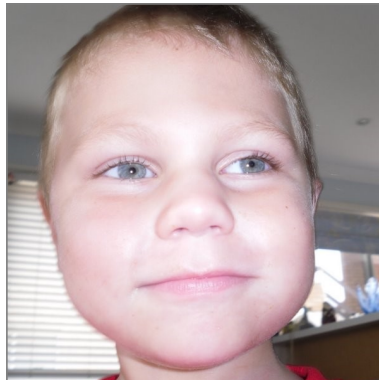




Understanding Chromosome & Gene Disorders

16p13.11 microduplications



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16p13.11 microduplications

A 16p13.11 microduplication is a very rare genetic variation in which there is an extra copy of a tiny piece of chromosome 16. The duplication is found near the middle of the chromosome at a place called p13.11. Because the extra bit is very tiny indeed, you will sometimes see it called a microduplication.

Most of what we know about 16p13.11 microduplications comes from studying people who have a reason for having a genetic test. The reason might be developmental delay, unusual behaviour or a health problem, or perhaps the 16p13.11 microduplication has been found in someone else in their family. This gives us a biased sample. If we looked for the 16p13.11 microduplication in the general population, we would have an unbiased sample, but it is very difficult to do. This means that at the moment we can't be sure about the cause and effect of a 16p13.11 microduplication. There is still a lot to learn, but this guide contains the best information we have to date.

You may read or hear the terms “incomplete penetrance” and “variable expressivity” in relation to 16p13.11 microduplications (see page 3). This is because the features of people with a 16p13.11 microduplication vary widely, even among members of the same family. Some people can have developmental delay, learning difficulties and behavioural problems, but many people with the microduplication have no apparent physical, learning or behaviour difficulties.

Why people show such variability in the range and severity of features, even when they have the same – or very similar - genetic change, are complex and not yet fully understood. Proposed explanations include a role for the cumulative effects of the variation in the DNA sequence across a person's whole genome; the outcome of interactions between other genetic variants across the genome; and the influence of environmental factors (both internal and external) on the individual's genome.

Sources

The information in this leaflet is drawn partly from 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 and information in the Unique database, referenced Unique. When this leaflet was written Unique had ten members with a 16p13.11 microduplication. These members range in age from babies to adults. There are over 200 further people described in medical literature. However, the majority were diagnosed as a result of several large studies of people with an intellectual disability, attention deficit hyperactivity disorder, schizophrenia or adult onset heart disease, and there is very little information available about some of these individuals (International Schizophrenia Consortium 2008; Itsara 2009; Kirov 2009; Mefford 2009; Ikeda 2010; Williams 2010; Cooper 2011; Ingason 2011; Kuang 2011; Allach El Khattabi 2018).

Penetrance refers to the proportion of people with a particular genetic change e.g. a duplication, deletion or gene mutation, who exhibit signs and symptoms of a genetic disorder. If some people with the genetic change don't develop the features associated with the disorder, the condition is said to have **incomplete** (or **reduced**) **penetrance**.

Variable expressivity refers to the range and severity of features that occur in different people with the same genetic condition. Some people may show no symptoms or be only very mildly affected; others may be more severely affected.

Both these phenomena can make it extremely challenging to provide accurate genetic counselling, since genetics professionals are unable to accurately predict how future generations in a family with a particular genetic change will be affected.

What does the 16p13.11 microduplication mean?

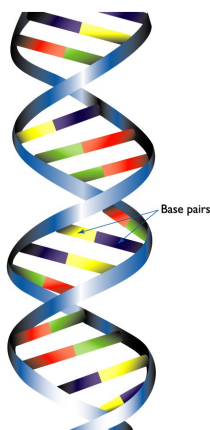
Chromosome 16 is one of the 23 pairs of chromosome in the cells of the body that carry genetic material.

The top bit down to the indent on the diagram on the right is known as the p arm. The bottom bit is called the q arm. Chromosomes are made up of DNA, which contains the genetic instructions for development and functioning. DNA has a ladder-like structure, with the ladder's rungs formed from chemicals known as base pairs. The size of the tiny extra bit of 16p13.11 is measured in base pairs. There are millions of base pairs on a chromosome so the numbers are usually shortened. One million base pairs is called a megabase, and written as 1Mb. Band 16p13.11

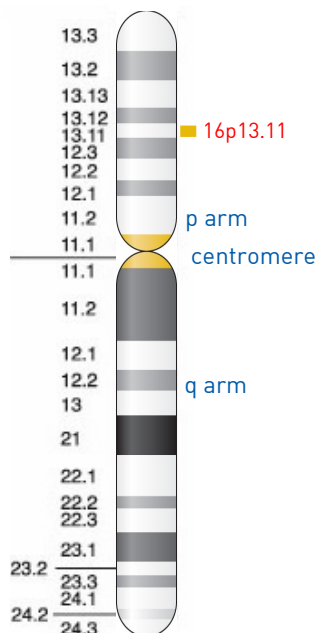
contains around 2Mb. This sounds a lot but it is actually quite small and is only two per cent of the DNA on chromosome 16.

Chromosome 16 has around 89 million base pairs and is about three per cent of the total DNA in our cells. Most people have a 16p13.11 microduplication that is

between 1.1 Mb and 1.65Mb in size. It is believed that the effects are caused by the presence of three copies of the genes in this region instead of two, as expected normally.



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



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 microduplication will send a report that is likely to read something like the following example:

arr[hg19] 16p13.11 (14910205_16305736)x3 (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
14910205-16305736

The base pairs between 14910205 (around 14.9Mb) and 16305736 (around 16.3Mb) have been shown to be repeated. Take the first long number from the second and you get 1395531 (1.4Mb). This is the number of base pairs that are duplicated.

x3 means there are three copies of these base pairs - not two as you would normally expect

Emerging phenotype: what to expect

Because only very small numbers of people have been identified, we can't yet be certain what the full range of possible effects of the microduplication 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:

- 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
- Behaviour and emotional disorders including attention deficit hyperactivity disorder and/or autism in some children
- Speech delay in some children

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

Yes, there are. The 16p13.11 microduplication can be silent. Some parents of children with a 16p13.11 microduplication have the same microduplication but do not have any obvious unusual features or delayed development (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 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 or unaffected, others may be more severely and obviously affected.

What is the outlook?

We can't be sure yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan. Several adults have been described in medical literature and *Unique* also has several adult members (see page 7). However, some adults with a 16p13.11 microduplication have developed an adult-onset cardiovascular disorder (Kuang 2011; Allach El Khattabi 2018) (see page 8).

Pregnancy

Most mothers carrying babies with a 16p13.11 microduplication experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. There is information available on five pregnancies of mothers carrying a baby with a 16p13.11 microduplication. Three had no pregnancy problems and no unusual findings on ultrasound scans. One baby had microcephaly (a small head) on a 20-week ultrasound scan. One mother had a low amount of alphafetoprotein (AFP) in a maternal screening test while pregnant. This test can indicate the presence of a chromosome disorder; however, the mother chose not to have an amniocentesis (Hannes 2009; Unique).

Feeding and growth

Feeding difficulties are not a consistent feature of 16p13.11 microduplications. However, two *Unique* babies were very picky eaters; one is still fussy at aged five years. He regularly sees a dietician. One child in medical literature has 'failure to thrive'. This is a term used to describe a baby who has poor weight gain and physical growth failure over a period of time. One child has suffered from constipation from birth (Hannes 2009; Ramalingam 2011; Allach El Khattabi 2018; Unique).

Three children are described as small and thin and one is described as tall (Nagamani 2010; Unique).

“ He was breastfed until 11 months old. He gagged on solids as a baby and even today he gags on some solid foods ” – 5 years

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

Often gross motor skills are unaffected in those with a 16p13.11 microduplication, although almost half the children in the medical literature and some children at *Unique* are described as having motor delay, which means that it may take a little longer for children to roll over, sit, crawl and walk. Children often benefit from physiotherapy. Two boys are described as clumsy. One child has hypertononia (increased musculature or stiffness) (Hannes 2009; Nagamani 2010; Allach El Khattabi 2018; Unique).

“ He walks, runs and climbs, but can be clumsy ” – 5 years

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

Fine motor skills may be affected and children may take longer to reach for and grab toys and hold a bottle or cup. One *Unique* child has a co-ordination disorder. Some children have occupational therapy to try to help overcome these difficulties (Unique).

Delay in starting to speak and language development

Some, although not all, children with a 16p13.11 microduplication have a delay in acquiring speech and language skills. In the medical literature, 51/62 (81%) of patients with a 16p13.11 microduplication had a speech delay, including a girl who had limited use of language, poor vocabulary and repetitive speech, and an 18-year-old who had delayed speech with prominent echolalia (involuntary repetition of words or phrases). A 7-month-old baby had vocal cord palsy (Ullmann 2007; Hannes 2009; Nagamani 2010; Unique; Allach El Khattabi 2018).

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

Learning

Some people described in medical literature have no learning difficulties. *Unique* also has several members who have no learning difficulties. However, there are people with a 16p13.11 microduplication 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. Most have a mild to moderate learning difficulty, but for a few a severe or profound learning disability has been reported. Many children with a learning difficulty benefit from attending a special educational school (Hannes 2009; Nagamani 2010; Ramalingam 2011; Allach El Khattabi 2018; Unique).

Some babies with a 16p13.11 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

Many babies with a 16p13.11 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 16p13.11 microduplication have only occurred in just a few babies, so they may be a coincidence, and it is still not clear if any of the birth defects reported here are actually caused by the 16p13.11 microduplication.

In a few babies the heart was affected: one baby had pulmonary stenosis (a narrowing of the pulmonary valve: a flap-like structure that allows blood to flow in one direction, meaning that the heart has to work harder to pump blood, which results in breathlessness) which the cardiologist expects to resolve by itself. One baby had Tetralogy of Fallot, which is a complex heart condition involving both a hole in the heart and an obstruction just below the valve in the artery that leads to the lungs. Blue (deoxygenated) blood cannot easily get to the lungs to pick up oxygen and some

of it flows through the hole into the other pumping chamber, from where it is pumped around the body. The majority of babies with Tetralogy of Fallot successfully undergo surgery in the first year of life. One baby had a complex heart condition involving several holes in the heart, aortic coarctation (a narrowing of the aorta: the major artery leading out of the heart), and transposition of the great arteries (TGA: where the two main arteries are reversed). Several adults with a 16p13.11 microduplication have developed a late-onset heart condition called thoracic aortic aneurysm dissection (TAAD) (see page 9) (Hannes 2009; Nagamani 2010; Kuang 2011; Allach El Khattabi 2018; Unique).

One finding is hypermobile joints, which affect at least one child at *Unique* and four people described in the medical literature (Nagamani 2010; Unique).

On investigation, some people with the microduplication have an anomaly of the brain structure that shows on magnetic resonance imaging (MRI). Various anomalies have been detected but these incidents are sporadic and there appears to be no consistent feature (Hannes 2009; Nagamani 2010; Ramalingam 2011; Allach El Khattabi 2018; Unique).

Children and adults with the microduplication may have hands and/or feet that are not perfectly formed. Several people have polydactyly (one or more extra digits). One child has large, puffy hands with small nails; another has deep creases in the palms and an incurving fifth finger (clinodactyly). Another child has arachnodactyly ('spider fingers', where the fingers are unusually long and slender). One child has large big toes with webbing between two of the toes and two people have flat feet (pes planus) (Hannes 2009; Nagamani 2010; Unique).

Four babies have microcephaly (a small head), one of whom has a large soft forehead. One person had macrocephaly (a larger head). One baby had brachycephaly (a flat head) and two babies have craniosynostosis (an abnormal head shape caused by premature fusing of the skull bones) (Hannes 2009; Nagamani 2010; Ramalingam 2011; Unique).

One *Unique* baby has laryngomalacia (the larynx is particularly soft and limp) but it has not affected her breathing or eating (Unique).

Two babies had an umbilical hernia (a soft skin-covered bulge at the belly button) (Hannes 2009; Unique).

One baby was born with a sunken chest (pectus excavatum) (Nagamani 2010).

One baby had tethered cord syndrome (the spinal cord is abnormally attached to the tissues around the spine, meaning the spinal cord can't move freely, which limits movement) (Unique).

Other concerns

■ Seizures

Seizures (epilepsy) appear to affect some of those with a 16p13.11 microduplication. At least 11 people in the medical literature and six at *Unique* have seizures (Hannes 2009; Nagamani 2010; Ramalingam 2011; Allach El Khattabi 2018; Unique).

■ Vision

Several people with the microduplication have eye problems. Two children registered

with *Unique* are long-sighted, which in one case is described as severe. One person has astigmatism (the cornea - the clear cover over the iris and pupil - is abnormally curved, which makes objects appear blurred) and one child has a mild squint (where the eye turns inwards, outwards, upwards or downwards). One child had nystagmus, where there is a continual uncontrolled movement of the eyes (Hannes 2009; Unique).

Behaviour

In general children with a 16p13.11 microduplication are happy and affectionate. However, they are as vulnerable to frustration as other children with a communication difficulty and a small minority succumb to temper tantrums and aggression (Hannes 2009; Unique).

Children with a 16p13.11 microduplication are more likely to have attention deficit hyperactivity disorder (ADHD), which is characterised by restlessness and a short attention span. Autistic traits or autistic spectrum disorder (ASD) have also been reported in at least 38 people with a 16p13.11 microduplication. A diagnosis of autism can be extremely helpful in accessing services and tailoring educational and behavioural therapy to meet the specific needs of a child with autism. Three people in the medical literature have anxiety. One adult has developed 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 (Ullmann 2007; Hannes 2009; Nagamani 2010; Williams 2010; Ramalingam 2011; Allach El Khattabi 2018; Unique).

Studies in the medical literature have shown that thirty-three out of 79 people who have a 16p13.11 microduplication are also affected by schizophrenia. Schizophrenia is a mental health condition that causes a range of different psychological symptoms, including hallucinations (hearing or seeing things that do not exist) and delusions (believing in things that are untrue). Schizophrenia can be treated using a combination of medical treatments such as antipsychotic medicines and psychological interventions such as cognitive behavioural therapy. All of these people were diagnosed first with schizophrenia and discovered that they carried the 16p13.11 microduplication when they took part in one of several large studies of people with schizophrenia.

These studies also identified 46 out of 79 people who are not affected by schizophrenia but who have a 16p13.11 microduplication. It has therefore been proposed that duplications of 16p13.11 increase the risk of schizophrenia (ISC 2008; Kirov 2009; Ikeda 2010).

While it would therefore be recommended that families mention any concerns regarding mental health to a health professional, mental health problems such as schizophrenia occur as the result of multiple physical, genetic, psychological and environmental risk factors, rather than just one single genetic difference such as 16p13.11 microduplication. Carriers may therefore never develop any of these mental health conditions.

“ He is in his own little world and finds it hard to play and communicate with others. He is very sensitive to noise ” – 5 years

Adults with 16p13.11 microduplications

At least 20 adults have been described in medical literature and *Unique* has two adult members with the microduplication. Some have no developmental delay or health issues and only discovered they carried the microduplication after their child was diagnosed.

One mother had mild learning difficulties and poor temper control although her sister who also carried the microduplication appeared to be unaffected (Hannes 2009; Unique).

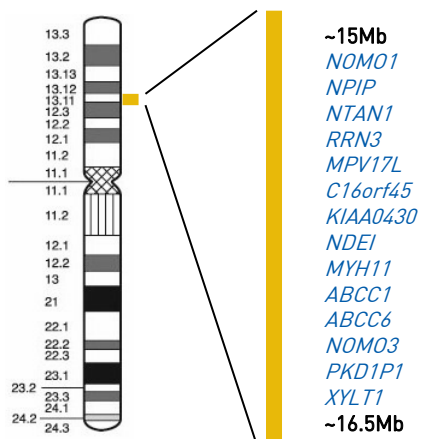
One study of individuals affected by an adult-onset cardiovascular disorder known as thoracic aortic aneurysm dissection (TAAD) identified 13 people who also had a 16p13.11 microduplication (Kuang 2011). A subsequent study noted a number of other carriers affected by TAAD (Allach El Khattabi 2018).

The aorta is the largest artery in the body and is the blood vessel that carries oxygen-rich blood away from the heart to all parts of the body. The section of the aorta that runs through the chest is called the thoracic aorta, and as the aorta moves down through the abdomen it is called the abdominal aorta. A thoracic aortic aneurysm is when an artery wall in the aorta weakens and the wall expands or bulges abnormally as blood is pumped through it. Aortic dissection occurs when the layers of the aorta tear and separate from each other. The age of onset of TAAD was between 42 and 67 years. The MYH11 gene is located at 16p13.11 and has been suggested as an important candidate gene for predisposition to TAAD (Kuang 2011; Allach El Khattabi 2018).

It is important to remember that the link between a 16p13.11 microduplication and TAAD is based on a very small number of cases and the likelihood of this problem occurring is unlikely to be very high. It is recommended that adult carriers of a 16p13.11 microduplication have a scan to look at their aorta as a precaution, while taking steps to keep their blood pressure under control is recommended to reduce the likelihood of any problems occurring (Allach El Khattabi 2018).

Ongoing research involving 16p13.11

A 16p13.11 microduplication is tiny, so it can only be found using molecular techniques such as array CGH or targeted cytogenetic testing using FISH. These techniques show whether there are extra copies of particular genes. The features of a 16p13.11 microduplication are likely to be a result of the extra copy of different genes found in this region. The typical 16p13.11 microduplication is between 1.1Mb and 1.65Mb and encompasses around 15 genes.



The genes *NDE1* and *NTAN1* are both expressed in the brain and have been proposed as candidates for the ASD, ADHD, learning difficulties and /or schizophrenia diagnoses (Williams 2010; Ingason 2011; Allach El Khattabi 2018).

MYH11 is the most likely candidate for the predisposition to TAAD, although it is thought that other risk factors (other genes and/or environmental factors) are required for TAAD to develop (Kuang 2011; Allach El Khattabi 2018).

A role for MicroRNAs (miRNAs) located in the region, which play an important role in regulating gene expression, has also been suggested as a possible explanation for why there is so much variability in the degree to which people with a 16p13.11 microduplication are affected (Allach El Khattabi 2018).

It is important to remember that while identifying the gene(s) responsible for certain features of a 16p13.11 microduplication is interesting and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is duplicated 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 microduplication occurred. The vast majority of children are believed to inherit the 16p13.11 microduplication from a parent (Allach El Khattabi 2018; Unique). However, in some cases the microduplication occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 16p13.11 microduplications 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 microduplication is inherited or *de novo*, as a parent there is nothing you did to cause the 16p13.11 microduplication 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 microduplication – 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 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 16p13.11 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 16p13.11 microduplication has been inherited from a parent, the possibility of having another child – either a girl or a boy – with the 16p13.11 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.

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Inform Network Support



Understanding Chromosome & Gene Disorders

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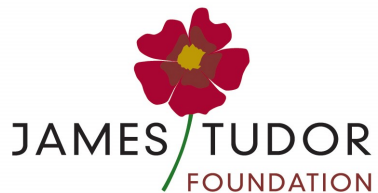
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This guide was developed by Unique with generous support from the James Tudor Foundation



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 Sandesh Nagamani, Texas Children's Hospital, USA; Dr Heather Mefford, University of Washington, USA; and by Professor Maj Hultén, University of Warwick, UK

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