16p11.2 microduplications
Sources & references
The information in this guide is drawn from what has been published in the medical literature about people with a duplication of 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 Unique’s database. When the guide was published, Unique had 7 members with a 16p11.2 duplication [Marshall 2008; Weiss 2008; McCarthy 2009; Bedoyan 2010; Bochukova 2010; Fernandez 2010; Jacquemont 2010; Rosenfeld 2010; Shinawi 2010; Schaaf 2011; Walsh 2011; Unique].

Finding out
What does it mean when someone in your family has a 16p11.2 microduplication? The person with the microduplication has a tiny bit of extra genetic material in the cells in their body. Generally speaking, for correct development, the right amount of genetic material is needed – not too little and not too much. However, some people with a 16p11.2 microduplication seem completely unaffected by it. Others have some problems with their development, speech, behaviour, learning or health that may be caused by the extra genetic material.

What does 16p11.2 microduplication mean?
This part of chromosome 16 is called p11.2. People with the microduplication have an extra bit of a tiny piece of p11.2. Its size is counted in ‘base pairs’, the ‘rungs’ of the DNA ladder. Typically, the extra bit starts around 29,670,000 and ends around 30,200,000.

Chromosome 16 is one of the 23 pairs of chromosomes in the cells of the body that carry genetic material. The top bit down to the line is known as p. The bottom bit is called q.
These boys have a 16p11.2 microduplication. But it is not the typical 16p11.2 microduplication.

The microduplication is between around 28.5Mb and 28.9Mb.

The boy, 7, on the left is a twin and is much smaller than his twin who has normal chromosomes [see inset picture].

Does everybody with a 16p11.2 microduplication have exactly the same amount of extra genetic material?

No. Most people have extra genetic material consisting of DNA that starts around base pair number 29,670,000 and ends around number 30,200,000, according to build 19 of the human genome (see page 5). This is the typical microduplication and includes 27 known genes. We know what some of them do, but not all. Many more people have a different disorder known as a 16p11.2 microdeletion where this segment of chromosome 16 is not extra but is missing. *Unique* publishes a separate information guide to 16p11.2 microdeletions.

Other people have a microduplication of a different part of 16p11.2. You can tell if your child has a typical 16p11.2 microduplication or a different one by checking the base pair numbers or by asking your geneticist. This guide is about the typical 16p11.2 microduplication.
In your family, is the 16p11.2 microduplication inherited or not?
16p11.2 microduplications can occur out of the blue for no obvious reason or they can be inherited from either parent. Studies so far suggest that most are inherited from one of the parents [Fernandez 2010; Rosenfeld 2010]. The only way to be certain is to check the chromosomes of both parents, even if they are themselves completely healthy. If one parent has the same microduplication, we can assume that it has been passed on.

If both parents have normal chromosomes, the 16p11.2 microduplication is in all likelihood a new occurrence. The genetic term for this is de novo (dn). A new 16p11.2 microduplication has been caused by a mistake that occurred either when the parents’ sperm or egg cells were formed or in the very earliest days after fertilisation. As a parent there is certainly nothing you could have done to prevent this from happening. No environmental, dietary, workplace or lifestyle factors are known to cause 16p11.2 microduplications. There is nothing that either parent did before or during pregnancy that caused the microduplication – so no one is to blame and there is no reason for anyone to feel guilty.

Are there people with a 16p11.2 microduplication who have developed normally and have no speech, behaviour, learning or health difficulties?
Yes, there are. The 16p11.2 microduplication can be silent. Some parents, brothers and sisters of children with a 16p11.2 microduplication have the same microduplication but do not have any obvious unusual features or delayed development [Fernandez 2010].

The signs in others with the duplication are so subtle that you would hardly notice. Some children with a 16p11.2 microduplication also develop normally.
The effect on development, health and behaviour of some genetic disorders ranges from being barely perceptible to being obvious and severe. In this sense they are like infections such as flu that can be mild or serious.

If one person in a family with the 16p11.2 microduplication is mildly affected, will others in the same family also be mildly affected?
Not necessarily. There is a lot of variation between different members of the same family who have the same microduplication. We know that if one person is mildly affected, others may be more severely and obviously affected.

Can it happen again?
Where both parents have normal chromosomes, it is unlikely that another child will be born with a 16p11.2 microduplication or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 16p11.2 microduplication. This is called germline mosaicism and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the duplication.

In families where the 16p11.2 microduplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 16p11.2
microduplication rises to 50% in each pregnancy. However, the effect of the microduplication on the child’s development, health and behaviour cannot be reliably predicted.

Your genetics centre should be able to offer counselling before you have another pregnancy.

**Will my child with a 16p11.2 microduplication have similarly affected children?**

As an adult, your child with a 16p11.2 microduplication may well want to have children. We have not known about the condition for long enough to be certain if it affects fertility but it is likely that fertility will be normal. In each pregnancy, someone with the duplication theoretically has a 50% possibility of passing it on and a 50% possibility of having a child without the duplication. Their ability to look after a child is very likely to be closely related to their own learning ability.

**Array CGH report**

The laboratory that finds the 16p11.2 microduplication will send a report that usually looks like something like this:

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arr[hg19] 16p11.2 (29674061-30235818) x3
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arr The analysis was by array (arr) comparative genomic hybridisation

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 The chromosome involved is 16 and the position of the duplication is in band p11.2

29674061-30235818 The base pairs between 29674061 and 30235818 have been shown to be duplicated. Take the first long number from the second and you get 561,757 (or 562kb or 0.562Mb). This is the number of base pairs that are repeated. This is the number of base pairs that are repeated x3 means there are three of these base pairs, not two – one on each chromosome 16 – as you would normally expect

**Is there a 16p11.2 microduplication syndrome?**

No, there isn’t. Although many people with a 16p11.2 microduplication have similar features, overall they are too varied to be called a syndrome. Also 16p11.2 microduplications have only been known about for a few years and it isn’t yet certain which features are definitely caused by the extra genetic material [Shinawi 2010].

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

It’s estimated that for every 10,000 people in the general population, three have a 16p11.2 microduplication. It’s slightly more common among people who have a language or psychiatric disorder, being found in four per 10,000 people [Weiss 2008]. If these estimates are correct, 16p11.2 microduplications are not really rare: in a world population of 7 billion, more than 2 million people would have this condition.
Most likely features
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.
The most common features are
- Delay in starting to speak and in language development
- Possibly very minor unusual facial or physical features
- Some delay in learning to sit, move and walk
- Some need for support with learning
- Increased likelihood of difficult behaviour
- Increased susceptibility to autism or an autism spectrum disorder
- Increased susceptibility to mental health problems
- In a few, a birth defect that might cause health problems
- Possible tendency to underweight
- Possible vulnerability to seizures
[Bedoyan 2010; Fernandez 2010; Jacquemont 2010; Rosenfeld 2010; Shinawi 2010]

Delay in starting to speak and in language development
A delay in speech and language is very common although not universal 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 usually appears to affect talking [expressive language] as much as understanding. Unique children generally smiled on time but didn’t say their first recognisable words until 16 months to 4-5 years. In some, words may emerge even later. But everyone known to Unique has started to talk although some of them use signing, gestures, objects or pictures to reinforce their meaning and their speech may not be completely clear [Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Unique].

“ She smiled at 2 months but wasn’t babbling at 6 months as most babies do and appeared to be only hearing vowels, not consonants. By 2½, she was making many more consonant sounds and could say Mama, Bye bye, Baba (for Barney) and book when asked. Today she can say some single words but also uses signing, gestures and vocal noises to get her meaning across. She isn’t really delayed in her receptive language. She understands a lot more than she can say. Sounds she finds difficult to make include anything where the tongue must move to the top of the mouth, like da, ta, etc – 4 years

“ As a young child he seemed to understand most of what was said but was unable to convert his thoughts into speech. He smiled when expected but babbled late and didn’t start to talk until he was 4 or 5 years old. At first he ‘dragged words out’. One relative recalls that he had a vocabulary of 75-200 words before abruptly stopping speaking. Today as a young adult, he understands and responds to speech and has a wide active vocabulary. However, his social communication is impaired: he tends to invade people’s personal space and can be annoyingly loud or get stuck on a topic or a question. He also speaks very quickly, making it hard to understand him – 22 years
**Possibly very minor unusual facial or physical features**

Your child with a 16p11.2 microduplication will most likely look much like other members of your family. They may well have one or two unusual facial features but these won’t necessarily be the same in others with a 16p11.2 microduplication. There isn’t a typical 16p11.2 microduplication ‘look’ and overall, your child is unlikely to stand out facially from other people. Some people but certainly not all have a slightly small head. As well as the photographs in this guide, you can see pictures in 3 articles [Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Unique].

Entirely normal at first glance

**Some delay in learning to sit, move and walk**

Delay in reaching baby milestones is apparently common although not among Unique members who generally sat, crawled and walked close to the expected age. It may be that the more severely affected people are the ones who go to hospital, so the information in the medical literature may be slightly biased toward more developmental delays. So far everyone with the microduplication has walked, often only slightly later than a typically developing child.

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. Some also have unusually bendy [lax] joints which may need support as they learn to move and walk.

Unique children walked independently between 11 months and 18 months and climbed stairs at around 2 years. In the early stages of walking, toddlers were often uncoordinated and tripped easily. Those with low muscle tone tired easily and an unusual way of walking could persist into adulthood. But they went on to enjoy a wide range of physical activities [Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Unique].

She was sitting up from 8 months but not attempting to crawl by 9 months. She managed this one week before her first birthday. She started walking at 18 months and by 2½ years had mostly caught up physically and could run well but still had trouble going down steps. She now walks very stably and for very long distances and enjoys swinging, climbing, sliding, dancing – 4 years

As a child he had extremely erect posture as child but as an adult it’s normal. He still has low muscle tone, has never been active or shown any desire to be. When walking outdoors he has a somewhat unusual ‘stomp’ like gait that isn’t noticeable indoors. He can’t ride a bike – 22 years

**Some need for support with learning**

There is a broad spectrum of need for special support with learning. Typically, ability ranges from normal to a mild delay and where an IQ has been measured it has fallen within the 50–110 range, with 100 representing the average for the general population. However, this probably underestimates the range of ability, since IQ testing would be more likely for people with developmental delays than for people with the microduplication and no delays. Unique’s experience is that most children can learn to read, write and use a computer. Depending on local schools, some
children start their education in a mainstream setting, usually working within a small group and moving to a more supportive learning environment to complete their education [Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Unique].

- She has a great memory and is helped to learn by being stubborn and determined – 4 years
- He has an exceptional memory, writes, reads newspapers, the internet and magazines and makes meticulous drawings. He also navigates the computer very well. He attended life skills classes after school but left because he was physically afraid of another student – 22 years

**Increased likelihood of difficult behaviour**

Various studies have found mood or behaviour difficulties in a minority of young people with a 16p11.2 microduplication. Most commonly children are overactive with a short attention span [ADHD/ attention deficit hyperactivity disorder] but other types of behaviour difficulty have been found. ADHD has been identified in 2/7 Unique children. One boy of 15 had an anxiety disorder that responded well to medication and in one study 4/10 youngsters had outbursts of aggression [Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Unique].

- When she was 2½, she loved to mouth things and craved oral stimulation. She had no fears and loved water, was beginning to pretend play and was very sociable, waving to everybody and wanting to be the centre of attention. By 4, she had developed ADHD and takes medication [Focalin/ dexmethylphenidate] to help her focus on activities – 4 years
- As a child, he lacked social interactions with other children and played alongside them rather than with them, even into adolescence. These days, at 22, other family members consider him obsessive/ compulsive. He used to take ADHD medications – Strattera/atomoxetine and Ritalin/ methylphenidate but has stopped, as he says they make him feel `weird`.
- He enjoys listening to music, watching TV, the computer and reading and spends a lot of time on the computer, living in imaginary worlds and imagining himself to be a professional sports character. He is also now exhibiting some unusual, very trying social behaviours including constantly repeating the same questions, standing very close to others when asking questions, loud speech, talking to himself and repetitive use of `bad` words reminiscent of Tourette`s syndrome – 22 years

**Increased susceptibility to autism or an autism spectrum disorder**

The typical 16p11.2 microduplication is found more often among children and adults diagnosed with autism or a disorder on the autistic spectrum such as Asperger syndrome than among the general population. Yet only a minority of people with the microduplication has autism or autistic features. Autistic traits have been observed in around half of Unique members, all male.

Rearrangements of 16p11.2 – both deletions and duplications – represent the second most frequent chromosomal disorder associated with autism but so far no genes responsible have been identified.
It is currently believed that having the microduplication increases the risk of autism but additional factors are likely to be needed for autism to develop. This is also true for people, especially boys and men, with a 16p11.2 microdeletion. The underlying suggestion for them is that a network of genes within the microdeletion/duplication 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 other types of cellular interaction [Marshall 2008; Weiss 2008; Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Unique].

Autism has never been diagnosed but family members agree that he shows signs.

Increased susceptibility to mental health problems
The typical 16p11.2 microduplication is found more often among children and adults diagnosed with mental health problems than among the general population. Yet only a minority of people with the microduplication has a mental health problem. Anxiety, depression, bipolar disorder and particularly schizophrenia have been found. It’s currently believed that having the 16p11.2 microduplication increases the risk of mental health problems but other factors are needed for mental health problems to develop. No Unique members have been diagnosed with a mental health problem [McCarthy 2009; Fernandez 2010; Unique].

Some babies with a 16p11.2 microduplication are born with a birth defect. Others are not. Birth defects can affect any organ in the body: there doesn’t seem to be any consistent pattern
Some babies with a 16p11.2 microduplication are born completely healthy. Others have a birth defect which can be quite minor or more serious. Most of the birth defects reported among babies with 16p11.2 microduplication have only occurred in just a few babies, so they may be a coincidence, and it is still not clear if all of the birth defects reported here are actually caused by 16p11.2 microduplication.

Any particular defect has usually only been seen or reported once but this is partly because so few babies, children and adults have been described in the medical literature or are known to Unique - just 41 when this guide was compiled. But two babies were born with a diaphragmatic hernia. This is a hole in the muscular wall separating the heart and lungs from the contents of the abdomen. Part of the bowel, stomach or liver take up space in the chest, potentially depriving the lungs and heart of room to develop properly. Once a baby’s condition has been stabilised, the hernia will be repaired surgically.

Two babies were also born with a cleft palate [an opening in the roof of the mouth, usually closed surgically], and one of these babies had a cleft lip as well.

On investigation, five/28 people with the microduplication have some anomaly of the brain structure that shows on magnetic resonance imaging [MRI].

In four babies the kidneys and drainage system for urine were affected. One baby has a ‘horseshoe kidney’, where the bottom points of the two usually separate kidneys are joined, creating a U [horseshoe] shape. Another baby has a double set
of tubes leading from the kidneys. Two babies had kidney reflux, where urine flows back from the bladder towards the kidneys.

Two babies were born with unusually-shaped chests. In one it was hollowed [pectus excavatum] and another baby was born with a ‘pigeon chest’ [pectus carinatum]. In three babies the spine was affected, but in quite different ways. One baby had spinal cord cysts [syringomelia]; another had a ‘tethered cord’, where the bottom end of the spinal cord that is usually free within the spinal column gets attached to one of the surrounding structures. If necessary the cord can be surgically released so that it can hang freely. Another had a curved spine [scoliosis].

In one baby the heart was affected: the baby had a persistent ductus arteriosus/PDA. This is a channel between the two major blood vessels leading from the heart which usually closes shortly after birth. When it stays open, the lungs receive more blood than they should and the heart has to work too hard. If it does not close naturally in time, a PDA can be closed using minimally invasive surgery.

One baby boy was born with hypospadias, where the opening usually at the end of the penis is on the underside, generally corrected with surgery.

One baby had malrotation of the intestines. This is a developmental anomaly of the digestive tract. Until the 10\textsuperscript{th} week of gestation, the intestines are located at the base of the umbilical cord. As the intestine returns to the abdomen, it makes two rotations and becomes fixed into its normal position. When rotation is incomplete and fixation does not occur, the defect is known as intestinal malrotation. Sometimes there are no symptoms or problems but if the intestine is obstructed or the blood supply is twisted, surgical repair is performed as soon as possible.

One baby had a wry neck [torticollis].

[Bedoyan 2010; Fernandez 2010; Rosenfeld 2010; Shinawi 2010; Schaaf 2011; Unique]

\begin{itemize}
\item **Possible tendency to underweight**

Preliminary data suggests that people with the 16p11.2 microduplication have a tendency to be underweight. Early information from Unique supports this, with individuals described as being relatively tall but proportionately thin or ‘lacking in body mass’.

By contrast, a tendency to overweight and obesity has been identified in almost half the children and adults with a 16p11.2 micro deletion, making the microdeletion the second most common genetic cause of obesity [Bochukova 2010; Jacquemont 2010; Unique].

\item **Possible vulnerability to seizures**

Most children with a 16p11.2 microduplication have never had a seizure or a seizure-like episode. All the same, a minority - up to around 15% - have. This has led to the suggestion that there is an association between the microduplication and a vulnerability to seizures, although seizure types and severity vary widely. Typically, they start under 12 months of age, are easily controlled with anti-epileptic medication and tend to resolve or decrease in severity during childhood. One baby
was diagnosed with a rare type of epilepsy called malignant migrating partial seizures of infancy. His seizures started on his first day of life; at first they were hard to treat but they were successfully treated by around 5 months. Another child has clusters of simple partial seizures which are controlled with anti-epileptic medications.

Among the genes that are duplicated, three have been suggested as being involved in the brain and possibly involved with seizures. These genes are QPRT, DOC2A and SEZ6L2 [Bedoyan 2010; Rosenfeld 2010; Shinawi 2010; Unique].

Suggested screening and management

It’s recommended that anyone with a 16p11.2 microduplication diagnosis should have a clinical examination; a general review of all their organ systems; and a developmental assessment. If there are symptoms that suggest seizures, a consultation with a neurologist and EEG is recommended. If there are any neurological symptoms related to the spine, the spine can also be imaged by MRI [Schaaf 2011], but this is not a general recommendation for all. 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.

Scientific articles

Bedoyan 2010: Duplication 16p11.2 in a child with infantile seizure disorder *American Journal of Medical Genetics* Volume 152A(6) pages 1567-74

Bochukova 2010: Large, rare chromosomal deletions associated with severe early-onset obesity *Nature* Volume 463(7281) pages 666-670


McCarthy 2009: Microduplications of 16p11.2 are Associated with Schizophrenia *Nature Genetics* Volume 41 (11) pages 1223-7 Free access

Rosenfeld 2010: Speech delays and behavioural problems are the predominant features in individuals with developmental delays and 16p11.2 microdeletions and microduplications *Journal of Neurodevelopmental Disorders* Volume 2 pages 26-38

Shinawi 2010: Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy and abnormal head size *Journal of Medical Genetics* Volume 47 pages 332-341

Schaaf 2011: Expanding the clinical spectrum of the 16p11.2 chromosomal rearrangements: three patients with syringomyelia *European Journal of Human Genetics* Volume 19(2) pages 152-156

Walsh 2011: Copy number variation in the dosage-sensitive 16p11.2 interval accounts for only a small proportion of autism incidence: A systematic review and meta-analysis *Genetics in Medicine* Volume 13(5) pages 377-384

Inform Network Support

Unique
Understanding Chromosome & Gene Disorders

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At www.simonsvipconnect.org there is an online community for families affected by 16p11.2 deletions and duplications, a short fact sheet about the 16p11.2 duplication and summaries of relevant recent journal articles.

Join Unique for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you can please make a donation via our website at www.rarechromo.org/donate 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 guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. 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. It was compiled by *Unique* and reviewed by Dr David Miller, MD PhD Clinical Geneticist and Clinical Molecular Geneticist, Children’s Hospital, Boston, USA and by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK.

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