kline 1993, Feenstra 2007).

Recent studies have shown that the *TCF4* gene on 18q21 is responsible for Pitt-Hopkins syndrome (PHS). PHS is characterised by learning disabilities, distinct

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.

In 18q- part of the long (q) arm of chromosome 18 is missing. Most deletions of 18q are terminal. This means that the tip of the long arm is included in the deletion. However, some 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.

Deletions of 18q include both interstitial and terminal deletions. In general, the breakpoints in terminal deletions occur in the distal region of the chromosome. In contrast, interstitial deletions tend to occur in the proximal region of the chromosome. The focus of this leaflet will be on terminal deletions. These deletions typically have a breakpoint between 18q21.1 and the end of the chromosome and include the end of the chromosome. Proximal deletions of 18q are covered in a separate leaflet available from *Unique*.

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* carried out in winter 2007/2008, referenced *Unique*. When this leaflet was written *Unique* had 71 members with a distal 18q deletion ranging in age from 10 months to 48 years.

Results of the chromosome test

Most people have a pure deletion (no other chromosome is involved). However, among *Unique* members 29 per cent of children with 18q- have the involvement of an additional chromosome, usually a duplication of material from another chromosome, caused by a translocation of one of the parents (see explanation in section on **Why did this happen?**, page 19). Six per cent of members with a deletion of 18q are mosaic. This is where the 18q deletion is only present in a proportion of the person's cells. The remaining cells have the usual two complete copies of chromosome 18. Due to the presence of these cells with two complete copies of chromosome 18, people with mosaic 18q- may be less severely affected.

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 an 18q deletion, the karyotype is likely to read something like the following example:

46,XY,del(18)(q21.2)de novo

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
(q21.2)	The chromosome has one breakpoint in band 18q21.2, and material from this position to the end of the chromosome is missing. This is called a terminal deletion. If the portion of the chromosome that is missing is internal to the chromosome (interstitial) then two breakpoints will be specified (e.g.18q21.2q21.3)

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

arr[hg19] 18q21.3q23(58,047,945-78,077,247)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
18q21.32q23	The region in the deletion is from band q21.32 to band q23 (the end of the chromosome)
58,047,945-78,077,247	The base pairs between 58,047,945 and 78,077,247 have been shown to be deleted. Take the first long number from the second and you get 20,029,302bp (20Mb). 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

Most likely features

Every person with 18q- 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 leaflet. However, a number of common features have emerged:

- Short stature
- Hypotonia (low muscle tone or floppiness)
- Children need support with learning. The amount of support needed by each child will vary
- Foot problems

although for others help with these tasks is needed (Fryns 1979, Miller 1990, Schinzel 2001, *Unique*).

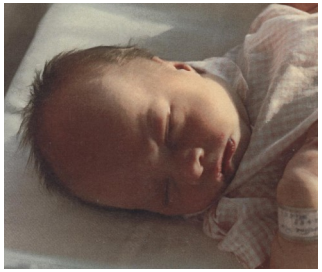
Five have attended college, commonly to study life skills. However, one has studied biology and genetics at university, and in addition to completing a degree course, she has recently obtained a postgraduate Masters degree and hopes to find employment in a laboratory. Another adult studied at horticultural college and now spends time at an allotment with a personal assistant, and is hoping to find supported employment as a gardener. Some of the adults surveyed travel alone on buses and trains and shop independently, although others need accompanying help. The majority enjoy active social lives with bowling trips, meals out and visits to the pub. A number find it hard to make friends with their peer group and therefore count their family and care workers as their closest friends. Others get on well with others and are sociable. Two are in long-term relationships, with one dreaming of marrying her fiancé (*Unique*).

Growing up with 18q-

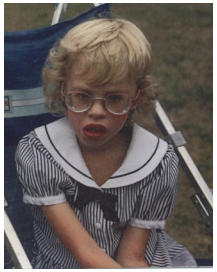
9 months

11 years

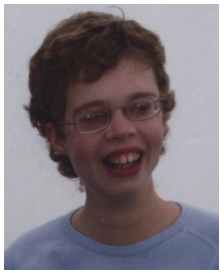
18 years



A few days old



7 years



21 years

2½ years

8 years

29 years

Puberty and Fertility

Puberty appears to proceed as expected. The *Unique* experience is that puberty occurs in girls between the ages of 11 years and 17 years, most often around 13 years. There is very little data available on puberty in boys (*Unique*).

Two *Unique* children have inherited a deletion of 18q from their mother. One passed a 18q22.2 deletion onto her son, and the other passed a 18q deletion on to her daughter. There are several reports in the literature that show transmission of 18q deletions from mothers to their children. One is a mother who passed a deletion of 18q22.2 on to her daughter. Another is family with a deletion of 18q in which the mother passed it on to four daughters. Affected females clearly can be fertile. Genetic counselling should be offered to help them understand what this may mean for future pregnancies (Subrt 1970, Fryns 1979, Schinzel 2001, Chen 2006, Linnankivi 2006, *Unique*).

" Puberty was no bigger hurdle than anything else. Takes a bit of adjusting to acknowledge that your immature child still develops sexually. " – boy 27 years

" She has reached puberty and coped really well - just like any other girl. " – 13 years

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

In a few people, a deletion appears to have only a mild effect. A mother with an 18q deletion has no problems due to the deletion, while her daughter who inherited the deletion has global developmental delay and learning difficulties as well as a hearing impairment. A 23-year-old woman with an 18q21.22 deletion had delayed development but caught up with her peers during puberty. She is described as having normal intelligence and job achievement with above average verbal skills (Netzer 2006, *Unique*).

Of those with 18q- with no learning difficulties, some may have other medical concerns. One with a deletion of 18q21.33qter had no developmental delay or learning disabilities, although she was born with a club foot, a hearing impairment, hypothyroidism and an umbilical hernia. A mother with an18q22.2qter deletion whose only learning difficulties have been due to dyslexia had some hearing loss and an overactive thyroid, although her son who inherited the deletion had developmental delay, hypospadias, nystagmus and hearing loss by the age of three years (*Unique*).

What is the outlook?

Life expectancy is thought to be normal and *Unique* has a number of adult members. A small number of adults have also been reported in the published medical literature. *Unique* has 11 members over the age of 18 years, nine of whom took part in the *Unique* survey. Of these five were girls and four were boys, and ranged in age from 20 to 33 years. Of these around half live at home, with the remainder living in residential group homes sharing with other adults. The majority achieved toilet training (often significantly later than their peers) and many can dress and undress themselves, although a number will need lots of encouragement. Others need help particularly with buttons and zips. Many are able to brush their teeth and wash themselves,

Pregnancy

The majority of mothers carrying babies with a deletion of 18q experienced no pregnancy problems and only discovered their baby was affected after the birth. Of the 24 families who have told us about their pregnancy experiences, four babies were small for dates and four showed reduced fetal movement. A foot abnormality was detected in one baby, and another was shown to have a small head (*Unique*).

There are several examples in the medical literature of prenatal diagnosis of 18q- by amniocentesis performed after fetal anomalies, such as clubfoot or a small head, were detected on prenatal ultrasounds. In both cases, the parents chose not to continue with the pregnancy (Chen 2006).

Feeding and Growth

People with deletions of 18q are frequently shorter than would be expected, with studies indicating that between 64 per cent and 80 per cent of children are affected. Birth weights recorded at *Unique* suggest that the growth delay does not start in all babies before birth. After birth, babies tend to grow more slowly than their peers, with some 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 18q- can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft palate or a high-arched palate can also find the action of sucking and swallowing difficult. Eight of the 27 mothers surveyed by *Unique* attempted breastfeeding but due to the difficulties encountered only two succeeded, although a number of parents fed their children expressed breast milk in a bottle.

Four of the 27 surveyed *Unique* babies benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat) and one had a gastrostomy tube (a G-tube, feeding direct into the stomach). The floppiness can also affect their food pipe and contribute to gastro-oesophageal reflux (in which feeds return readily up the food passage). In the *Unique* survey, just under half of all 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 of the end of the bed for sleeping. If these measures are not enough, feed thickeners and prescribed medicines to inhibit gastric acid may control reflux (Wilson 1979, Hale 2000, Feenstra 2007, *Unique*).

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. Many children are described as being frail, slim or skinny. However, some children are of average or even above average height and build. One *Unique* member is on the 98th centile for height. Some of the adult *Unique* members who were skinny as younger children have grown up to be average or even plump. Indeed obesity has been described in a number of people with 18q- (Feenstra 2007, *Unique*).

" Feeding was a big problem because she just didn't seem to have the ability to suck. It took painstaking hours to get any fluid into her. Because of her inability to suck, we used to squeeze the feeding bottle until a small amount of fluid was in her mouth and then let her swallow it. " – now 25 years

While the small stature of some people with 18q- has been known about for some time, it has only recently been shown that some cases are due to growth hormone deficiency. In the light of this, children with 18q- and short stature are now often tested for this deficiency and if necessary children are given growth hormone treatment to help normalise growth. A number of *Unique* children have, or had in the past, growth hormone treatment with generally positive experiences. However, one girl of small stature has seen no improvement after two years of treatment. It is recommended that these issues are discussed with a paediatric endocrinologist. In addition to helping to normalise growth, there is some evidence that treatment with growth hormone may also improve a child's development (see section on Learning) (Cody 1997, Ghidoni 1997, *Unique*).

It has been suggested that the loss of one of more genes from the 18q23 region may be one cause of the small stature. However, not all children who have deletions of this region show growth deficiency, so other, as yet unknown, factors also play a role (Kine 1993, Cody 1997).

In addition to small stature, many people with 18q- have microcephaly (small head size) (Line 1993, Feenstra 2007, *Unique*).

Appearance

In addition to short stature, children with 18q- sometimes have facial features in common. These features are not medical or developmental issues and may only be noticed by a medical professional. They may have midface hypoplasia (the middle of the face may look flat), low-set ears and a mouth that turns down at the corners (often referred to as a "carp-like" mouth). Their eyes may be wide-set with eye openings that may be short or slant upwards or downwards. However, children with 18q- generally resemble their siblings and look little different from children without 18q- (*Unique*).

" We think he is gorgeous! " – 6 years

" A doctor has told us that her eyes are set further apart and she has low-set ears, which are typical of her syndrome. We would never have noticed and think that she looks "normal" – whatever that is. " – 14 years

How might an 18q deletion alter a child's ability to learn?

Formal research evidence suggests that learning difficulties are common in children with 18q-. However, the learning difficulties experienced vary enormously, ranging from no difficulties at all through borderline, mild or moderate learning difficulties to a small minority with severe learning problems and intellectual disabilities. The evidence from *Unique* reflects this variability. Around half of *Unique* children attend a specialist educational needs school. The remaining half go to mainstream schools, some having 1:1 help in the classroom or the benefits of a special needs unit attached to the school. Many *Unique* children master reading to some degree: some can recognise their name and some basic words; others love to read and devour books. Writing is also achieved by the majority of children although the hypotonia and shaky hands that affect many with 18q- can make writing a challenge. A number of individuals have reached an unusually high level of achievement. One *Unique* member has not only completed a university degree course but has also attained two postgraduate qualifications!

Kidneys

A small number of children with 18q- have changes in the kidneys. Kidney problems were reported in 15 per cent of *Unique* children. One problem is kidney reflux, also known as vesico-ureteric reflux, where the urine flows from the bladder up towards the kidneys. This makes the kidneys more prone to infections. Children with kidney reflux are treated by a low dose of long term antibiotics which prevents urinary tract infections which in turn prevents damage to the kidneys. As the bladder wall matures and thickens with age, many children grow out of the reflux. Other problems include kidney stones and one *Unique* child has a dilated left kidney (*Unique*).

Behaviour

7 years

In general, children with an 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 corroborate this. Behavioural problems are common in both sexes, and include temper tantrums, aggressive behaviour (both towards themselves and others) and hyperactivity. A small minority of *Unique* children have sleep problems which in the more serious cases can be helped by medication. Management strategies include typical parenting techniques: avoid confrontation, distraction, praise for positive behaviour while ignoring inappropriate behaviour and firm restraint if behaviour is aggressive. Children with behavioural difficulties seem to benefit from having a structure or routine built into their day.

A small number of children and adults with 18q- have had the support of professional mental health care professionals and/or appropriate medication. An information leaflet on behaviour difficulties is available from *Unique* (Mahr 1996, Verhoeven 2006, *Unique*).

" She is very restless and can be very aggressive. She headbutts, pinches, screams and pulls hair. " – 14 months

" He has days where he does not sleep. It is as if he has forgotten how to get to sleep. " – 4 years

" He is a happy little boy: affectionate, funny and excitable. But he finds new situations or new people very difficult. He will cry and try to avoid the situation by getting out of the room, banging doors and grinding his teeth. " – 5 years

" She changes like lightning: she can be very happy, giggly and excited one minute and very grumpy and cross the next. She can be very immature and child-like, but can also be very grown up and say very sensible things. " – 13 years

" If she is naughty she gets a verbal warning. If she continues, we take her cuddly toy away. It is not an easy process but it does work. " – 13 years

" He never sits still: he runs round the house or paces. He has his music on all of the time. He sometimes pulls hair or digs his nails and bites others. He is boisterous and highly demanding. He has no sense of danger in or outside of the house and doesn't realise his own strength. " – 20 years

Vision problems

12 years

Vision problems are common in 18q-, with just over half of *Unique* children surveyed affected in one way or another. The most common feature was a squint affecting around a quarter of children. Another recognised feature that affected around 15 per cent of *Unique* children is nystagmus (jerky eye movements), which some children grow out of as they get older. Other problems that have been reported in children with a deletion of 18q are both short and long sight (with short sight more common) and cortical visual impairment, in which the visual systems of the brain do not consistently understand or interpret what the eyes see (Cody 1999, Linnankivi 2006, *Unique*).

Hernias

An umbilical hernia is often seen in babies with an 18q deletion, and was present in 42 per cent of *Unique* babies. An umbilical hernia is a soft, skin-covered bulge at the belly button (umbilicus) that can look bigger when the baby strains or cries. The bulge contains a small piece of abdominal lining and sometimes part of the abdominal organs. It is caused by incomplete closure of the ring of muscle that the umbilical cord passed through in early life. The hernia is often quite small and may resolve naturally by the age of 3 or 4 years. Some babies have a larger hernia or one that does not disappear, in which case it can be surgically stitched in a small operation (*Unique*).

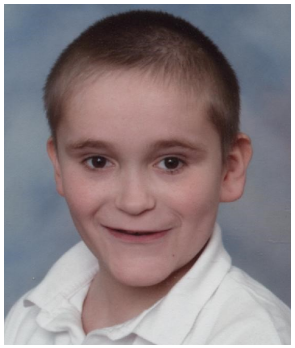
Palate

Cleft lip and palate (the roof of the mouth) have been reported to be more common in babies with 18q-. 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. In the *Unique* survey only one baby out of 27 was born with a cleft palate, which was repaired surgically. More common was a high arched palate, which was seen in around a quarter of surveyed children. Both cleft and high palates can contribute to the early feeding difficulties seen in children. A cleft or high palate may make speech more difficult (*Unique*).

Genital region

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. The *Unique* survey revealed that almost a third of boys with 18q- had cryptorchidism (undescended testes) and 23 per cent had micropenis (a small penis). In the case of cryptorchidism, the testicles can be brought down by a straightforward surgical operation. A less common finding was hypospadias, where the hole usually sited at the end of the penis is on the underside instead. Depending on how mild this is, it may need no treatment or require corrective surgery to re-site the hole (Linnankivi 2006, *Unique*).

Girls may also have minor genital anomalies. The most frequent genital anomaly in girls is unusual labia. The labia can have extra folds, be underdeveloped or in one case be completely absent (Cody 1999, *Unique*).



10 years

For many children a lot of encouragement, repetition and well-ordered routines are helpful for the learning process. For some, a teaching assistant to help their child to focus has proved invaluable (Cody 1999, Strathdee 1995, Semrud-Clikeman 2005, *Unique*).

One of the reasons that may explain some of this variability in learning is the vast difference in the size and region of the deletions seen in children with deletions of 18q. A recent study suggested that those people with terminal deletions distal to 18q21.33 are only mildly affected, if at all. However, the data from *Unique* correlating the size and the region of 18q that is missing with the degree of learning difficulties are conflicting and offer no clear correlation (Feenstra 2007, *Unique*).

There have been several reports published by the team at the Chromosome 18 Clinical Research Center describing the benefits of growth hormone therapy on the cognitive function of children with 18q deletions. In a study involving 13 children with 18q- who were given growth hormone therapy, most of the children showed increased height as expected. However, the majority also showed an improvement in cognitive ability. The mechanism by which growth hormone affects cognitive function is not presently known. Further research and evaluation of the benefits of growth hormone therapy is needed (Hale 2000, Cody 2005).

“ He does exactly the same as other children, but with much more difficulty. ” – 3 years

“ He still scribbles but he does draw circles. He likes books and recognises print. He can match all of his classmates’ names to their photographs. ” – 5½ years

“ He is very good with computers and hand held games consoles. Computers and his 2-year-old sister are what help him to learn best! ” – 6 years

“ He loves reading. He reads holiday brochures, biographies and newspapers. ” – 10 years

“ He can write but not very legibly and with no punctuation. ” – 11 years

“ She learned to read at the age of 7-8 years with the help of symbols and a computer program. She loves music and remembers the words to songs and can fill in the lyrics. ” – 12 years

“ She reads the odd comic but finds reading a book difficult to concentrate on. ” – 12 years

“ His memory is AMAZING! He can remember almost anything, going back to age 4-5. ” – 13 years

“ Her memory is fantastic – it has got her where she is today. Her writing is about a year behind her peers. ” – 13 years

“ He was helped to learn by adapting learning to subjects he is interested in, for example reading sports books, and not the usual school books – he had no interest in them at all. ” – 21 years

“ His memory is very good – with things that are relevant to him! ” – 27 years

How might 18q- affect my child's ability to communicate?

Language skills may develop later than in other children. *Unique* has seen that children begin speaking between 15 months and 8 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. The 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. 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 (*Unique*).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. Additionally, many children with 18q deletions have some hearing loss which contributes to the delay. 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 cleft or high palate may also have specific difficulty with certain sounds (*Unique*).

For many children, receptive language is markedly better than their expressive language skills – they understand far more than they are able to express (*Unique*).

" He uses his voice to attract our attention, but we are unclear about what he wants. At present he does not have any way to tell us what he wants. We are encouraging him to use eye contact so that he can watch faces and learn some basic signs to communicate his needs. We are encouraging him to increase his awareness of sounds and voice using his bone conduction hearing aid and radio aid (See explanation in section on Ears and hearing, page 11-12). " – 3 years

" He understands a lot and often finds it frustrating when he cannot communicate his needs. His understanding of signs is better than his expressive signing. " – 5½ years

" She definitely understands a lot more than she can express. She listens intently to presentations at school, watches movies/shows/concerts. She can speak many words and three word phrases, but she does not initiate requests or communication or start discussions. " – 12 years

" She can speak in sentences and have a conversation but not always clearly and she tends to miss beginnings of words and/or sentences. " – 13 years

" She understands well if requests are made short and simple. She tends to switch off in long conversations. " – 13 years

" Her understanding is that of a much younger child. She also expresses her feelings like a younger child by crying and having tantrums. " – 14 years

" Although his speech was quite delayed and he still has some problems, on the whole he speaks very well with much vocabulary. " – 21 years

" She knows Makaton and British Sign Language (BSL) and has over 500 signs " – 25 years

" She talks and also uses Makaton. She is also a very good lip reader. " – 30 years

Unique children are to eggs, dairy, nuts and wheat. Dietary changes and antihistamines can help manage some of the allergies. However, for a small number of people the trigger may result in a severe allergic reaction known as anaphylaxis, where multiple systems can be affected. In these cases, it may be necessary to carry adrenaline (in an injectable form) that has to be administered in cases of anaphylactic shock (*Unique*).

Allergies also play a role in asthma, which also affects many *Unique* children with 18q -. When a person with asthma comes into contact with something that irritates their airways (an asthma trigger), the muscles around the walls of the airways tighten so that the airways become narrower and the lining of the airways becomes inflamed and starts to swell, creating breathing difficulties. In most cases of childhood asthma, the trigger is a viral infection. Asthma sufferers often carry an inhaler with them to aid their breathing if an attack occurs. Many children outgrow some or all of their allergies and may also outgrow their asthma (*Unique*).

Skin

Eczema is another type of allergic reaction that seems to be common in children with 18q-, affecting 81 per cent of children in the *Unique* survey. In mild forms the skin is dry, hot and itchy, whilst in more severe forms the skin can become broken, raw and bleeding. Parents have found that gentle moisturising creams and emollients can help keep it under control, with steroid cream employed in more severe cases (*Unique*).

Other skin complaints have been noted. Some children have skin dimples, often on the shoulders. One *Unique* child had a strawberry birthmark which disappeared by the age of 4 years and another has a very dry swirl-like pattern on half of his body (*Unique*).

Thyroid

Thyroid problems can affect people with 18q-. The thyroid hormones regulate a number of functions in the body, including how fast your heart beats and how quickly you burn calories. In a study of 120 people carried out by the Chromosome 18 Clinical Research Center, 12 per cent of people had hypothyroidism (low levels of thyroid hormone). In the *Unique* survey the number affected was significantly higher at 26 per cent. Hypothyroidism can be treated by taking a thyroid hormone supplement, thyroxine. Because thyroid problems can arise at any time in life, it is recommended that people with 18q- undergo regular thyroid screening (Schaub 2005, *Unique*).

Heart problems

Heart conditions have been found in 23 to 35 per cent of babies with 18q-, although most of these are relatively minor. Nonetheless, it is likely that all children with 18q- will undergo a cardiac investigation. The data from *Unique* show that heart conditions were found in 58 per cent of those children surveyed. However, 40 per cent of those with heart conditions had innocent heart murmurs. Of the remainder, the most common was pulmonary stenosis, a narrowing of the pulmonary valve, meaning that the heart has to work harder to pump blood which results in breathlessness. One *Unique* child with an extremely narrow valve, had surgery to stretch the valve. For others, no treatment, just monitoring, has been necessary. Other problems that can occur include small holes in the heart that will often close naturally over time (Cody 1999, *Unique*).

will need a grommet (a small ventilation tube) inserted into the eardrum. A further cause of hearing impairment in some people with 18q- is changes in the nerve that moves sound from the ear to the brain.

Due to the number of factors that can result in hearing loss, children with 18q- are advised to have regular hearing screening (*Unique*).

Seizures

Epilepsy is commonly observed in people with chromosome disorders and has been associated with 18q-. Epilepsy has been described in the published medical literature in people with 18q- with an occurrence of between 10 and 31 per cent. However, in the *Unique* survey 46 per cent of children are or have been affected by seizures. For the majority of children, seizures occur during the first few years of life and are well controlled using medication. Some children appear to have just one or two seizures. The seizures then stop, and in most cases do not return. However, one *Unique* member had a few seizures as a small child and was seizure-free until one seizure at the age of 26 years. For another, the first seizure occurred at the age of 18 years, while another has had an episode of seizures as adult. In addition, a case of adult-onset seizure disorder in 18q- has been reported recently (Adab 2006, *Unique*).

One *Unique* child, who does not have epilepsy, has a complex movement disorder which results in jerking and shuddering (Wilson 1979, Strathdee 1995, Grosso 2005, *Unique*).

Infections

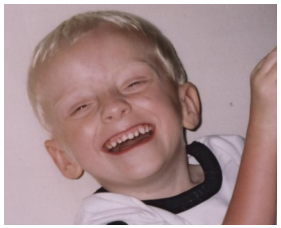
Many children with 18q- have decreased resistance to infections. One explanation for this is that low levels of an infection-fighting antibody, IgA (immunoglobulin A), are found in some people with 18q-. IgA plays an important role in defending the body against infection that invades the body through the mucous membranes, such as the nose, eyes, lungs and intestines. Therefore, people with low IgA are more susceptible to infections and colds. One study has found that as many as 24 per cent of people with 18q- have decreased IgA. This figure is supported by the 26 per cent of the *Unique* members with 18q- who have an IgA deficiency. In most cases, this deficiency is managed by treating infections promptly (Ghidoni 1997, Cody 1999, *Unique*).

Allergies and asthma

The occurrence of allergies and asthma has not been well studied in people with 18q -. However, evidence from the *Unique* survey suggests that allergies are extremely common with 64 per cent of children reporting an allergy of some kind. An allergy is when the body has an adverse reaction to a particular substance. When the body comes into contact with the substance (the trigger) it triggers the immune system to react as if it has come into contact with something harmful and releases special chemicals, called antibodies, to destroy it. It is the release of antibodies which causes the symptoms of an allergic reaction (*Unique*).

Airborne particles, such as dust and pollen can trigger an allergic reaction. In these cases, symptoms arise in areas in contact with air, such as eyes, nose and lungs. Hayfever and dust allergies are the ones that most commonly affect *Unique* children. Allergic reactions can also result from foods and medications leading to abdominal pain, vomiting or diarrhoea. The most common food allergies amongst

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



3½ years

The hypotonia that is a common feature of 18q- means that it may take a little longer for them to roll over, sit, crawl and walk. *Unique* children sat unaided between the ages of five months and two and a half years, with an average of around one year. Walking was mastered between 15 months and seven years, at an average age of two years and 11 months. The foot problems that are common (see section on **Feet**, page 10) in children with 18q- can also affect walking and result in clumsiness and an increased tendency to trip over. Many *Unique* parents describe their children as having poor balance, poor co-ordination and poor depth perception which can lead to bumping into things and falling over. A number of children do not seem to have the saving response so when they fall they go down with full force. Bow legs (genu varum) and scoliosis (curvature of the spine) may also affect the way that some with 18q- walk and can lead to gait abnormalities (*Unique*).

12 years

Many children need support while learning to walk but eventually most walk independently, although this is not possible for all. Many children learn to skip, jump, climb and run, some learn to swim and horse ride, and one *Unique* member plays cricket for his county's disabled cricket team. One *Unique* girl has found the martial art, Tae Kwon Do, to be extremely good in helping to stretch muscles and improve balance (*Unique*).

" He didn't really crawl; he was a bottom shuffler until he was 20 months and has walked since. He is generally fine, although he can be a bit wobbly on his feet. He is very active and confident physically, enjoying running and climbing. **"** – 3 years

13 years

" She does not walk but is starting to sit with lots of physiotherapy. **"** – 8 years

" He has had no mobility problems **"** – 13 years

" He moves around well but walks as a toddler would and tends to drag his feet. **"** – 20 years

" She walks normally and can get around quite well. She has poor depth perception thus she is tentative when she experiences uneven ground or comes to a kerb or change in level. **"** – 22 years

" He has an uneven gait. We have encouraged walking and cycling to build up muscle. Keeping as fit as possible has made a difference. **"** – 27 years

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

Hypotonia can affect fine motor skills in children with 18q- and they may take longer to reach for and grab toys and hold a bottle or cup. Fine motor skills are also affected by the poor co-ordination described in some 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 cutting up food 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 and go on to achieve good fine motor skills and pincer grip (*Unique*).

A small number of *Unique* children have shaky hands, known as action or intention tremor. This can affect fine motor skills and in particular cause trouble with holding a pen to write. Indeed, this has also been reported in the literature and it has been suggested to be linked to the impaired myelination seen in the brains of many people with 18q- (see section on Brain) (Miller 1990, *Unique*).

" She cannot hold or grasp onto anything. She seems to be trying but cannot co-ordinate her hands. We are constantly stimulating her hands with different textures. " – 2 years

" His fine motor development is a little clumsy at times – he often prefers to use his hands to eat. We encourage him to use his cutlery and find he is getting better, although his 18 month old sibling is more dexterous at feeding! " – 3 years

" His pincer grip is delayed, although improving all the time. " – 5½ years

" Now at age 12 she has managed to cope with writing and other co-ordination tasks. " - 12 years

" She never held her bottle and has only started feeding herself at 10 years. " – 25 years

" He had delays in holding cutlery, bottle etc, but everything happened eventually without intervention. " – 27 years

Medical concerns

Feet

The feet of babies with 18q- are often not perfectly formed. Some babies are born with clubfoot (talipes) where the foot is at an unusual angle. Some children have "rocker bottom feet", where the arch of the foot is unformed, leaving the sole curved. Sometimes feet are small, with overlapping toes or a wide gap between the 1st and 2nd toe. Other children have flat feet or feet with high arches. Weak ankles that "turn over" easily have also been described in *Unique* children. Many children need special, supportive special footwear or surgery and the difficulties often delay the age at which children learn to walk (Cody 1999, *Unique*).

Hands

Hands can also be affected in children with 18q-. Thumbs may be short or proximally placed (positioned unusually low, or close to the wrist). Fingers are often long and tapering, sometimes with an incurving 5th finger (clinodactyly). In general, the hand anomalies do not greatly affect the function of the hands, although they can lead to problems with fine motor skills (Cody 1999, *Unique*).

Joints

There have been some reports of people with 18q– affected by rheumatoid arthritis. However, *Unique* has only one member who has reported being affected by arthritis. One *Unique* child, however, had aches and pains in her joints when younger, but these are rare now that she is 13 years old. Additional research will be required to better understand the relationship, if any, between 18q- and rheumatoid arthritis. Some children are hypermobile: they have flexible, double-jointed hands, legs or hips (Petty 1987, Rosen 2004, *Unique*).

Brain

Changes in the amount of myelin in the central nervous system have been seen on magnetic resonance images (MRIs) of the brains of people with 18q deletions. Myelin is the substance that covers nerve cells, much like the plastic coating covers the wire in an electric cord. Myelination, the formation of myelin, is an ongoing process that starts in the womb and continues after birth and into middle age. It appears that many people with 18q- have less myelin. The start of myelination is delayed, progresses at a lower rate and never achieves normal adult levels. This is often referred to as dysmyelination. It is not yet clear if or how these changes affect a child's development, although it has been suggested that the dysmyelination is associated with the tremor or shaky hand movements that occur in some people with 18q- (Miller 1990, *Unique*).

Ears and hearing

Children who have a loss of 18q often have narrow ear canals (stenosis) or ear canals that end before reaching the ear drum (atresia). Both ears are usually affected, although one canal may be narrower. Published medical literature suggests that this is one of the most consistent features of 18q- with 66 per cent of children affected. *Unique's* experience agrees with this finding: 69 per cent of surveyed children are affected (Nuijten 2003, Veltman 2003, Dostal 2006, *Unique*).

Narrow ear canals may lead to hearing loss in these children, although the degree of loss can vary from mild to severe. Most children with an 18q deletion and hearing loss have hearing aids to improve their hearing. Sometimes these are conventional hearing aids (an ear-mould placed in the ear canal that amplifies sound), but often a bone anchored hearing aid (BAHA) is fitted. A BAHA is a permanent implant surgically inserted into the skull bone behind the ear which transfers the amplified sound by vibrations directly to the cochlea (the inner ear) (*Unique*).

Babies and children with 18q- may also have more frequent ear infections than other children. The small differences they may have in the structure of the midface (the area between the forehead and the lower jaw) result in bacteria and viruses having easy access from the back of the throat to the ear, leading to an increased chance of ear infections. These slight changes in the structure of the midface, together with the narrow ear canals, can also lead to poor aeration of the middle ear. This causes a build up of secretions called glue ear and can temporarily affect hearing. Indeed a number of *Unique* children suffer from glue ear and frequent ear infections. Ear infections can be treated with prescribed medicine. 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. However, while glue ear persists, many children