



Inform Network Support



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At <https://www.simonsearchlight.org/> there is an online community for families affected by 16p11.2 deletions and duplications

Facebook

<https://www.facebook.com/Microdeletion16p112SupportAndInformation/>
<https://www.facebook.com/16p11.2/>

Join UniquE for family links, information and support.

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Please help us to help you!

UniquE mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it. This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by UniquE and reviewed by Dr David Miller, Clinical Geneticist and Clinical Molecular Geneticist, Children's Hospital, Boston, USA and by Professor Maj Hultén BSc PhD MD FRCPATH, Professor of Reproductive Genetics, University of Warwick, UK, 2010.

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16p11.2 microdeletions



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Sources & references

The information in this guide is drawn from what has been published in the medical literature about people with a deletion from 16p11.2. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain articles from Unique. The leaflet also draws on information on the Decipher database (decipher.sanger.ac.uk) and on Unique's database. When the guide was published, Unique had 40 members with a 16p11.2 deletion (Hernando 2002; Rosenberg 2006; Ballif 2007; Ghebranious 2007; Kumar 2008; Marshall 2008; Weiss 2008; Battaglia 2009; Bijlsma 2009; Bradley 2009; Glessner 2009; Hempel 2009; McCarthy 2009; Shimojima 2009; Shinawi 2009; Shiow 2009; Bochukova 2010; Fernandez 2010; Girirajan 2010; Walters 2010; Hanson, 2010; Nik-Zainal 2011; Schaaf 2011; Decipher; Unique).

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 16p deletion, the chromosome has broken in two places, leaving out the material between them.

Why did the 16p11.2 deletion occur?

Many 16p11.2 microdeletions occur out of the blue for no obvious reason. The genetic term for this is de novo [dn], meaning 'new', and when analysed, both parents have normal chromosomes. Less often, 16p11.2 microdeletions are inherited from a parent with the same microdeletion. Sometimes the parent appears to be affected by the microdeletion; sometimes they do not (Weiss 2008; Bijlsma 2009). The only way to know whether your child's microdeletion is inherited or a new deletion is for both parents' chromosomes to be analysed.

The general theory of what has caused a new microdeletion 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 there are many 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.

What is certain is that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary, workplace or lifestyle factors are known to cause 16p11.2 microdeletions. There is nothing that either parent did before or during pregnancy that caused the microdeletion.

Could this happen again?

For a parent with normal chromosomes, the risk of having another affected child is almost certainly very low, but still higher than for parents who never had a child with 16p11.2 deletion. Your genetics centre should be able to offer counselling before you have another pregnancy and if you already have a child with the microdeletion, prenatal diagnosis is technically possible by chorionic villus sampling at 11-13 weeks or amniocentesis at 15-18 weeks, if that is what you choose. However, it isn't yet possible to predict how mildly or severely any child will be affected. If either parent has the same 16p11.2 microdeletion as the child, they have a 50 per cent chance of passing it on in each pregnancy.

Will my child have similarly affected children?

In each pregnancy, someone with the microdeletion is likely to have a 50 per cent risk of passing it on and a 50 per cent chance of having a child without it. A baby who inherits the deletion may be affected or may not. We haven't known about the syndrome for long enough to be certain of the range of possible effects or how obvious they will be.

One child had constipation, attributed to too little fluid intake. One child was born with a blockage in the digestive tract [duodenal stenosis] that was repaired surgically at 4 days.

Structural brain abnormalities

Of the two children who have had brain imaging, neither has any visible structural anomalies (Unique).

Heart

No heart abnormalities were found in 5 Unique children.

Spine

One child was found to have a wedge-shaped bone in the spine known as a hemivertebra (page 16). Hemivertebrae are caused by incomplete development of one side of the vertebra. In most cases there are no symptoms or they are mild but they can cause a curve in the spine resulting in scoliosis, kyphosis or lordosis and will therefore be monitored.

General health and wellbeing; puberty

Four Unique members were reported generally healthy, although the youngest, a 16-month-old, had two urinary infections and several virus infections and another was prone to chest and ear infections before the age of 5 but outgrew the tendency. One child of 5 was prone to both skin infections and to colds, with breathing difficulties interrupting his sleep. One child has a squint [strabismus]; otherwise there are no reported vision problems. There are no hearing problems reported. One child was reported to have unusually placed teeth (Unique).



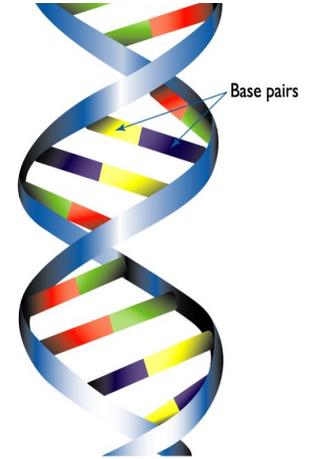
16p11.2 microdeletion syndrome

People with a 16p11.2 microdeletion have lost a small amount of DNA from one of their chromosomes. Generally, people with a 16p11.2 microdeletion belong to one of three groups:

Group 1: Typical microdeletion of around 550,000 base pairs (550kb) from band 11.2 of the short arm of chromosome 16. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. The missing base pairs are generally between around 29,562,499 and 30,192,499. These numbers show a position on chromosome 16 between position 1 (the end of the short arm) and position 90,354,753 (the end of the long arm). Around 25 known genes are included in the lost material. We know what some of them do, but not all. See pages 4-16

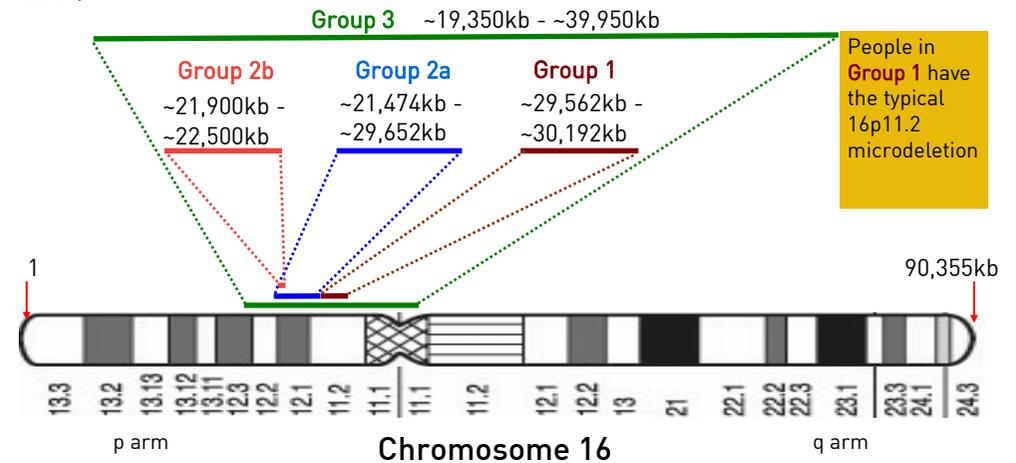
Group 2: Deletion of varying size, not overlapping the typical microdeletion but from the region flanking it and closer to the end of the short arm of chromosome 16. See pages 16-23

Group 3: Larger deletion including the typical microdeletion. See pages 23-26



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

Loss or gain of material from 16p11.2 is increasingly recognized as one of the most common structural chromosome disorders. The 16p11.2 microdeletion has been found in around 1:100 people with autism; in around 1:1000 people with a language or psychiatric disorder; and in around 3 in 10,000 people in the general population (Weiss 2008; Bijlsma 2009).



The numbers in this diagram refer to the human genome build 19 (hg19; see page 4 for more details). Your child's report may refer to a different human genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Results of the array test

In the past, chromosomes were directly visualised under a highly powered microscope. The typical 16p11.2 microdeletion is too small to be detected by this method. It is usually detected by a molecular analysis such as array CGH, also called a microarray.

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken. The results are likely to read something like this:

arr[hg19] 16p11.2(29673954-30198600)x1 dn

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

16p11.2 A change was found in band 16p11.2
(29673954-30198600)x1

The first base pair (the chemicals in the DNA molecule that form the ends of the 'rungs' of its ladder-like structure, as in the image on page 3) that is shown to be missing is number 29673954-The last base pair shown to be missing is 30198600. Take the first long number from the second and you get 524646. In some array reports on 16p, the first number is larger than the second. In this case, just take the smaller number from the larger one. The result is the number of base pairs that are missing. x1 means there is only one copy of these base pairs, not two – one on each chromosome 16 – as you would normally expect.

de novo or dn 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 and has almost certainly occurred for the first time in this family with this child.

Group 1: 16p11.2 microdeletion syndrome

Some people with the typical microdeletion share similar features. These features add up to an emerging syndrome known as the 16p11.2 microdeletion syndrome. Much remains to be discovered but the following points are reasonably clear:

- The most common features are:
 - delay in starting to speak and in language development
 - some developmental delay or learning difficulty. Developmental delay is more likely to affect thinking and language skills than mobility skills
 - an increased susceptibility to autism or an autism spectrum disorder
 - very minor unusual facial or physical features
 - low muscle tone in babies
 - tendency to overweight
 - in a few, a seizure disorder



- The features vary, even between members of the same family. They do not affect everyone, and in any individual they can be more or less obvious.
- People with a 16p11.2 microdeletion do not usually have any major birth defects.
- Some people are apparently unaffected by their 16p11.2 microdeletion. They have no learning, speech or developmental difficulties.

In most Unique families, children were too young to know whether they would have a learning difficulty. A 5-year-old was expected to have a mild learning disability on testing.

Influence on susceptibility to autism or autism spectrum disorder

Despite all carrying the typical 16p11.2 deletion for autism, there are no reports of autism among Unique members. Families generally report that their children are warm and loving towards familiar people, if shy with people they do not know.

Minor unusual facial or physical features

Parents of 3/6 Unique children report no unusual facial features. Two others report a flat midface, broad forehead and small chin and lower jaw; as well as downslanting eyes, a skinfold across the inner corner of the eyes [epicanthic fold], low set ears, thin upper lip and flat philtrum [groove between nose and upper lip] and small, crooked teeth in one. One reports coarse hair on top of the head (Unique).

One young child has kidney reflux; one was born with a hemivertebra (page 16). Otherwise children are healthy.

“ Generally surprisingly healthy compared to siblings - 4 years

No evidence of a seizure disorder

Unique members aged to 7 years have been free of seizures.

A tendency to overweight

A tendency to overweight was found in 4/8, including two older Unique children (4 and 5 years), but not the younger children. One Unique child fed well as a baby but by 5 years had developed a 'voracious appetite' and food cravings (Bochukova 2010; Unique).

“ He has no tendency to overweight but eats an unusually large amount - 21 months

Behaviour

A 16-month-old is 'mostly happy and content'; a 21-month-old is generally happy with no problematic behaviour but can be unpredictable – happy one minute, then agitated and difficult the next for no obvious reason; a 4-year-old can be 'very stubborn and has the occasional tantrum' and is socially reserved with new people but 'warm and loving' towards people she knows; a 7-year-old is well-behaved, happy and confident.

Pregnancy and birth

In two/4 Unique pregnancies, the baby was small for dates. In two pregnancies there was repeated bleeding in the first three months.

Early feeding

Unusually for babies with a chromosome disorder, no families reported early feeding difficulties. Two babies had mild gastro oesophageal reflux [where feeds return up the food passage], causing screaming and back arching but no possetting or vomiting in one; in the other the symptoms were most obvious while she was learning to get upright and passed by the age of 2½ years

First signs

Among 6 Unique families, the first signs were varied. One baby was floppy (hypotonic) and couldn't lift her head at 6 months; another showed general developmental delay, being late to smile, crawl and walk; prenatal ultrasound showed irregularities in the kidneys and possibly the brain and spine in a third.

Delay in starting to speak

Speech is delayed among all Unique children, with a 16-month-old toddler communicating by pointing and babbling but not yet speaking and a 4-year-old using speech and signing. In two children the first signs of speech delay were noticed at 12 and 15 months. In one child speech and language is the most affected area of development. Another started talking at 2½ years. One child of 5 has a severe articulation difficulty (Unique).

“ Communicates by pointing and babbling - 16 months

“ Starting to sign. Has a few words but struggles with pronunciation. Seems to understand well but cannot respond in speech. Can join two words eg Dadda's car; shut door - 2 years

“ Uses mostly single words, recently up to 3-word phrases. Has difficulty with s and rolled r - 4 years

Mobility

Mobility (gross motor) skills were delayed in 4/5 children, although one child developed normally to the age of 12 months. Babies rolled over at 5 months – 2 years; became mobile from 11 months; and started to walk from 21 months . One child never crawled or shuffled, moving direct from sitting to standing and then walking. Hypotonia or altered muscle tone underlay the delay in two children, one of whom wore a supportive lycra body suit (Unique).

“ He was late to roll over, crawl and walk but is now walking well and has good physical ability. He enjoys playing in the park, jumping and climbing - 21 months

“ She moves around by walking, running (a bit wobbly), climbs stairs mostly on all fours. Loves to kick ball. Runs and jumps but falls a lot - 4 years

Fine motor skills

Fine motor skills delays were noted in two older children, aged 4 and 5 years, but not in younger toddlers and children.

“ She sometimes prefers to use her hands rather than cutlery; she can hold a pen but not draw anything identifiable - 4 years

Personal care and toilet training

Toilet training was achieved in a 4-5-year-old. Information from *Unique* suggests that help with washing, tooth cleaning and other aspects of personal care will be needed for longer than in typically developing children, with reminders to finish the task in hand required.

A degree of learning difficulty

- Women and men who carry a 16p11.2 microdeletion can pass it on to their children. The microdeletion can affect the child differently to the parent.

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. 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. Unique has member families with the microdeletion with healthy parents and children but also children with developmental delay (Weiss 2008; Bijlsma 2009; Glessner 2009; Shinawi 2009; Unique).

Delay in starting to speak

A delay in speech and language is common and may be the first sign of developmental delay. Parents may notice that their baby isn't babbling or their toddler isn't saying words. The delay particularly affects expressive language, with understanding relatively preserved. The speech delay can exist separately from any learning difficulty. Twenty/26 Unique members had an obvious speech delay. The ages at which children said their first recognisable words have ranged from 12 months to seven years and words may emerge even later. Speaking in phrases emerged from two to 12 years among Unique members. Difficulties with consonant articulation were common and could be persistent, especially when a child was tired or in a hurry. Families found that simultaneous signing could help a child who was talking but not being understood (Ghebriannous 2007; Weiss 2008; Bijlsma 2009; Shinawi 2009; Unique).

“ She is now using 2-3 word phrases. She has difficulty saying s, r, w and anything that uses the tongue at the front of the mouth - 2 years 5 months

“ When there is no speech you learn new ways to communicate and one very fleeting smile from her can keep me smiling for hours. She had no spoken words, only sounds, when she was three and a half. Within nine months she was making vowel sounds, signing a little and gesturing - 4¼ years

“ His main area of delay is with his expressive language. At nearly four, he had only 4 or 5 spoken words with some new sounds emerging but used Makaton sign language for keywords. At four, he was starting to vocalise but found it difficult to say consonants before vowels and multisyllabic words - 4¾ years

“ We noticed the first signs of speech delay at 18 months. Today he communicates using gestures, showing and words. There can be a lot of difference between his understanding and expression, and sometimes he gets frustrated as he knows what he wants to say but can't put the words together to say it. After 3 his speech was understandable but he still finds it hard to say m, f, v, l and p. He uses a lot of single to maybe 3 word phrases, maximum 5-word sentences - almost 5 years

“ She communicates verbally and in the past year has been creating 5/6 word sentences but her speech is very repetitive and obsessive and her grammar is poor - 5 years

“ Communication is coming: he uses speech, signing, vocal noises, and at school a picture exchange schedule. He spoke his first words around 4 but they were not clear until 5 years 10 months. By 5, he was using 2/3 word phrases and occasionally 4/5 word phrases by 6; today he still mainly uses 2/3 words at a time. He has difficulty saying th, s and d, talks really fast and is very hard to understand - 6 years 10 months

“ He uses speech and signing, Makaton at home and school, mixed with his own signs at home. He can speak and uses lots of words and tries to make huge sentences but without signs is hard to understand. Among the sounds he has difficulty saying are f, d, s, g, t and p. But he has whistled for years. We were amazed when he couldn't speak but would communicate using whistles. Now he tries to whistle songs - 8 years

“ At 2 he had no words and started speech therapy, progressing very slowly with sentences only from about 6. Now he talks quite well and his sentences are quite complete, although he still has some problems with sounds (s, sh, j, r, g and l) and grammar. He uses simple language and words and gets muddled trying to get out what he wants to say. Understanding has always been a strength, expression a weakness: he understands everything in two languages but speaks only English - 8¼ years

“ We first noticed her speech delay at 12 months and she started speaking at 3. She now has problems with talking too fast, slurred speech, the r sound, hypernasality and verb-noun agreement. She uses Tarby speech books to slow her rate down with short phrases and pausing on longer sentences - 9 years

“ His speech delay was first noticed at his 2 year assessment. He made vocal noises before 7; by 12 he has limited speech, uses 2/3 word phrases and communicates also with signing and a Vocabox. He finds the beginnings of words hard to say - 12 years

Developmental delay

Two people in three have shown some developmental delay. The pattern and severity of the delay is individual, with speech, gross motor and fine motor skills affected variably. Some families report advanced skills in some areas, delay in others. Any delay may be obvious from early babyhood, at toddler or pre-school checks or when a child has difficulty keeping up at school. Once the delay has been confirmed, starting therapies early is helpful, with all Unique members making significant progress and some entirely overcoming their initial delay, particularly in mobility.

Here, Unique parents describe their child's delay and the first signs they noticed.

“ He had significant developmental delay that was apparent from an early age. He was referred at 16 months to an early intervention scheme since he had no expressive language and showed some autistic traits.

“ She started to not meet her baby milestones from about 3 months. She didn't make noises, she just lay still.

“ We first noticed the delay in communication. He never crawled but sat upright and walked on time and even now when he is almost seven years old does not like to crawl. He wouldn't play with toys, was very quiet and would just sit and not engage with anyone.



hearing loss and it's suggested that the loss of the OTOA gene is responsible.

One child has an intermittent squint [strabismus], which has not been treated, and is slightly short-sighted. Two girls have needed specialist dental treatment to straighten their teeth. In one boy, the first teeth emerged tiny; the adult teeth came in crooked and unevenly spaced.

One boy was born with undescended testicles and an inguinal hernia; another with small genitalia (Unique). Puberty proceeded normally in the one girl for whom information is available (Ballif 2007; Battaglia 2009; Hempel 2009; Unique).

“ Generally very healthy; he seems to have a strong immune system - 7 years

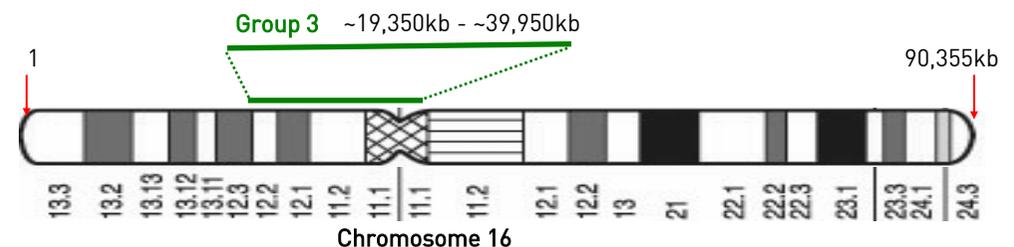
Group 2b: 16p12.1 microdeletion

Within this area, a microdeletion has been identified in the 16p12.1 band. This covers around 600,000 base pairs from around 21.9-22.5 Mb. The break point at 21.9Mb coincides with the 'hot spot' mentioned in group 2a deletions (Decipher; Girirajan 2010).

This microdeletion is found in unaffected people but about four times as often in people with developmental delay. Among those who are affected, the most common features are: speech and developmental delay; typical facial features; behavior or psychiatric issues; low muscle tone; seizures; a heart problem, most often hypoplastic left heart syndrome, where the left side of the heart has not developed properly and the aorta, the artery that takes blood from the heart around the body, is tiny; growth delay; small head [microcephaly]. The microdeletion is found in around 1/15,000 newborn babies but may be more common.

Group 3

Group 3 deletions encompass the typical 550kb 16p11.2 microdeletion (29.6-30.2Mb) but are larger, including more genes. The 8 reported cases, including 6 from Unique, vary in size from around 900kb to around 12.5Mb. With so few cases, any statements are tentative. As more people are reported or join Unique, the picture will become clearer (Bochukova 2009; Unique).



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

So far, children and adults with this larger deletion have shown signs of developmental delay. Information on two people is however very limited (Bochukova 2009).

[bringing feeds back] and constipation. At 10 years, she tends to swallow food without chewing it, a tendency put down to the low muscle tone in her mouth and tongue. Chewing difficulties were seen in three other children (Ballif 2007; Unique).

“ 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 - 10 months

Structural brain abnormalities

Four children have had imaging of the brain. In two it was normal; in one it revealed slightly enlarged ventricles [fluid-filled spaces within the brain]; in the other the 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 (Battaglia 2009; Bijlsma 2009; Unique).

Heart

Congenital heart disease is quite common in babies, so it is not surprising that it has been found in babies with a 16p11.2 microdeletion and could be a coincidence. In one child no abnormalities were detected; in another a harmless [functional] murmur was detected; in another a small hole between the two upper collecting chambers of the heart was found at the age of 13, but no treatment was needed; and in a fourth child, two holes and a leaky valve resolved naturally. A further child had a slow heart beat [bradycardia] and two further babies had leakage from the pumping chamber to the collecting chamber through the tricuspid valve [Ebstein's anomaly]. Two babies needed heart surgery soon after birth: one to correct an unusually narrow entrance to the artery that takes blood to the lungs and one to fit a pacemaker (Ballif 2007; Battaglia 2009; Unique).

Spine

In two/10 children a mild spinal curve was diagnosed but did not need treatment. One child also had a twist in the top three pairs of ribs near the spine; again, no treatment was needed (Unique).

General health and wellbeing; puberty

Three Unique members had repeated urinary tract infections as babies, resulting in kidney reflux and longterm antibiotic protection. Otherwise, all girls have been generally healthy, as has a fourth girl who had no urinary infections. Three children had repeated respiratory infections, one to such an extent that he was tested for cystic fibrosis.



One girl is long sighted and one has a surgically corrected squint [strabismus], a feature also seen in a girl with a larger deletion. One child had fibres with a thickened myelin sheath around the papilla at the point where the optic nerve enters the eye (Unique).

Five Unique members had repeated ear infections as babies, without hearing loss, while 6 children needed tube [grommet] placement in the eardrums, sometimes repeatedly; one Unique member has a narrow left ear canal. Two children have been reported with



He never cried if someone else held him or took him out of my arms. We had no eye contact since infancy, and he never cooed as a baby, would only growl.

“ He was a very happy baby, fed and slept well and reached the normal milestones. At 8, we think he is at the level of a child perhaps two years younger. His awareness of himself and his environment seems a bit diminished; he has a high pain tolerance and frequently knocks things over and spills things.

Mobility is typically less affected than thinking but delay in baby milestones is still common. Babies and toddlers may be slow to sit, crawl and walk but so far everyone with the microdeletion has walked, often only slightly later than a typically developing child.

Unique children rolled over between one and 10 months; they sat independently between 6 and 12 months, became mobile by crawling or bumshuffling between 7 and 22 months, walked independently between 10 months and 2½ years, most typically at around 20 months, and climbed stairs between 11 months and 4 years. Some babies first sat with a noticeably 'slumped' posture. Some children never crawled or only did so months or years after learning to walk. Walking style in young children is sometimes immature. Some babies, although not all, have a low muscle tone and feel floppy to hold; this hypotonia is one of the causes of their slow progress in reaching their mobility milestones (Bijlsma 2009; Shinawi 2009; Unique).

Family descriptions show mobility at different ages.

“ She walks but keeps falling over and needs help on stairs - 2 years 5 months

“ He is very 'clumsy' and tires easily so we use a buggy - 4 years

“ She climbs at every opportunity onto anything and tries to jump. Her favourite physical activity is swimming - 4¼ years

“ Normal range of activity. His favourite activities are the trampoline and bike - almost 5 years

“ She has normal mobility but took longer to climb stairs foot over foot. She most enjoys the swing and swimming (splashing) - 5 years

“ He can ride a two-wheeler bike skilfully and has very good hand-eye coordination with ball skills - 6 years

“ He used to fall a lot, so his hips were x-rayed but no abnormalities were found. He still has problems climbing stairs one foot at a time but otherwise gets around well. He most enjoys playing chase and swimming - 6 years 10 months



“ We first noticed a delay in his walking. Now he has no problems sitting or standing, climbs stairs two feet at a time, loves swimming and recently tried football at school but had a lot of fright with children running towards him. If he has done too much, he has pains in the evening and overnight in his legs, requiring medicine and massage. He uses a wheelchair for long distances - *8 years*

“ He has pretty good hand-eye coordination and ball skills, but can't ride a bike and has troubles with a scooter. He runs well but tends to trip a lot. He climbs and has developed good balance and enjoys swimming - *8½ years*

“ She moves fairly well, though she is slow in running due to her weight. She had no deficits on a physiotherapy evaluation. Her favourite activity is riding her bike - *9 years*



8½ years

“ He has difficulty holding cutlery and pencils and anything small - *11 years*

“ He was slow to feed himself and to hold writing implements - *12 years*

Personal care

The level of personal care that children achieve is very variable. Younger children, those with fine motor delay and those with a more significant learning difficulty need more help, explicit teaching and supervision, while those with good fine motor skills and a milder degree of learning difficulty can become quite independent in personal care.

“ She does everything in her own fashion; she is very stubborn so sometimes things are on the wrong way but she won't let you change them - *4¼ years*

“ He needs help with dressing; tighter clothes and pants in particular - *almost 5 years*

“ Mostly independent for self care - *5 years*

“ He can dress himself but not wash or brush his teeth. He needs help with socks but can do shoes - *6 years 10 months*

“ He can brush his hair and teeth but they will need re-doing. He can dress but has no concept of inside out or back to front - *8 years*

“ He wears simple clothing without buttons or zippers and with Velcro on shoes. He can forget underwear or puts clothes on the wrong way round - *8½ years*

Fine motor skills may also be delayed, so babies can be late to grasp and play with toys and to develop a pincer grip. This varies: some children's fine motor skills are not apparently affected, while others are more affected than in mobility.

“ She has always had very good fine motor skills - *4¼ years*

“ He holds writing implements high off the paper and doesn't draw yet with pencils or crayons but has just started using a magnetic drawing toy (Megasketcher) - *almost 5 years*

“ She has no fine motor delays - *5 years*

“ He is just starting to use a knife to cut simple food such as fish but has to be reminded to use a fork as he would much rather eat with his hands -

few invites. 50% she is pleasant and loving; 50% she talks back, throws things and hits (very immature, sometimes abusive) and is bossy and needy. She does very well with adults or younger children but not her peers and is very compassionate to animals - *13 years*

Pregnancy, birth and newborn

Information on pregnancy and birth weight shows no consistent pattern. One pregnancy was characterised by repeated early bleeding and little fetal movement; 7 babies were small for dates at birth, weighing 2.21-3kg (4lb 14oz - 6lb 10oz), in one case

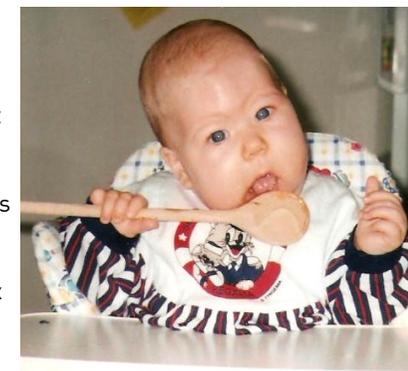


following a pregnancy where premature labour threatened repeatedly from 28 weeks but the pregnancy went to 38 weeks, and in two further cases where the baby was born prematurely (Hempel 2009; Unique). But other pregnancies were uncomplicated and babies weighed up to 8lb 4oz (3.75kg) (Battaglia 2009; Bijlsma 2009).

One child was born with a cleft lip and palate [split in upper lip and the roof of the mouth]; one had club feet [talipes], corrected with casts, surgery and braces; two had cafe au lait spots; one had hypospadias [the hole usually at the end of the penis is on the underside instead] and a hydrocele [fluid round the testis in the scrotum] and two had an inguinal hernia [in the groin], one also undescended testes (Ballif 2007; Hempel 2009; Unique).

Early feeding

Early feeding information is available on 13 babies (Ballif 2007; Battaglia 2009; Hempel 2009; Unique). Three babies had low muscle tone in the face and mouth, leading to latching on, sucking, swallowing and feeding difficulties. Eight babies had early feeding difficulties and reflux; of these a boy of 2½ and a girl of 13 are fed by a tube direct into the stomach to ensure they are properly nourished. One baby was unable to breast feed because of his small mouth and recessed chin but learned to latch on at 5 weeks and to suck through a straw at 10 months. Another found both breastfeeding and bottle feeding difficult but was able to take small amounts of formula using a teat for premature babies. One baby breastfed without problems but tended to fall asleep from exhaustion. She later developed reflux



A tendency to overweight

Six /20 people have a tendency to overweight with an increased appetite and food intake and four are frankly overweight, with the eating and weight problem increasing at puberty (Battaglia 2009; Bochukova 2009; Unique). Three have raised fasting insulin levels. In three cases, the parents were also overweight, but this is not true of the Unique children. In the Unique children weight control is by diet and increased exercise.

- “ He’s extremely active and although he enjoys his food, he does not eat large amounts, but his weight is difficult to control - 7 years
- “ Not strictly overweight but from a baby has been on upper limit of normal - 10 years
- “ She’s always hungry, eats anything and has had weight issues from a toddler - 13 years

Possibly, a seizure disorder

A seizure disorder has been diagnosed in one Unique member, who had complex-focal epilepsy from 5½ years but remained seizure-free from 7 years. One child of 13 had staring spells but no diagnosis of epilepsy (Ballif 2007; Unique).

Behaviour

Although 7 children’s behaviour has received comment and one child of 5 years is treated with risperidone, there is not enough information to say there is a consistent behaviour pattern or ‘behavioural phenotype’. Some of the earlier studies suggested that there may be a higher incidence of ADHD (Weiss 2008), but other studies have suggested that ADHD is not particularly common among people with a 16p11.2 deletion. One child of 21 months is described as irritable with head banging and hand flapping; a child of 8 is described as hyperactive with a short attention span; one child of 13 as anxious and energetic and another as introverted (Ballif 2007; Battaglia 2009; Bijlsma 2009; Hempel 2009; Unique).



- “ He is prone to frequent temper tantrums and gets irritated easily when he cannot do what he wants to do - almost 4 years
- “ He is excluded from mainstream school due to extreme aggressive behaviour. He is also very friendly and over-social - 7 years
- “ Despite her diagnoses at first she seems completely normal and no different from other children. It is only with time that one realises her behaviour corresponds more to that of a child of 5 and that she has learning difficulties. She hides it very well. She has difficulty occupying herself and often doesn’t understand other children’s reactions when playing and is less happy playing with her peers than with children much younger or older than herself. She often sits doing nothing. She has a lack of distance, lack of attention and concentration, doesn’t complete tasks and talks to strangers. Socially she’s very sweet and smiles when she doesn’t understand but is rarely able to create her own play ideas. She enjoys painting mandalas, playing cards and the recorder, listening to music and crafts such as knitting - 10 years
- “ At 7 she was displaying rages and extreme behaviours. She has always had an issue with food, and this precipitated the visit to the geneticist. Now at 13, she has made great progress emotionally. She loves to ‘hang’ with friends but has very poor social skills so gets very

- “ No personal care help needed - 9 years
- “ He needs help in the shower and bath and with dressing as he can’t manage buttons or shoe laces - 11 years
- “ He’s independent in personal care - 15 years

Toilet training

Toilet training is typically somewhat delayed, with most Unique families reporting children being dry by day by school age and at night by the age of 10 or 11.

Some learning difficulty

There is a broad spectrum of need for special support with learning. Typically, ability ranges from normal to a mild delay. Some people have no learning difficulty at all; a few score in the gifted range in certain areas of learning; within Unique, one child has an IQ score of 135. Others have a specific learning difficulty; perhaps the largest group has a level of difficulty that would be described as borderline, ‘slow normal’ or mild, with a tested IQ in the 60-79 range; and others have greater learning challenges ranging from moderate to severe and need more support.

Information from Unique suggests that language-based learning may be specifically affected with mathematics and art relatively spared. However, this is not true for all, and some children have advanced language skills.

Some children attend mainstream [regular] school, others attend a speech and language unit, others attend a school for children with special needs, yet others a unit for children with an autism spectrum disorder. Depending on local schools, some children start their education in a mainstream setting, moving to a more supportive learning environment from the age of 7 or to complete their secondary education (Ghebriannous 2007; Weiss 2008; Bijlsma 2009; Fernandez 2010; Decipher; Unique).

- “ She learns in her own time with patience, lots of gestures and cuddles and encouragement. She loves to put things into groups and recognises M for mummy and T for her own name - 4¼ years
- “ His level of learning disability isn’t known yet but he is not near his peers’ level. He attends a kindergarten and we try to do more at home but he isn’t cooperative. He can draw faces and cars and enjoys TV, computers, video games, playdoh and to a limited extent with playing with others - almost 5 years
- “ Developmentally he’s around a 3-4 year level and can read simple books but finds writing especially difficult. He hates to write and colour but can write his own name and type his own and his sister’s name using a keyboard. He’s following the Handwriting without Tears programme - 6 years 10 months



“ He attends a special school and is in a class with 2 support staff. He always tries very hard but has problems with reading, writing, maths and IT. If he fails, he is reluctant to try again. He learns best ‘hands on’ by going on trips, seeing and feeling what the class is talking about. He can write own name and surname and can draw people, trains, cars etc. He is learning keyboard skills at school and is good with a mouse - *8 years*

“ He goes to a very small public school which offers individual learning and stayed back one year but has no learning support. His teacher says that his reading and maths are at grade level and spelling – which he finds especially difficult - is below. As things become more difficult he will fall further behind but he reads simple books, likes numbers and is artistic, starting to draw mainly abstract pictures himself. He learns best when it’s made fun and with a firm and encouraging but not too pushy teaching style - *8½ years*

“ She currently has the ability of a 6-year-old. She attends a mainstream junior school where she finds English especially difficult. She reads simple early years books and writes neatly but it doesn’t make sense. She loves to write, draw and colour pictures - *almost 10 years*



“ He attends an SLD school with mostly 1:1 learning support. He is willing to learn and is on Stage 1 reading and writing and can write familiar words such as mom, dad, nan - *12 years*

“ He has mild learning difficulties mild and is in a supported class at a mainstream secondary school. He’s good at music but has more difficulty with English, maths and science and lacks confidence. His reading age is 8 years 8 months and he has a scribe for exams as his writing isn’t very good - *15 years*

Influence on susceptibility to

autism or autism spectrum disorder

The typical 16p11.2 microdeletion is found more often among children and adults diagnosed with autism or a disorder on the autistic spectrum such as Asperger disorder – than among the general population. Yet not everyone with the microdeletion has autism – perhaps one in three to one in five does. Boys are more likely to be affected and affected seriously. Seven/26 Unique members show autistic features, five of them boys, but only one has a formal diagnosis of autism.

It is currently believed that having the microdeletion increases the risk of autism but does not necessarily cause it. The underlying suggestion is that a network of genes within the microdeletion region is disrupted, possibly causing changes in brain development that may manifest as developmental delay or autism. These genes include genes involved in cell-to-cell signalling and interaction (Kumar 2008; Marshall 2008; Weiss 2008; Bijlsma 2009; Glessner 2009; Mefford 2009; Shinawi 2009; Fernandez 2010; Decipher; Unique).

Minor unusual facial or physical features

to moderate range but children can display advanced skills in specific areas of learning. Low muscle tone and difficulties with fine motor skills make drawing and writing more problematic. A girl of 13 with a reported IQ in the 50s can trace her name and count to 12. Where more than one member of the same family has the microdeletion, the level of learning difficulty may be different. Children are educated both in mainstream [public] schools and in special schools and generally thrive in small groups (Ballif 2007; Hempel 2009; Unique).

“ He has poor concentration and is not motivated to read and write but is very determined when it comes to physical skills. He is a visual learner and can write his name with help but is not reading yet; he has excellent mouse and keyboard skills - *7 years*

“ She has mild learning difficulties and a global IQ of 79. She needs frequent repetition; her long term memory is good, her short term memory less so. She has special education at a Waldorf school with 12 children to one teacher and one learning support assistant. She is particularly good at crafts, knitting and painting but has greater difficulties with writing, mathematics and sport. She can read short, simple stories but prefers to look at pictures. She is good at copying but rarely writes independently - *10 years*

“ She attends a very small private special education school with a 1:12 teacher ratio specifically focused on individual needs and has made great strides educationally. Overall, she is 2-3 years behind but she is good at science and spelling and finds maths and reading comprehension hard. She is a visual learner and responds well to 1:1 attention. She only reads as required by school, and can’t be motivated to read otherwise - *13 years*

Minor unusual facial or physical features

Children and adults may look like each other: there are evident facial similarities between one Unique member and a father and son with a similar microdeletion (Bijlsma 2009; Unique). Many have a long, narrow face; a prominent forehead; downslanting, relatively narrow eyes; and rather large, fleshy earlobes. Features noticed in children with larger deletions included a flat face, low set ears, deep set eyes and a thin upper lip. Muscle tone in the face may be low, leading to an inexpressive face with an open mouth and dribbling (Ballif 2007; Battaglia 2009; Hempel 2009).



Different children

Mobility

Mobility [gross motor] skills were somewhat delayed in all children, but improved over time with physical therapy [physiotherapy]. Babies rolled over at 8-10 months; became mobile [rolling, bumshuffling, crawling, pushing along the floor on the back] at 7-22 months; started to walk at 18-36 months; and could climb stairs by 3-4 years. An immature walking style persisted in some children. One child had lax joints and very low muscle tone in the upper torso and benefited from years of occupational and physical therapy (Unique).



- “ He is a phenomenal athlete. He has a small basketball goal, loves to shoot baskets and will do this for hours - *almost 4 years*
- “ He’s very active and physically age-appropriate – amazing given his earlier delay. As a younger child he had physiotherapy, a standing frame and orthotic boots; now he needs none. At school, he excels at physical activities like football and tennis - *7 years*
- “ She can do everything, ride a bicycle and run, but she tires quickly and must then rest; she sits a lot. Her favourite activity is playing ball - *10 years*
- “ Normal activities, enjoys swimming, tennis, bike riding - *13 years*

Fine motor skills

Fine motor skills



were also delayed in 6/7 children for whom information is available (Battaglia 2009; Hempel 2009; Unique).

- “ He seems to have good hand control. He can use safety scissors to cut paper. He cannot write any letters or his name. When he draws it is in sporadic scribbles without any definition. When it comes to sports he has excellent hand control. He can throw a baseball hard and with accuracy - *almost 4 years*
- “ He has some hypermobility in his hands and uses specialist caring cutlery - *7 years*
- “ She was delayed in handling cutlery, toys and writing implements. Today she accommodates or has overcome her difficulties, although writing implements are still an issue - *13 years*

Personal care and toilet training

Toilet training was achieved, albeit with a delay. One child was dry during the day at 3½ years and at night by 8¾ years. Information from Unique suggests that help with washing, tooth cleaning and other aspects of personal care will be needed for longer than in typically developing children, with reminders to finish the task in hand required. At 13, two girls still needed help with personal care (Ballif 2007; Unique).

- “ No help needed most of the time, sometimes with buttons and zippers - *13 years*

A degree of learning difficulty

Information suggests that learning difficulties are in the borderline

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. However, an unusually large head has been found in one series, with children with a 16p11.2 microduplication by contrast having a small head. Within Unique, around the same number of children have an average-sized head as have a large head and two children have a small head.

In one series, children and adults with a 16p11.2 microdeletion shared certain facial features, including a broad forehead; a small chin and lower jaw; widely spaced eyes; and a flat midface. This was only partly reflected in the Unique series, with 7/18 reporting a broad forehead and a small chin and lower jaw but 2/17 reporting widely spaced eyes and 1/17 a flat midface.

Other slightly unusual facial features noticed include small and sometimes downwards-slanting eyes; hooded eyelids [ptosis]; tiny skin folds across the inner corners of the eyes; a small nose; unusual-shaped [simple, pointed] ears set low on the side of the head; a thin upper lip; a lower jaw set back from the upper jaw; a thick/ broad neck.

Among other unusual physical features mentioned, webbed toes [usually toes 2 and 3] are especially common. Other features affecting the feet include small individual toes; unusually formed toe nails; a hammer toe; underlying or overlapping toes. Unusual hand features include a single palm crease; very small hands with short fingers; slightly webbed fingers; unusually shaped [pointed, tapered, stubby] fingers; incurving fifth fingers; fetal finger pads [pads on the inner surface of the finger tips that usually disappear by 15 weeks gestation] (Kumar 2008; Bijlsma 2009; Shinawi 2009; Decipher; Unique).

A tendency to overweight

A tendency to overweight and obesity has been identified in almost half the children and adults with a 16p11.2 microdeletion. This makes the microdeletion the second most common genetic cause of obesity. Overweight can follow a period as a baby when gaining weight is very difficult despite feeding well. Weight is variable in childhood and some children are small and thin, but obesity follows by adulthood at the latest. Under 2s are not affected; children may be overweight or obese; teenagers and adults obese. At the age of 28, twins with a 16p11.2 microdeletion were a similar height to their unaffected brother and much heavier 84-88 kg (13 stone, 3/12lb) compared with 71kg (11 stone, 2lb).

One possible causative gene - SH2B1 - positioned at 28.73-28.95Mb has been identified, although other genes very likely play a role.

Children in one study who have lost one copy of this gene have rapidly gained weight as children, with most of their weight gain being accounted for by fat. They had a tendency to overeat significantly and they showed raised insulin levels, with marked insulin resistance. Overall, growth does not seem to be affected.

Unique’s experience is that 9/15 children showed a marked tendency to put on weight. Rapid weight increase occurred at different ages between 2 and 7 years. Five of the nine have a large appetite and a further child with no weight problem has a ‘ferocious



appetite'; in the 3 children whose insulin levels were checked, they were not raised. In 3/5 families, the parents also have a weight problem.

Knowing about the possible tendency to overweight can help parents trying to keep their child healthy. Unique families tried to control their child's weight by watching their food and drink intake and building exercise into their daily routine; limiting high fat, high calorie foods and using low-fat substitutes, putting food out of reach and limiting sugar and starch intake. Screening for hypertension (high blood pressure) and diabetes is recommended in children and adults who are overweight or obese (Ghebriannous 2007; Bijlsma 2009; Bochukova 2010; Perrone 2010; Walters 2010; Decipher; Unique).

“ It's hard controlling at the moment what he eats as he has preferences sometimes for crispy food, nothing pale or too colourful; he will scream for food sometimes - *almost 5 years*

“ He is extremely active and although he enjoys his food, he does not eat large amounts, but his weight is difficult to control - *9 years*

“ He would carry on eating if allowed to - *12 years*

“ As a baby I had trouble gaining weight, then as I got older I had trouble keeping it off - *adult*

In a few, a seizure disorder



Generally speaking, people with a 16p11.2 microdeletion are fit and healthy. There is some uncertainty whether seizures are more common than in other typically developing children. The data suggest that one in four - in some series, more - has a seizure disorder or has had one but the evidence is that seizures are well controlled with medication and tend to resolve or become milder during childhood. Epilepsy has developed between babyhood and puberty with seizures in one series starting typically in

the first year of life. Twin brothers each developed seizures between 11 and 13 years. Among 25 Unique members, 9 have had seizures, although three children only had febrile convulsions [with a raised temperature] with no further signs of epilepsy by the age of 10 or 11. The pattern and age of onset of seizure activity in other children was varied. Two children have had seizures with apparently normal electroencephalogram [EEG] recordings. No families reported that their child's seizures were hard to control (Ghebriannous 2007; Bijlsma 2009; Shinawi 2009; Decipher; Unique).

Behaviour

In a series of 16 children with the 16p11.2 microdeletion, six had a behaviour problem such as attention deficit hyperactivity disorder [ADHD] (Shinawi 2009). Another study of 21 patients with 16p11.2 deletion did not find a high incidence of hyperactivity (Hanson 2010). 'Difficult' behaviour was common in the Unique group, found in 12/22 children and the reason for seeking a diagnosis in two; but 8/22 children showed no 'problem' behaviour at all. Nine children were reported to be positively sociable; seven displayed disproportionate anxieties, in one case severe but fairly well controlled with methylphenidate.

“ She's a good girl but gets frustrated. Socially she doesn't interact very well on a bad day but on a good day she's fine - *2 years 5 months*

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

So far only one adult has been reported (Bijlsma 2009). He had a small (200kb) deletion and worked as a truck driver and had learning difficulties as a child. He passed the microdeletion on to his son, who had a learning disability.

Absence of autism

It's been suggested that people with this deletion do not have autism, but they have not necessarily had formal testing for autism. Autism is still a clinical diagnosis based on specific behaviour patterns (Battaglia 2009). Two Unique members have a diagnosis of an autistic spectrum disorder (Ballif 2007; Hempel 2009; Unique).

“ He has been labelled as having autistic traits, mainly sensory integration such as disliking loud noises and certain textures, liking routine, but not crowds - *7 years*



Delay in starting to speak as the first sign

The first sign of anything wrong was usually general developmental delay, obvious from early babyhood in at least two children who did not reach their baby 'milestones' of sitting up and becoming mobile on time. In one baby, low muscle tone and unusual facial features were noticed at 6 weeks; in another, epilepsy was suspected at 4 months. One baby was noted to have club feet [talipes] on a pregnancy ultrasound scan. Fifteen children went on to exhibit speech delay: a baby was not babbling by 12 months; in one child speech was sometimes 'barely comprehensible' at 5 years; an 8-year-old was only using single words and simple phrases; one 13-year-old had a sign vocabulary of around 50 signs but very few spoken words, while another communicated with sounds and signs, using few words. In four children followed up beyond early childhood, the speech and language delay improved significantly or resolved with age and therapy; in six children the delay was persistent. Behaviour difficulties in toddlers also alerted parents to a problem (Ballif 2007; Battaglia 2009; Bijlsma 2009; Hempel 2009; Unique).

“ 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 - *almost 4 years*

“ He uses 7-8 word sentences but his speech is immature eg 'Me want wear long sleeved T-shirt, no like short sleeves' - *7 years*

“ She has global delays but they are not immediately obvious because she demonstrates her good sides. Her speech is completely normal but she uses simple sentences and the present tense. She has difficulty with complicated words and sentence construction and sometimes forgets words - *10 years*

“ Her speech and language problems were identified early through the school and she has received speech therapy from the age of 3. She now communicates normally through speech and uses complete sentences - *13 years*

children who had brain imaging, no essential abnormalities were found in six. One child had a harmless venous anomaly; and one an unspecified abnormality in the white matter of the brain (Unique).

Spine

In a small number of children, one or more wedge-shaped bones in the spine known as hemivertebrae have been found. The first sign in one Unique baby, born with a curved spine [scoliosis], was a lump on his back at 9 months. He has two hemivertebrae; at 8 years, they are being monitored and 'he seems to be growing with it'.

Hemivertebrae are caused by incomplete development of one side of the vertebra. In most cases there are no symptoms or they are mild but they can cause a curve in the spine resulting in scoliosis, kyphosis or lordosis and will therefore be monitored.

Finding these hemivertebrae has led to speculation that there may be genes within a typical 16p11.2 deletion that influence the development of the spinal column. The gene known as TBX6 is one so-called 'candidate' gene (Shimojima 2009; Hernando 2002; Unique).

Management recommendations

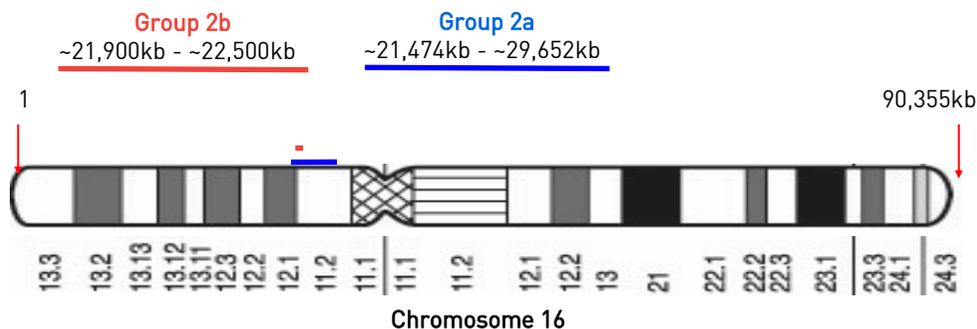
It's recommended that anyone with a 16p11.2 deletion diagnosis should have a clinical examination; a general review of all their organ systems; and a developmental assessment.

Therapies introduced early will usually improve outcomes. Speech therapy in particular should be introduced early and assisted or augmentative communication started where needed. Routine developmental assessment and screening should follow.

Group 2a

Group 2 microdeletions are found in an area flanking the typical 16p11.2 microdeletion but slightly closer to the end of 16p, extending across 16p12.1 and as far as 16p12.2. They vary in size from around 200kb to much larger deletions of 7.1-8.7Mb between around base pairs 21,566,499 and 29,744,499. Break points vary but there seems to be a 'hotspot' at 21.9Mb (Ballif 2007; Battaglia 2009; Bijlsma 2009; Hempel 2009; Bochukova 2010; Unique).

Few people (20) have been reported or joined Unique with a 16p11.2 microdeletion in this region, so statements are tentative. As more people are reported or join Unique, the picture will become clearer.



“ Her behaviour is changeable, swinging from loving to grumpy in seconds and can be very challenging - 4 years

“ Socially she's needy and can be a turn-off to peers. She's very obsessive if she knows something is going to happen such as visiting someone or doing something. And she is easy to tantrum: we treat this with time out and distraction - 4¼ years

“ He showed autistic traits from an early age, although these have lessened with age. His behaviour changes with the day. Usually he is happy and outgoing, but has days when he is unresponsive and reticent. Socially, he is usually happy and wants to join in - 4½ years

“ He tries to interact socially with others: can say Hi and Excuse me. If he's in trouble he can get very emotional. His behaviour is better but he still has 'moments' - 6 years 10 months

“ Normally very happy and loving and utterly devoted to his mother. I feel like the most loved mother in the world. But he does have some problematic behaviour. He can be defiant and very bossy; often it's his way or no way. He hits his brother all the time and cannot top his impulses. A trial of Ritalin trial was suggested but we decided against it. He is quite social but finds it hard to keep up with children of his age so he separates and plays by himself. He is very connected to nature and loves animals - 8 years

“ Happy but hyper. Gets bored easily and gets naughty - 8 years

“ A very happy little boy. Socially, he is friendly to everyone and will shout and babble to children at the swimming pool, park or shops; sadly, they don't understand - 8¾ years

“ She is polite and talkative, lovable and funny - 9 years

“ Quite placid most of the day but seems to get hyperactive by evening - almost 10 years

“ His behaviour is very good usually. On bad days he can be aggressive but is usually lovable and caring - 12 years

Other features

Possible vulnerability to psychiatric conditions

Early data suggest that 16p11.2 microdeletions are found more often than you might expect in groups of people with schizophrenia, bipolar disorder and panic disorder, and duplications of this same chromosome fragment may also increase susceptibility to schizophrenia (McCarthy 2009). Before any definite conclusions can be drawn further study is needed (Weiss 2008).



Possible susceptibility to infections

One person with a 16p11.2 deletion on one chromosome 16 and a mutation of the CORO1A gene on the other chromosome 16 had severe combined immunodeficiency [SCID] (Shiow 2009). This has led to the recommendation that people with a 16p11.2 deletion who have frequent infections should be tested for this type of SCID.



Childhood infections can appear more frequent and more prominent in children with low muscle tone and a chromosome disorder and chest infections are likely to be more common among children who bring back part of their feeds [reflux] and then inhale this [aspiration]. Five/15 Unique families said that their child had frequent infections as a baby or young child, but an immune deficiency was not investigated. Families found the infections became less frequent with age, as in most typically developing children.

“ She’s normally quite healthy although when she is ill, she is very ill - *2 years 5 months*”

Pregnancy, birth and newborn

In a series of 16 children with the typical microdeletion, the pregnancy was unremarkable in all and all were born an appropriate size for gestation except for one baby who was large for dates. Three babies needed ventilation after delivery and other health concerns in the newborn period included jaundice, polycythaemia [too many red blood cells], hypoglycaemia [low blood sugar] and an unstable temperature (Shinawi 2009).

In a Unique series of 18 pregnancies, one mother had extreme hyperemesis [severe sickness] needing three hospital admissions in the first trimester, one mother experienced bleeding, in two further pregnancies premature labour threatened but was averted at 28-30 weeks and one baby was born prematurely. In one pregnancy the baby’s growth was a concern from 30 weeks and growth delay was diagnosed in three babies, with the delivery date questioned in one pregnancy. A further pregnancy was described as ‘difficult’. One baby was born by emergency Caesarean after a fall in the heart rate, another was delivered by deep forceps after failure to progress. Four babies with the microdeletion were born by Caesarean section to a mother with the microdeletion because she ‘couldn’t deliver normally’.

Five/15 babies had some evident congenital anomaly, including a gap in the partition between the chest and abdomen [diaphragmatic hernia]; a split in the roof of the mouth [cleft palate]; extra fingers or toes; a heart problem; a malformed kidney; fused lower ribs; significant narrowing of the outlet from the stomach to the intestines [pyloric stenosis](Shinawi 2009). Developmental anomalies of the uterus [womb] and of the spine in the form of a syringomelia [a fluid-filled area within the cord that damages the spinal cord] have also been found (Nik-Zainal 2011; Schaaf 2011).

In the Unique series, only one baby had a major birth defect [heart problems] but five other babies had minor abnormalities including an ear tag, a birthmark on the lower back or the nape of the neck, small and unformed third toe and a small, sticky eye. One baby initially had low blood sugars and two had jaundice, in one case persisting for two months.

Birth weights at term ranged from 5 pounds 13 ounces [2.636 kilos] to 8lb 6oz [3.798 kilos].

Two babies spent time in special care, one after developing breathing problems. Most babies went home 2-3 days after delivery but the babies who needed special care were in hospital for 1-5 weeks.

“ He wouldn’t even move when the nurse tried to wake him for pictures by rubbing the bottom of his feet with a cold cloth.”

Feeding

Around half of 16 babies had mild feeding problems in their first weeks or months (Shinawi 2009). Unique’s experience reflects this: some babies breastfed or were bottle fed without problems, while others struggled to latch on, to coordinate sucking with swallowing and had difficulty with bottle feeding, losing weight initially. Some babies fed better with a teat designed for premature babies or a large-holed teat but still took only very small quantities of milk. Some babies needed tube-feeding either initially before moving to a bottle, or if they failed to gain weight satisfactorily and one child is gastrostomy-fed. One baby was diagnosed with failure to thrive [a significant difference in weight gain compared with other babies of the same age] and investigated in hospital for two weeks. Some babies were frequently sick, bringing back their feeds readily and were switched to non-dairy milks or needed thickeners to help keep milk down.

Weaning presented further difficulties, either because babies took very small quantities of food or because they were reluctant to chew or else gagged and brought back their food.

Generally, feeding development was delayed, with some pre-school children still mainly on finger foods.

Some children went on to develop a large appetite and to put on weight very fast (see pages 11-12) (Unique).

“ She wouldn’t take any bottles, she would scream. Professionals ignored my concerns. She still has problems chewing - *2 years 5 months*”

“ Once home, he screamed constantly for weeks. The pediatrician did not think he had reflux and we gave him simethicone drops, thinking it was gas. Now we feel it was more sensory issues than reflux.”

Babies

Pyloric stenosis has occurred in three babies, but not in the Unique series. In pyloric stenosis, the passage between the stomach and the small intestine narrows so that feeds cannot get through. The condition affects young babies usually between two and eight weeks old and causes forceful vomiting. After first treating any dehydration and mineral imbalances caused by the vomiting, the tight pyloric muscle is repaired surgically. There are usually no long term effects and the problem is unlikely to recur (Bijlsma 2009; Shinawi 2009).

Structural brain abnormalities

When children’s brains were imaged after finding that they were unusually large [macrocephaly], 7/10 were abnormal (Shinawi 2009). However, among 9 Unique