Support and Information

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There is a Facebook group for 16p11.2 deletions at www.facebook.com/groups/103871962994301

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This information 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. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr Philip Giampetro, Department of Medical Genetics, Dr Shereif Rezkalla, Department of Cardiology, Marshfield Clinic, Marshfield, Wisconsin, USA and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK 2007. Revised 06/2009: the new section on 16p11.2 microdeletions was reviewed by Dr Emilia Bijlsma, clinical geneticist, Leiden University Medical Centre, The Netherlands. (PM)

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16p proximal deletions

Sources & references

The information in this leaflet is drawn partly from the published medical literature. Recently a number of important reviews have been published revealing effects of the emerging 16p11.2 microdeletion syndrome. 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 abstracts and articles from *Unique*. The leaflet also draws on *Unique*'s database which contains regularly updated information that reveals how children and adults develop. Information is also drawn from the Decipher database (http://decipher.sanger.ac.uk).

Proximal 16p deletions

A chromosome 16p deletion means that a part of one of the body's chromosomes has been lost or deleted. If the missing chromosome material contains genes with important instructions for the brain or body, developmental delay, some learning and behaviour difficulties and health problems may occur. How apparent and important these problems are depends on how much of the chromosome has been lost and where the deletion is.

Genes and chromosomes

Our bodies are made up of billions of cells. Most of the cells contain a complete set of tens of thousands of genes. Genes act like a set of instructions, directing our growth and development and how our bodies work. Genes are carried on structures called chromosomes. There are usually 46 chromosomes, 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in 'pairs'. Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy) the chromosomes are numbered 1 to 22, generally from largest to smallest. Each chromosome has a short arm (on the left in the diagram on page 3) called p from petit, the French word for small, and a long arm called q (on the right). In a 16p deletion, material has been lost from the short arm of one of the two chromosome 16s.

Looking at 16p

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. By looking at chromosomes in this way, it is possible to see the points where the chromosome has broken and what material is missing, if the missing piece is large enough. The missing piece of chromosome can be tiny or much larger. If it is visible under a microscope, it is called a deletion.

Sometimes the missing piece is so tiny that it can only be identified using new, more sensitive molecular techniques for analysing chromosomes such as array comparative genomic hybridisation (array-CGH, also known as microarrays). It is then called a microdeletion. Smaller deletions generally remove fewer genes and molecular techniques can usually show whether particular genes or parts of genes are present or not.

In the diagram on page 3 you can see the chromosome bands are numbered outwards from the point where the short arm meets the long arm (the centromere). In a proximal 16p deletion, the chromosome has broken in two places, leaving out the chromosome material between them. The word proximal means that the chromosome material lost is from closer to the centromere than to the tip of the short arm. Distal means closer to the tip of the arm.

Could this happen again?

Assuming that both parents have normal chromosomes, the 16p deletion is very unlikely to happen again. If one parent has a chromosome change in 16p or the same deletion as the child, the possibility of having another affected pregnancy would be much greater. A genetic specialist can give you more precise guidance for your family.

Will my child with a proximal 16p deletion have similarly affected children?

Adults with small 16p deletions and 16p11.2 microdeletions may form close relationships and want to have children. It is not yet known whether having the deletion affects fertility but given the number of families where both a parent and child have the microdeletion, it seems likely that fertility will be normal. In each pregnancy, someone with the deletion is likely to have a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the deletion.

Why did the 16p deletion occur?

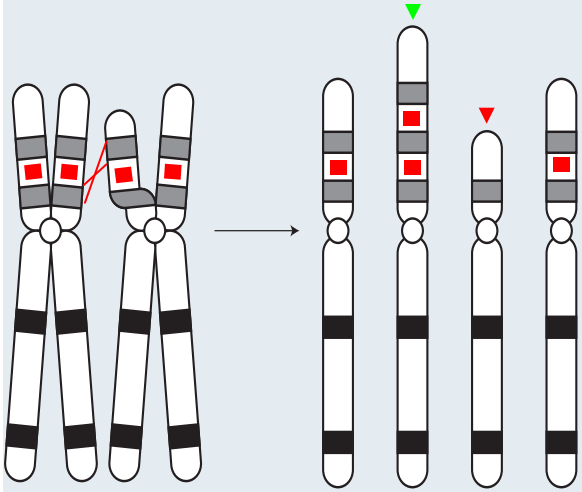
Some deletions can be the result of a rearrangement or change in one parent's chromosomes. For this reason, a blood test to check the parents' chromosomes is always advised.

The test may find exactly the same small deletion in one parent. Sometimes the parent appears to be affected by the microdeletion; sometimes they do not (Weiss 2008; Bijlsma 2009).

If tests find normal chromosomes in the parents, this means that the deletion occurred for the first time in the child. The term that geneticists use for this is de novo (dn), meaning 'new'.

The general theory of what has caused a de novo (new) deletion involves a mistake that occurs when the parents' sperm or egg cells are formed. At one point in the formation, all the chromosomes including the two chromosome 16s pair up and swap segments. To pair up precisely, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. However, throughout the chromosomes and in this area of 16p there are many short DNA sequences that are so similar that it is thought that mispairing can occur. At either end of the common 16p11.2 deletion there are short DNA sequences that are 99% similar and it is very likely that they can cause a mismatch. Although no-one has ever seen this happen, it is believed that when the exchange of genetic material, known as 'crossing over', occurs after mismatching, it is unequal, missing out a length of the chromosome.

Children from all parts of the world and from all types of background have 16p deletions. No environmental, dietary, workplace or lifestyle factors are known to cause them. There is nothing that either parent did before or during pregnancy that can be shown to have caused the deletion to occur and equally nothing could have been done to prevent it. So there is no reason for anyone to feel guilty.



One way that a deletion (and a duplication) could theoretically arise when egg or sperm cells are forming. 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 that enable correct pairing. The red blocks between the similar DNA sequences are segments of the chromosome. 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 (red arrow) and one with a duplication (green arrow).

16p11.2 microdeletions

Recently, many new diagnoses of 16p11.2 microdeletions have been made by array-CGH and many people have been found to have a similar-sized deletion. Generally, people with a 16p11.2 microdeletion belong to one of these two groups:

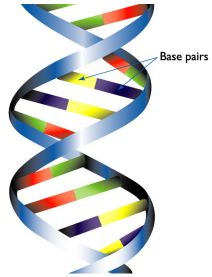
Group 1: Typical deletion including around 25 known genes. We know what some of the genes do, but not all (Bijlsma 2009; Kumar 2009; Kumar 2008; Marshall 2008; Weiss 2008; Ghebrianous 2007; Rosenberg 2006; *Unique)*. We consider these on pages 3-6.

Group 2: Smaller deletions close to this area, including fewer genes (Bijlsma 2009; Schäfer 2009; *Unique*). We consider these on page 7.

There is a third Group 3 of people with a variable-sized deletion between bands 16p11.2 and 16p12/13. The deletion in these people is usually relatively large. We consider these people on pages 7 to 13.
Unique publishes a separate information guide to 16p13 deletions.

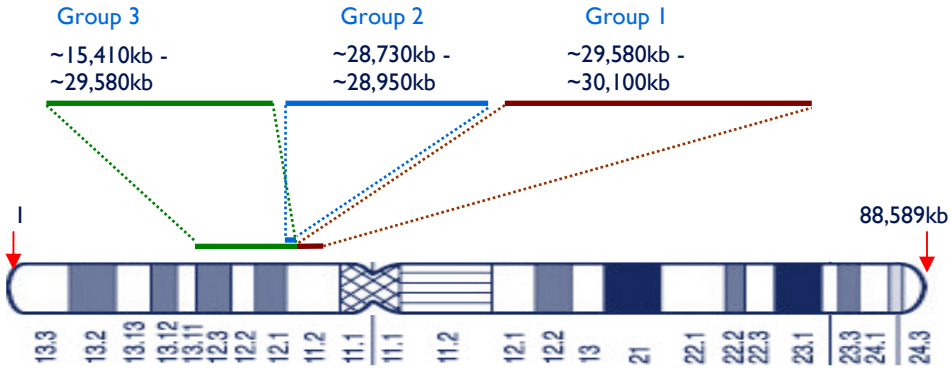
Group 1: Typical deletion

Since array-CGH became available in the early 2000s, first in research laboratories and then for routine diagnosis, more than 50 people have been diagnosed with microdeletions of similar size in band 16p11.2 and either reported in the published medical literature or registered with *Unique*. Since some people with the microdeletion share similar features, it has been suggested that they have a disorder known as 16p11.2 microdeletion syndrome. This is an emerging syndrome and much remains to be discovered but the following points are reasonably clear:



Two strands of DNA are held together in the shape of a double helix by the bonds between base pairs.

People with the typical deletion have lost a small part of one of their chromosome 16s. The part is lost from the short arm and includes around 5-600,000 base pairs, often referred to as 5-600kb (1kb=1,000 base pairs). Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. A typical array-CGH report will show base pairs missing between around 29,580,000 (29,580kb) and 30,100,000 (30,100kb). The numbers show a position on chromosome 16 between position 1 (the tip of the short arm) and position 88,589kb (the tip of the long arm).



Chromosome 16

Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken. You may be given a karyotype, a way of describing how chromosomes look that shows the bands where the chromosome has broken and rejoined. With a 16p11.2 deletion, the results are likely to read something like this:

46,XX,del(16)(p11.2p11.2)de novo

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(16)	The deletion is from chromosome 16
(p11.2p11.2)	The chromosome has two breakpoints, both in band 16p11.2 and the material between them is missing
de novo	The deletion occurred *de novo* (or as a 'new event'). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 16p11.2. The deletion is very unlikely to be inherited. If the same deletion is found in one of the parents, mat is written for mother or pat for father.

Instead of a karyotype, you may be given the results of molecular analysis such as array-CGH for your child. The results are likely to read something like this:

arr cgh 16p11.2(29581455->30106101)x1

arr cgh	The analysis was by array-CGH
16p11.2	A change was found in band 16p11.2
(29581455->30106101)x1	The first base pair shown to be missing (see diagram on page 3) is number 29581455 counting from the left of the chromosome. The last base pair shown to be missing is 30106101.

How common is it to have a 16p11.2 microdeletion?

The typical 16p11.2 microdeletion has been found in around 1:100 people with autism; in around 1: 750 people with dyslexia; in around 1:1000 people with a language or psychiatric disorder; and in around 1 in 10,000 people in the general population (White 2004; Bijlsma 2009).

Five years

Are there people with a 16p11.2 deletion who are healthy, have no major medical problems or birth defects and have developed normally?

Yes, there are. Some people with a 16p11.2 microdeletion are apparently unaffected by it. They have no learning, speech or developmental difficulties. When the parents of 14 individuals with the deletion had their chromosomes checked, three entirely normal and healthy parents (two mothers, one father) had the same 16p11.2 microdeletion as their affected child. In another study, two people in a general population of almost 19,000 had the 16p11.2 microdeletion (Weiss 2008; Bijlsma 2009).

when you talk. He observes everything and then will sit in one spot and try to figure out how things work – *16p11.2p13.1 deletion, at 12 months*

- " His teachers say that he plays behind other children, but not with them as he cannot communicate with them. He often leaves the line of students when he sees something more interesting – *the same child, at 4 years*
- " She is not reading yet but is trying to write her name – *undetermined deletion, at 8 years*
- " An excellent long term memory and socially she is very capable. She can write her first name and sometimes her second – *16p12.2p13.11 deletion at 14 years*

Two unrelated girls, each with a 16p12.2p13.11 deletion

■ Personal care and development

From the small amount of information available from *Unique*, it seems that personal care development is likely to be somewhat delayed. Day time toilet training was achieved between 3 and 5 years and may develop even later. Children learned to dress, wash and feed themselves somewhat later than their typically-developing peers but in general were helped in some cases by having almost age-appropriate fine motor skills.

- " He is not toilet trained and shows no interest in doing so. His physical therapist says that this is due to low muscle tone – *4 years*
- " At 14, she is capable of dressing, washing and toileting and does this beautifully if we are going somewhere at the weekend but not always on school days!

■ Behaviour

No consistent pattern of behaviour is clear. Families of younger children report no real behaviour challenges, although a four-year-old has frequent temper tantrums when unable to do what he wants and has no understanding of danger. One child, aged 8 years, has aggressive tantrums and can self harm, the outbursts being especially hard to handle when she is tired. One child at 14 years is restless and hyperactive in her home environment but passive elsewhere. The families of two of these children have had psychological and behaviour therapy input and one child was successfully treated for a while with methylphenidate (Ritalin). Other reports show in individual cases possible insensitivity to pain; irritability and repetitive behaviours such as head banging and handflapping; anxiety; attention deficit hyperactivity disorder; high energy levels; a short attention span and difficulties with concentration (Battaglia 2009; Ballif 2007; *Unique*).

Children behaving beautifully

2½ years

3¾ years

14 years

How can communication be affected?

13 months

Some delay in the emergence of speech and language is to be expected, but the extent of the delay is variable and partly reflects the level of cognitive ability.

Children have started to use single words between one and five years and in general once first words have emerged, there has been clear progress. Some problems of articulation are common to most of the children, so that speech may only be clearly understandable in part. Children are generally helped by learning to sign as well as to speak in the early months and years and may acquire a vocabulary of hundreds of signs but the general picture is that by mid-childhood children can communicate in short phrases which eventually lengthen into sentences and conversation. Receptive language (understanding) may be slow to develop and understanding of non-concrete ideas may be very late to develop.

Early intervention with specifically targeted speech therapy will enable children to maximise their communication potential and minimise their difficulties. Children's generally sociable disposition helps them to communicate well.

" He is able to use about 400 sign language signs. He can only speak about 20 words. He still has difficulty manipulating his tongue in his mouth and cannot feel food placement on his tongue. This often leads to him stuffing his mouth full of food and choking on the food as he fills his mouth so full that he can no longer chew. We believe that this problem will have to be fixed before language can occur – *16p11.2p13 deletion, 4 years*

" When she says 'I love you' I just want to cry as we were told she may never speak or walk – *8 years*

How can a child's ability to learn be affected?

A child with a proximal 16p deletion can be expected to need some support with their formal learning and as far as we can judge, it seems most likely that children will have a difficulty in the mild to moderate range. The extent of learning difficulty does not appear to be predictable from the chromosomal make-up but those with a larger deletion appear to be at greater risk for marked learning disabilities than those with a microdeletion.

Strengths shown by individual children include a good long term memory for names and directions; an ability to sing, positive response to music and general musical talent; good social interaction.

While some children may start their education in a mainstream school, with some support and special classes and withdrawal for specific therapies, other children have thrived better within a special setting where their needs can be appropriately catered for.

" He has an excellent memory. He can remember songs and where a toy is hidden. He learns best with music. He can clap in beat with a song. He has been taking children's music classes and excels in them. He likes to read books. He likes to study your face

Main features

The features linked with losing this small piece of DNA vary. They even vary between different members of the same family. The most common features are

- delay in starting to speak
- a degree of developmental delay or learning difficulty
- an influence on susceptibility to autism or an autistic spectrum disorder
- very minor unusual facial or physical features, such as widely spaced eyes or partly joined toes
- tendency to overweight
- in a minority, a seizure disorder
- usually no major birth defects

These features do not affect everyone and in any individual person, they can be more or less obvious.

Delay in starting to speak

Most children with a 16p11.2 microdeletion do appear to be late to start speaking. The ages at which children said their first words have ranged from 18 months to over four years and it is possible that words will come even later in some children. Once speech develops it has been characterised in one child as nasal; another child had a lisp. Evidence from *Unique* suggests that delayed speech development can be persistent in some (Ghebrianous 2007; Weiss 2008; Bijlsma 2009; *Unique*).

Developmental delay

Two people in three with the 16p11.2 microdeletion have shown some degree of developmental delay. They may be slow to sit, crawl and walk but so far everyone with the microdeletion has walked, although their walking style may be clumsy. Fine motor skills may also be delayed, so babies can be late to grasp and play with toys and to develop a pincer grip. Low muscle tone with lax joints has occasionally been reported, and in one case raised muscle tone (Bijlsma 2009; *Unique*).

A degree of learning difficulty

Among adults and children with a 16p11.2 microdeletion, there is a broad spectrum of need for special support with learning. A few people have no learning difficulty at all (one *Unique* member has an IQ of 135); others have a specific learning difficulty, in particular dyslexia; perhaps the largest group has a level of difficulty that would be described as mild, with a tested IQ in the 60-79 range; and a few have greater learning challenges and need more support. Information from *Unique* suggests that language-based learning may be specifically affected (Ghebrianous 2007; Weiss 2008; Bijlsma 2009; *Unique*).

Influence on susceptibility to autism or autistic spectrum disorder

The 16p11.2 microdeletion is found far more often among children and adults diagnosed with autism or a disorder such as Asperger syndrome within the autistic spectrum than among the general population. Yet by no means everyone with the microdeletion has autism. According to a recent estimate, about one person in three with the microdeletion also has autism.

It is currently believed that having the microdeletion increases the risk of autism but

does not necessarily cause it. Nor is the autism associated with the microdeletion any particular variant of autism, although one study found what researchers believed was a trend towards difficult behaviour with overactivity and aggression.

The underlying suggestion is that a network of 12 genes within the microdeletion region is disrupted, causing the features of autism. These genes include genes involved in cell-to-cell signalling and interaction (Kumar 2008; Weiss 2008; Bijlsma 2009).

Minor unusual facial or physical features

Children and adults with a 16p11.2 microdeletion do not look particularly like each other and there is no recognisable pattern of facial or physical similarities as there is in some other chromosome disorders. In individuals, slightly unusual facial features have been reported in around one person in three. Some of these unusual facial features include: small eyes; hooded eyelids; tiny skin folds across the inner corners of the eyes; unusual-shaped ears set low on the side of the head; a lower jaw set back from the upper jaw. Other unusual physical features mentioned include sloping shoulders; webbed toes; a single palm crease; and small hands (Kumar 2008; Bijlsma 2009).

A tendency to overweight

A tendency to overweight, with a body mass index of more than 25, has been identified in almost half of all children and adults with a 16p11.2 microdeletion. At the age of 28, twin brothers with a 16p11.2 microdeletion were a comparable height to their unaffected brother and much heavier (84-88 kg (13 stone, 3-12lb) compared with 71kg (11 stone, 2lb). This tendency is not a necessary feature, and some children with the deletion are small and thin. However, knowing about this possible tendency may be helpful for parents trying to keep their child as fit and healthy as possible (Ghebrianous 2007; Bijlsma 2009; *Unique*).

In a small minority, a seizure disorder

Generally speaking, people with a 16p11.2 microdeletion are fit and healthy. One in four has a seizure disorder or has had one but the evidence is that seizures are well controlled with medication. Epilepsy has developed between babyhood and puberty. Twin brothers each developed seizures between 11 and 13 years (Ghebrianous 2007; Bijlsma 2009; *Unique*).

Left: having an EEG

Right: making cookies

(Battaglia 2009; Ballif 2007; *Unique*). The four-year-old also has frequent nose bleeds and allergies, including a milk allergy.

General health and well being

One child repeatedly suffered severe dehydration after catching viral gastrointestinal infections and was treated in hospital. Both times she was rehydrated using a nasogastric tube after hospital staff failed to find a vein for cannula insertion. A child with a 16p12.2p13.11 deletion had a bone infection at 8 years but at 14 years was in excellent health without medication. Puberty started and proceeded normally in this girl.

Teeth

Dental development has been disrupted or taken an unusual pattern in three of five children. One baby teethed very early, cutting her first tooth at eleven weeks, adjusted for prematurity. Two children with a small jaw had malformed teeth and one required orthodontic correction. One child had two extra milk teeth and needed all milk teeth removed to allow the permanent teeth to emerge properly.

Development

Sitting, moving: gross motor skills

Babies and children with a proximal 16p deletion typically face some delay in reaching their mobility milestones and this may be quite marked at first. Babies learned to roll over between 12 and 17 months, sat between six and 28 months, became mobile between seven and 23 months and mastered walking in their third year, although one was walking by 18 months. Most children are quite active, and running and climbing may follow rapidly after walking. Underlying some of the delay in mobility is a low muscle tone, making a baby or child feel unusually floppy to hold and making their joints very flexible. Children may need to wear supporting boots to stabilise their ankle joints or may be helped by using a walking frame in the early days of mastering walking. Once walking, children's mobility generally normalises, but a 14-year-old is stiff and has difficulty in planning her movements and a 13-year-old still has an unsteady gait. A four-year-old born with severe club feet was still tripping while walking but was running and was a 'phenomenal athlete', shooting baskets for hours (Battaglia 2009; Ballif 2007; *Unique*).

Both girls' families were told they might not walk

Using their hands: fine motor and coordination skills

Hand and eye coordination skills such as holding a bottle and playing with small toys may not develop in line with gross motor skills. The experience of this small group is that fine motor skills may be age-appropriate, at least in early childhood, so children may have the skills needed to feed themselves and to carry out personal care tasks. This is not, however, true for all and some children do show a marked delay in holding a cup, dressing and feeding themselves. At the age of four, one boy had excellent hand control for sport, throwing a baseball hard and accurately, but was not yet drawing or writing with definition.

At 3½ years

Medical concerns

- Heart conditions

Seven of the 19 babies were born with a heart condition. In one child the ductus arteriosus that allows blood to circulate without returning to the lungs to be recharged with oxygen failed to close as normal after birth. A persistent ductus arteriosus (PDA) may be allowed to close naturally, it may be closed surgically or its closure may be encouraged, as in this case, with medication. Whichever approach is chosen, the outlook for this common condition is good. A baby with a 16p11.2p13.1 deletion was born with two holes between the upper or lower chambers of the heart (septal defects). A septal defect will be carefully assessed and treatment decided depending on a number of factors including the size of the holes. In this baby they have been allowed to close naturally. A third baby was born with the complex heart condition known as tetralogy of Fallot that requires surgical correction. After surgery at the age of seven months, this baby has progressed well although at eight years she tires easily and does not walk long distances. The fourth child was born with pulmonary valve stenosis, reducing blood flow to the lungs, but surgically corrected. Heart problems were identified in a fifth baby at 20 weeks of pregnancy; these led to his death at 5 months. One girl had episodes where the heart beat slowed and two were born with Ebstein's anomaly where the valve between the upper and lower heart chambers is unusually low on the right side, increasing the size of the upper, filling chamber and decreasing the size of the lower, pumping chamber (Hernando 2002; Ballif 2007; *Unique*).

- Breathing

One baby had small nasal passages which limited his oxygen intake in the first few months of life but he outgrew the problem naturally. A child with a significant heart condition also had asthma so at the age of 8 she needed nebulised treatments when she caught a cold in the winter months.

- Possibility of seizures

The only seizures seen in this group involved a child reacting to his first whooping cough (pertussis) immunisations. The reaction was not repeated at later immunisations. However, a further 13-year-old child has 'staring spells' (Ballif 2007; *Unique*).

- Other medical concerns

Other medical concerns seen in individual children include: a split (cleft) in the top of the mouth at the back (soft palate; this can cause problems with feeding and speech production) as well as a small, recessed lower jaw (known as Pierre Robin sequence); narrow nasal passages, outgrown within the first few months of life; hip dislocation with a shallow socket; partly fused vaginal labia at birth that self corrected within the first year of life; abnormal placement of the anus; spinal curvature, causing a humped appearance (kyphosis); constipation; multiple cysts (fluid-filled pockets) seen in one kidney in a fetus (Hernando 2002; Decipher; *Unique*).

One baby with a deletion from 16p12.3 to p13.12 was born with cataracts and one *Unique* child with an undetermined deletion (either 16p12p13.1 or 16p11.2p12) has a squint (strabismus), requiring monitoring. A four-year-old child with a large deletion between 16p11.2 and 16p13 wears glasses to correct his nearsightedness and has tubes in his ears. These have reduced his frequent ear infections, a problem he shared with five girls with a large deletion, in one case including the typical 16p11.2 microdeletion

Group 2: smaller deletions with fewer genes

Two children and an adult have been diagnosed with a microdeletion flanking the 'critical region' for the 16p11.2 microdeletion syndrome. In a 10-year-old girl, the deletion extends from at least 28,730kb to 28,950kb; in the other 5-year-old child and his father, it extends for a slightly shorter extent over the same stretch of the chromosome (Bijlsma 2009; Schäfer 2009; *Unique*).

The 5-year-old boy had hypotonia and developmental delay, walking at the age of two and talking but not always comprehensibly at five. His behavioural problems are treated with risperidone. He had certain unusual facial features including a long, narrow face, a prominent forehead, narrow eyes that slanted downwards, and an open mouth with downturned corners. An MRI scan of his brain was normal. His father, with the same deletion, had similar facial features and had learning difficulties at school but worked as a lorry driver.

The 10-year-old girl has mild learning difficulties with a global IQ of 79, lax joints, a low muscle tone, strabismus (a squint) corrected by surgery and seizures as well as certain unusual facial features including small skinfolds across the inner corners of the eye (epicanthic folds), a broad nose, a long groove between the nose and upper lip and a narrow palate. A brain scan revealed periventricular nodular heterotopy – a disorder characterised by round or oval collections of grey matter protruding into the ventricles within the brain and frequently associated with seizures.

Group 3: Deletions beyond the typical 16p11.2 microdeletion

Information on 19 individuals with deletions of varying size beyond the typical 16p11.2 microdeletion (see page 3) is taken from Battaglia 2009; Ballif 2007; Hernando 2002; Decipher; and *Unique*. Although only outline information on features is available from Decipher, all cases have had a molecular analysis, allowing quite precise delineation of the size of the missing piece.

Appearance

For many children with a proximal 16p deletion there seems to be usually little sign in their facial appearance of any underlying disorder. Doctors may notice what are known as 'dysmorphic features' which may or may not be obvious to a parent. Most of these are descriptions of head shape or facial features which may mean that children and adults with these deletions look more like each other than like other members of their family. Features commented on include downslanting, deep-set eyes, low set ears, an open mouth due to low facial muscle tone, a flat face, a wide nasal bridge and tiny skin folds across the inner corners of the eyes (Battaglia 2009; Ballif 2007; *Unique*).

One unborn baby with a small deletion from 16p12.3 to 16p13.12 was severely affected

Unrelated children with a group 3 deletion beyond the typical 16p11.2 microdeletion

with facial features associated with the failure of the front part of the brain to divide into two hemispheres (holoprosencephaly), including a split in the upper lip and failure of the nose to develop. A girl with a large deletion at 16p11.2p12.2 was also born with a cleft lip and palate (Ballif 2007; Decipher).

Hands and feet

Above: casting for talipes, at one month.
Left: after treatment, at two years.
Far left: at four years.

Various minor anomalies of the hands and feet are relatively common in children with chromosome disorders. In children with a16p deletion, these are usually no more than cosmetic. Unusual features observed in individuals include a single crease across the palm, incurving fifth fingers, bent or long, thin fingers and very small hands and feet, in one child approximately the size of a child of three or four years at eight years old. Shoe size at 8 years in this child was first size 10½-11½.

One child has a 'sandal gap', a large gap between the big and second toes. A child with a 16p11.2p13.1 deletion was born with very severe talipes (clubfoot, affecting both feet), identified during pregnancy. After fifteen months of treatment using braces, casts and tendon lengthening surgery, this child's feet looked 'normal'. Two years on, he was wearing splints at night to maintain his foot position. A child with a deletion just beyond the typical 16p11.2 microdeletion and an 18-year-old with a microdeletion at 16p12.3p13.12 have hammer toes, while an adult with a larger deletion in the same region has clawed feet, with raised arches. Others have skin joining the toes (Battaglia 2009; Ballif 2007; Decipher; *Unique*).

What about food and eating?

All babies have had some level of feeding difficulty but the amount of difficulty is extremely variable and does not relate in any precise way to the chromosome make-up. Babies with low muscle tone of the face and mouth have had swallowing and mouth closure difficulties. The baby with the least difficulties has a 16p12.2p13.11 deletion. After initial reluctance to breastfeed as a newborn, she was tube fed expressed breast milk and by the age of one week was successfully breastfeeding and continued to do so to the age of three months. Two babies were unable to latch on or suck at first and had great difficulty even drinking from a bottle. One, born with a recessed lower jaw and unusually small mouth, learned to breastfeed at five weeks and continued to the age of 13 months, but that was not possible in the other case. The baby who breastfed successfully was eating most foods by the age of four but needed them cut up small. He had to be reminded to take small bites as he could not feel how much food he had in his mouth and tended to overfill. He also had difficulty manoeuvring his tongue.

In babies with a significant heart condition, feeding difficulties have been quite severe and long-lasting. After initial tube feeding, babies have moved on to small, frequent bottle feeds with a calorie-dense formula milk to ensure an energy-rich intake.
The general picture here is of vulnerable mothers and babies who may need considerable support to establish feeding and further support at transitions to weaning, taking lumpy foods, chewing and self feeding.

Above: 12 months
Left: three years

Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food passage, is fairly common in babies with a chromosome disorder and affected one baby in this group quite severely. Reflux raises a baby's risk of inhaling food contents and setting up an infection in the lungs known as aspiration pneumonia. Reflux can be eased by careful semi-upright positioning during and after feeds, sleeping in a prescribed sleep chair rather than a bed, raising the head end of the baby's cot and if necessary by prescribed medication that helps to keep the feed within the stomach and counteract any acidity. Babies who have continuing problems can have a surgical procedure called a fundoplication to improve the action of the valve at the junction of the food passage and stomach. Where feeding and reflux problems are persistent, a gastrostomy tube (PEG, button) can be inserted to allow direct feeding into the stomach until the baby is sufficiently mature to tolerate feeding by mouth. In the five babies considered here none had problems that could not be managed with medication.
A further possible problem is constipation, which affected at least two children to a marked degree.

> " At 10 months his speech therapist gave us an empty plastic honey bear bottle with a piece of plastic tubing as a straw. It took him less than 20 minutes to figure out how to make the straw work. At 4, we have to remind him to take small bites and chew due to the choking hazards of him overfilling his mouth - *16p11.2p13.1 deletion*

Is there a typical growth pattern?

Some babies have grown slowly in the womb and are born small for dates. The evidence from *Unique* is that some of these children catch up in height, while others remain proportionately small. Children and adolescents with a proximal 16p deletion seem to be most typically somewhat short for their age. The most typical body build is thin or very thin, although one adolescent has developed a certain plumpness. It is not yet known what the eventual adult height of these children will be (Battaglia 2009; Hernando 2002; *Unique*).

> " She has always been of fine build and normal/long for her age, unlike her heavy-set parents - *16p12.1p13.11, at 3 years*

> " He is solid muscle through the middle and a little on the slim side - *16p11.2p13.1 deletion, at almost 4 years*