



Understanding Chromosome & Gene Disorders

16p13.11 microdeletions



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Sources

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from a survey of members of Unique conducted in 2011, referenced Unique. When this leaflet was written Unique had 13 members with a 16p13.11 microdeletion. These members range in age from a child of one year to an adult aged 37 years. There are 52 further people described in the medical literature. However, the majority [36/52] were diagnosed as a result of several large studies of people with epilepsy and there is very little additional information available about these individuals [de Kovel 2010; Heinzen 2010; Mefford 2010].

16p13.11 microdeletions

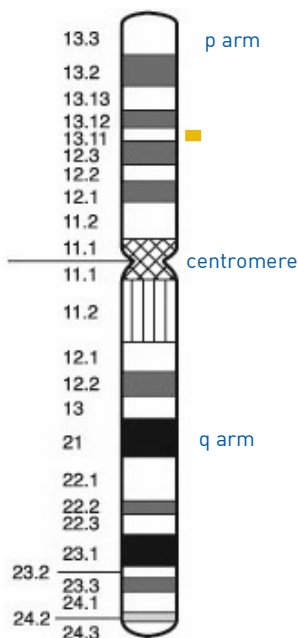
A 16p13.11 microdeletion is a very rare genetic condition in which a tiny piece is missing from one of the 46 chromosomes – chromosome 16.

Chromosomes are made up mostly of DNA and are the structures in the nucleus of the body's cells that carry genetic information (known as genes), telling the body how to develop, grow and function. Chromosomes usually come in pairs, one chromosome from each parent. Of these 46 chromosomes, two are a pair of sex chromosomes, XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm (shown at the top in the diagram below) and a long (q) arm (the bottom part of the chromosome). People with a 16p13.11 microdeletion have one intact chromosome 16, but the other is missing a tiny piece from the short arm.

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 16p13.11 microdeletion seem completely unaffected by it. Others have some problems with their development, speech, behaviour, learning or health that may be caused by the missing genetic material.

Looking at chromosome 16p

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. Even if you magnify the chromosomes as much as possible, to about 850 times life size, a chromosome 16 with the microdeletion at p13.11 looks normal. People who have missing material on a chromosome are said to have a **deletion** but when the amount is so small that it can't be seen even under a high-powered microscope, it is called a **microdeletion**. The 16p13.11 microdeletion can be found using molecular techniques such as array comparative genomic hybridisation (array CGH). This technique shows whether particular genes are present or not (Unique has prepared an information guide on array CGH). It is believed that the effects are caused by the presence of only one copy of these genes instead of two, as expected normally. The 16p13.11 region is denoted by

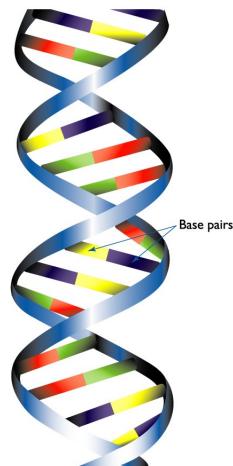


the yellow bar on the diagram on page 2. In the diagram of chromosome 16 on page 2 the bands are numbered outwards starting from where the short and long arms meet (the centromere). People with a 16p13.11 microdeletion have all or part of the band p13.11 missing.

Band 16p13.11 contains around 2 million base pairs. This sounds a lot but it is actually quite small and is only two per cent of the DNA on chromosome 16.

Chromosome 16 has around 89 million base pairs and is about three per cent of the total DNA in our cells. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.

1 base pair = bp
1,000 base pairs = 1kb
1,000,000 base pairs = 1Mb



Array CGH report

The laboratory that finds the 16p13.11 microdeletion will send a report that is likely to read something like the following example:

arr cgh 16p13.11 (15154687-16292235)x1 (hg19)

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

16p13.11 The chromosome involved is 16 band p13.11
15154687-16292235

The base pairs between 15,146,187 (around 15Mb) and 16,292,235 (around 16Mb) have been shown to be deleted. Take the first long number from the second and you get 1137548 (1.14Mb). This is the number of base pairs that are deleted. x1 means there is one copy of these base pairs, not two – one on each chromosome 16 – as you would normally expect

Emerging phenotype: what to expect

When only very small numbers of people have been identified, we can't yet be certain what the full range of possible effects of the microdeletion are. Additionally, 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 learning to sit, move and walk
- Delay in starting to speak and language development
- Children may need support with learning. The amount of support needed by each child will vary, although most benefit from supportive services for special needs
- Increased risk of developing seizures
- Microcephaly (a small head)

Are there people with a 16p13.11 microdeletion who have developed normally and have no speech, learning or health difficulties?

Yes, there are. The 16p13.11 microdeletion can be silent. Some parents of children with a 16p13.11 microdeletion have the same microdeletion but do not have any obvious unusual features or delayed development (Ullmann 2007; Hannes 2009; Unique).

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 16p13.11 microdeletion 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 microdeletion. We know that if one person is mildly affected or unaffected, others may be more severely and obviously affected.

Pregnancy

Most mothers carrying babies with a 16p13.11 microdeletion experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. There is information available on nine pregnancies of mothers carrying a baby with a 16p13.11 microdeletion. Three had no pregnancy problems and no unusual findings on ultrasound scans. One baby had intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed resulting in babies that are smaller than expected for the number of weeks of pregnancy.

One mother had an ultrasound scan at 12 weeks which showed increased nuchal translucency where subsequent chorionic villus sampling (CVS) failed to detect the microdeletion due to its small size. After birth the baby was diagnosed with a 16p13.11 microdeletion by an array CGH test. Three babies had unusual findings on prenatal ultrasound scan: one had a cleft lip diagnosed at 18 weeks; one had talipes (clubfoot) and another had rocker bottom feet and unusual hands. One mother developed pre-eclampsia (pregnancy induced high blood pressure) and one mother had polyhydramnios (an unusually high volume of amniotic fluid). One Unique baby was born prematurely at 34 weeks (Ullmann 2007; Law 2008; Hannes 2009; Balasubramanian 2011; Unique).

Newborn

Newborns with a 16p13.11 microdeletion may not have any signs or symptoms. However, two Unique babies were suspected to have Down's syndrome which led to genetic testing. Two Unique babies did not cry or vocalise as expected with a newborn. One Unique baby was born with rocker bottom feet and clenched hands (and was unable to straighten his fingers). Birthweights recorded at Unique and in the published medical literature show a considerable variation with an average of 3.38 kilos (7lb 7oz). Most babies have a normal birth weight. One Unique baby had a low birth weight (below 2.6 kilos or 5lb 12oz) at term (Ullmann 2007; Balasubramanian 2011; Unique).



Feeding

Feeding difficulties affect some babies with a 16p13.11 microdeletion. The hypotonia that affects some babies with a 16p13.11 microdeletion can lead to difficulties with sucking and swallowing, and/or latching onto the breast. One baby in the published medical literature benefited from having a nasogastric tube (NG-tube, passed up the nose and down the throat). A baby at Unique also benefited from having a temporary NG-tube which was removed at 6 months. At 18 months he takes a bottle and eats puréed food well but does not chew or eat lumps (Balasubramanian 2011; Unique).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). GO reflux has been described in two children. GO reflux can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Balasubramanian 2011; Unique).

“ She has poor oral muscle tone and has a tendency to over stuff her mouth as she cannot tell when it is full. This can lead to her choking. She finds it hard to keep foods and in particular liquids in her mouth. She is monitored by a speech therapist and has facial muscle exercises and a chewy tube to strengthen her muscles ” - 4 years

Appearance

Children and adults with 16p13.11 microdeletions may look similar. They often have a small head (microcephaly) with a short nose and low-set ears. They may have a wide mouth and a thin upper lip with a Cupid's bow shape.

Development: sitting, moving, walking (gross motor skills)

Often gross motor skills are affected in those with a 16p13.11 microdeletion and this means that it may take longer for children to roll over, sit, crawl and walk. One Unique child mastered walking at 13 months and another at 19 months. However, a 3-year-old can sit unaided but cannot yet roll, crawl or walk. A 15-month-old cannot yet walk but can pull herself up and has been crawling since she was 12 months. A 3½-year-old cannot sit, crawl or move on his own. There is limited information on the mobility of children in the medical literature but a 19-month-old and a 5-year-old have no motor delay; a 9-month-old and a 9-year-old both have motor delay; a 4-year-old is described as having motor development of a 3-year-old and an adult is described as having an unusual way of walking (gait). Children may need considerable support while learning to sit, stand and/or walk. Many children have a standing frame and special supportive chairs (Hannes 2009; Nagamani 2011; Unique).



3 years

These delays may be attributed to hypotonia (floppiness or low muscle tone) that affects some, although not all, with a 16p13.11 microdeletion. Two children had hypertonia (increased muscle tone) which results in one child finding it very difficult to straighten her arms and legs. She is due to have botulinum toxin (Botox) injections in her Achilles tendons and hamstrings to loosen the muscles. Three children have hypermobile (lax or loose) joints. Joint laxity in the feet and ankles can make learning to walk more difficult and some children wear supportive shoes with special insoles (Ullmann 2007; Hannes 2009; Nagamani 2011; Unique).

“ She has a special trike with leg callipers and trunk support. This gives her some much needed exercise as the pedals go round whilst the trike is being pushed. She also loves the trampoline ” – 4 years

Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Hypotonia can also affect fine motor skills in children with a 16p13.11 microdeletion and they may take longer to reach for and grab toys and hold a bottle or cup (Ullmann 2007; Nagamani 2011; Unique).

Toilet training is also likely to be affected. From the limited information that is available one boy wet the bed until the age of 9½ years and had problems soiling his underpants until the age of 5 and an adult had some problems toilet training and wet the bed and soiled underwear into adolescence (Unique).

“ Her fine motor skills are quite delayed. She can hold a spoon or fork and bring it to her mouth but cannot load it independently. She also holds a two handled baker for drinking and can drink independently. She uses a pincer grip to pick up small items such as raisins. She holds a crayon with an immature palmar grasp. She sometimes tries to pick something up and doesn't realise she hasn't got hold of it ” – 4 years

“ She wears a nappy at night. She can brush her hair and teeth and dress herself ” – 5 years

Delay in starting to speak and language development

A delay in speech and language is very common, although not universal. Two Unique babies did not cry or vocalise as newborns. In the medical literature many children are described as having speech delay. One adult had some speech difficulties when young and still gets words mixed up sometimes. A 4-year-old has language corresponding to an 18-month old; a 12-year-old has only isolated words; a 19-year-old has echolalia (the repetition of speech just spoken by somebody else in an involuntary and meaningless way); an adult has difficulty in expressive language but another adult is described as 'very talkative' (Ullmann 2007; Hannes 2009; Nagamani 2011; Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak.

“ She communicates with a combination of eyes, pointing, reaching and vocal noises. She is starting to use Makaton pictures to make a choice between two items. She approximates the Makaton sign for 'more' and can wave. She says 'ayo' for 'hello' when she sees someone or something she wants to interact with. She will lean into your line of sight to catch your attention and if she is close enough will tug your sleeve or pat your arm (or tweak your nose!) ” – 4 years

“ She is trying to talk and we are in the process of getting her a communication device. The iPad has been amazing for her as it make is much easier for her to communicate ” – 5 years

Learning

Many people described in the medical literature (23/32) have no learning difficulties. Unique also has several members who have no learning difficulties. One boy at the age of 10 does well in school and does not have any learning difficulties. An 11-year-old is of average intelligence. An adult had a hard time learning at school but worked very hard and obtained a masters degree. However, there are people with a 16p13.11 microdeletion both in the medical literature and known to Unique who have learning difficulties and there is a broad spectrum of need for support with learning. One has a borderline learning difficulty, one has a moderate learning difficulty, three children have severe learning difficulties and one has a profound learning disability. Many children with a learning difficulty benefit from attending a special educational school (Ullmann 2007; Hannes 2009; Law 2009; de Kovel 2010; Heinzen 2010; Unique).

“ She enjoys books and will sit and look at books for a very long time. She has a good memory for people/faces and seems to recognise when she arrives at familiar places. She learns best with 1:1 help or in small groups. Music and food are good motivators for her and can be used to help her learn ” – 4 years

“ She has a very good memory. She can write her name and half her ABCs. She is a visual learner ” – 5 years

Increased risk of developing seizures

Seizures (epilepsy) appear to be a common feature for those with a 16p13.11 microdeletion. There have been three large-scale studies of people with epilepsy which have attempted to identify a genetic basis for their epilepsy. These studies have resulted in 36 people with epilepsy being diagnosed with a 16p13.11 microdeletion. A further three people in the medical literature and two at Unique have seizures. There is a wide range in the severity and type of seizures. Two children had West syndrome (also known as infantile spasms affecting children under the age of one year). Generally, seizures appear to be well controlled with medication although one adult in the medical literature has epilepsy that has been resistant to therapy. The 16p13.11 microdeletion is the most common single genetic risk factor for developing seizures identified to date (Hannes 2009; de Kovel 2010; Heinzen 2010; Mefford 2010; Balasubramanian 2011; Unique).

Some babies with a 16p13.11 microdeletion 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

Many babies with a 16p13.11 microdeletion 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 16p13.11 microdeletion 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 the 16p13.11 microdeletion.

However, one common finding is that on investigation, 17 people with the microdeletion

have some anomaly of the brain structure that shows on magnetic resonance imaging (MRI). Various anomalies have been detected and there appears to be no consistent feature (Ullmann 2007; Hannes 2009; Heinzen 2010; Balasubramanian 2011; Nagamani 2011; Unique).

Children and adults with the microdeletion may have hands that are not perfectly formed. One child has fingers which are fused (syndactyly). Two children have fingers which do not fully straighten. These features do not usually cause medical problems but in some cases do have an impact on functionality (Balasubramanian 2011; Heinzen 2011; Unique).

The feet of children with 16p13.11 microdeletions may also not be perfectly formed. One child had rocker bottom feet. He had serial casting on his feet for 6 weeks from birth which brought his feet into the correct position. He then wore special boots for 23 hours a day for 4 months to maintain the correct position. He will continue to wear his boots at night until he is 4 years old (he is now 3½). Another has feet that pronate (roll inwards) and wears ankle foot orthotics (AFOs) on both feet to correct her foot position and help her to bear weight (Unique).

In five babies the heart was affected: three babies had small holes in the heart which all resolved spontaneously and needed no treatment. Another baby had cardiomegaly (an enlarged heart) at birth but on follow-up at 3 months the heart was normal. Another baby had hypertrophic cardiomyopathy (the muscle of the heart is thickened) which needed no intervention (Ullmann 2007; Law 2009; Balasubramanian 2011; Unique). Two baby boys were born with undescended testes and one had a very small penis (micropenis). 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 (Balasubramanian 2011; Unique).

Two babies had brachycephaly (a flat head) which necessitated wearing a cranial helmet (Unique).

One baby was born with a cleft palate (an opening in the roof of the mouth, usually closed surgically) (Hannes 2009).

In one baby the kidneys and drainage system for urine were affected (Balasubramanian 2011).

One baby was born with a hollow chest (pectus excavatum) (Hannes 2009).

One girl had a urethral caruncle for a short period which resolved itself. A urethral caruncle is a soft, fleshy protrusion of the urethral lining from the urethral opening. The urethra is the tube that drains urine from the bladder) (Unique).

One baby had a twisted neck (torticollis) (Unique).



5 years

Other concerns

■ Constipation

One problem is constipation which affects a number of people with the microdeletion. Dietary changes and/or medication can help to manage the problem (Balasubramanian 2011; Unique).

■ Vision

Eye findings in people with the microdeletion are common. Two children have strabismus (a squint) where one or both eyes can turn inwards, outwards or upwards. Other problems reported in just one child include nystagmus (rapid uncontrolled eye movements); cortical visual impairment (a form of visual impairment that is caused by a brain problem rather than an eye problem); astigmatism (the cornea - the clear cover over the iris and pupil - is abnormally curved which makes objects appear blurred) which is corrected with glasses. One child has a lazy eye and wears bifocal glasses. Another child had cataracts (clouding of the eye's lens) diagnosed just after birth and had an operation to correct them at the age of 18 months (Ullmann 2007; Nagamani 2011; Unique).

■ Ears and hearing

Some children with 16p13.11 microdeletion have a hearing impairment. One child has a conductive hearing loss caused by fluid in the middle ear (glue ear). Glue ear usually resolves as children get older secondary to growth and an improving immune system. Therefore, any hearing loss caused by glue ear is usually temporary. Permanent sensori-neural hearing loss has also been reported in two children in the published medical literature and in the left ear of one child at Unique. One child has mild high frequency hearing loss. One child has an atretic auditory canal (the ear canal ends before reaching the ear drum) (Hannes 2009; Balasubramanian 2011; Nagamani 2011; Unique).

Behaviour

In general children with a 16p13.11 microdeletion are happy, kind, affectionate and social. However, they are as vulnerable to frustration as other children with a communication difficulty and a small minority succumb to temper tantrums and aggression. One adult described in the medical literature was very talkative with intermittent verbal aggression and self-mutilation (Ullmann 2007; Hannes 2009; Nagamani 2011; Unique).

Autistic traits or autistic spectrum disorder (ASD) have also been reported in several people with a 16p13.11 microdeletion. A diagnosis of autism can be extremely helpful in accessing services and tailoring the educational and behavioural therapy to meet the specific needs of a child with autism. Two children find socialising difficult, one of whom has been diagnosed with an anxiety disorder. Four children have obsessive compulsive disorder (OCD), an anxiety-related condition in which people experience frequent intrusive and unwelcome obsessional thoughts, often followed by repetitive compulsions, impulses or urges. Sensory issues have also been reported to affect four children. One person has Tourette syndrome (a neurological disorder characterized by repetitive, stereotyped, involuntary movements and vocalisations called tics).

One person in the medical literature is described as having psychotic depression (depression accompanied by hallucinations and delusions) which developed after the onset of epilepsy and another has psychosis (a condition that affects a person's mind and causes changes to the way that they think, feel and behave and can result in an inability to distinguish between reality and imagination) which is controlled with medication (Ullmann 2007; Heinzen 2010; Unique).

“ He loves other people interacting with him and making him laugh and smile. He loves being tickled, stroked and sung to ”- 3½ years

“ She loves music and dances and claps along. She has a very sweet personality and a good sense of humour and is very sociable. Despite her difficulties she is generally happy, well behaved and easy going. She sometimes gets a bit grumpy when she is hungry or tired. She also dislikes being dressed or having her hair brushed and tends to extend her arms/legs/back to get away. She is sensitive to sudden loud noises but is getting better. She also struggles with cold textures (e.g. she does not like eating ice cream) ” - 4 years

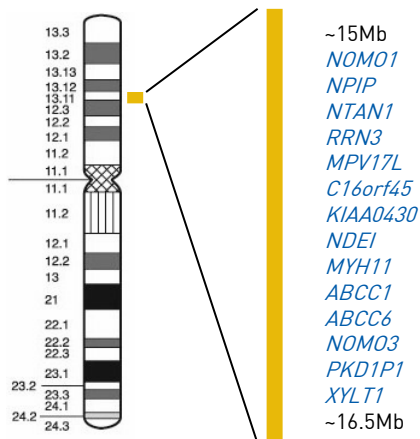
“ A sensory swing has been amazing because she has such severe sensory issues [she has a sensory processing disorder]. She has a sensory diet at school and at home. She has no bad behaviour. She follows directions, listens and is a great kid 99.9 per cent of the time ” - 5 years

Adults with 16p13.11 microdeletions

A number of adults have been described in the medical literature and Unique has three adult members with the microdeletion. Many have no developmental delay or health issues. One man discovered he had the 16p13.11 microdeletion when his son was diagnosed. He had learning difficulties and left school early to be a fisherman. A mother, who only discovered her 16p13.11 microdeletion after her son with learning difficulties was diagnosed, had a similar facial appearance to her son but had no other unusual features and did not have delayed development. Two other mothers where the microdeletion was discovered after their children were diagnosed, always struggled in school (Ullmann 2007; Hannes 2009; Unique).

Ongoing research involving 16p13.11

A 16p13.11 microdeletion is tiny, so it can only be found using molecular techniques such as MLPA or microarrays (array-CGH) or targeted cytogenetic testing using FISH. These techniques show whether particular genes are present or not. The features of a 16p13.11 microdeletion are likely to be a result of the loss of a number of different genes found in



this region. The typical 16p13.11 microdeletion is 1.65Mb and encompasses around 15 genes. Some people have a slightly larger deletion, however, it seems that these people have the same features as those with the smaller, typical microdeletion.

NDE1 which is expressed in the brain has been postulated to be responsible for the microcephaly that is often seen in those with a 16p13.11 microdeletion. Mutations in *NDE1* in humans have been shown to cause microcephaly. Mice missing this gene have a small brain (Alkuraya 2011; Balasubramanian 2011; Nagamani 2011).

NTAN1 is a candidate for some of the features of a 16p13.11 microdeletion. Mice missing this gene have altered social behaviour and memory (Balasubramanian 2011).

It is important to remember that while identifying the gene(s) responsible for certain features of a 16p13.11 microdeletion is valuable and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is missing it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 16p13.11 microdeletion occurred. At least six parents have been known to pass a 16p13.11 microdeletion on to their child (Ullmann 2007; Hannes 2009; Unique). However, in some cases so far the microdeletion occurred when both parents have normal chromosomes by an analysis of a blood sample. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 16p13.11 microdeletions are caused by a change that occurred when the parents' sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined.

Whether the microdeletion is inherited or *de novo*, as a parent there is nothing you did to cause the 16p13.11 microdeletion and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. There is nothing that either parent did before or during pregnancy that caused the microdeletion – so no-one is to blame and there is no reason for anyone to feel guilty.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 16p13.11 microdeletion 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 16p13.11 microdeletion. 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 deletion.

In families where the 16p13.11 microdeletion has been inherited from a parent, the possibility of having another child – either a girl or a boy – with the 16p13.11 microdeletion rises to 50% in each pregnancy. However, the effect of the microdeletion 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.

Inform Network Support



Understanding Chromosome & Gene Disorders

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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 Meena Balasubramanian, Sheffield Clinical Genetics Service, UK; Dr Heather Mefford, University of Washington, USA and by Professor Maj Hultén, Professor of Medical Genetics, University of Warwick, UK
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