16p13.11 microduplications
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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.

The features of people with a 16p13.11 microduplication vary widely, even among members of the same family. People can have developmental delay, learning difficulties and behavioural problems. Many people with the microduplication have no apparent physical, learning or behaviour difficulties.

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 p. The bottom bit is called q. 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.

References:


Notes
The laboratory that finds the 16p13.11 microduplication will send a report that is likely to include the following:

**Array CGH report**

The laboratory that finds the 16p13.11 microduplication will send a report that is likely to include:

- **arr cgh 16p13.11 [14910205-16305736]x3** (hg19)
  - **16p13.11**
    - The chromosome involved is 16, band p13.11
    - The base pair numbers refer to the 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.
    - The chromosome involved is 16, band p13.11
    - 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 has two adult members (see page 7). However, 13 adults with a 16p13.11 microduplication have developed an adult-onset cardiovascular disorder (Kuang 2011; 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 do not appear to be common. 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 picky eater; one is still fussy at aged five years. He regularly sees a dietician.

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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. 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 researchers involved in this study suggest that the 16p13.11 microduplication increases the risk of developing TAAD [Kuang 2011].

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 NDEI 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]. 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].

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

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

Often gross motor skills are unaffected in those with a 16p13.11 microduplication, although three children in medical literature and three 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 hypertonia (increased musclotone or stiffness) [Hannes 2009; Nagamani 2010; 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. A girl in medical literature has limited use of language, poor vocabulary and repetitive speech; an 18-month-old has delayed speech with prominent echolalia [involuntary repetition of words or phrases]. Eight further children are described as having delayed speech. A 7-month-old baby has vocal cord palsy (Ullmann 2007; Hannes 2009; Nagamani 2010; Unique).

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. Two people have mild learning problems; four have a moderate learning difficulty; one has a severe learning difficulty; and two have a profound learning disability. Ten further individuals are described as having learning problems. Many children with a learning difficulty benefit from attending a special educational school [Hannes 2009; Nagamani 2010; Ramalingam 2011; 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 four 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 7] (Hannes 2009; Nagamani 2010; Kuang 2011; Unique).

One finding is hypermobile joints, which affect one child at Unique and four people described in the medical literature [Nagamani 2010; Unique]. On investigation, three people with the microduplication 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 [Hannes 2009; Nagamani 2010; Ramalingam 2011; Unique].

Children and adults with the microduplication may have hands and/or feet that are not perfectly formed. Two 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 acrachnodactyly ('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].

One person had macrocephaly [a large 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].

One baby had an umbilical hernia [a soft skin-covered bulge at the belly button] [Hannes 2009].

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. Two people in the medical literature and one at Unique have seizures [Hannes 2009; Nagamani 2010; Ramalingam 2011; Unique].

Vision

Several people with the microduplication have eye problems. 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] [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 14 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; Unique]. Thirty-three out of 79 people in medical literature 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 2009].

“ 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.