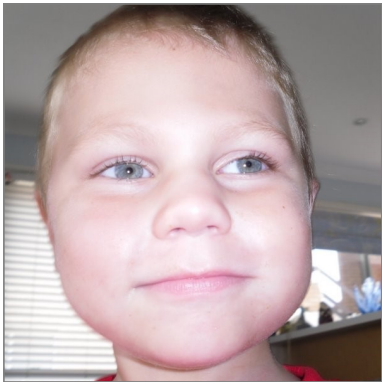
Understanding chromosome disorders

Unique

16p13.11 microduplications



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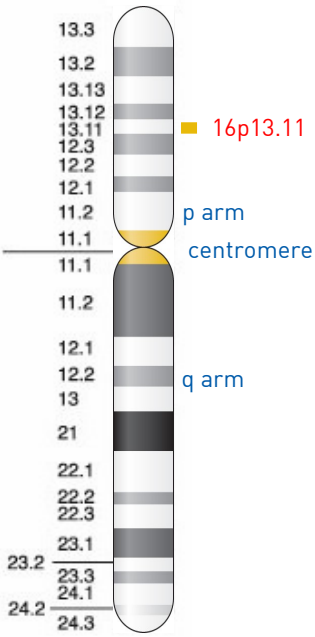
What is a 16p13.11 microduplication and what causes it?

A 16p13.11 microduplication is an example of a rare structural chromosome disorder. Structural disorders occur when there is a break in a chromosome and include duplications, deletions, inversions, translocations and ring chromosomes.

Most structural disorders, including duplications, result in so-called copy number variation (CNV), which simply means that there is too much or too little of the part of the affected chromosome compared to normal. In the case of a 16p13.11 microduplication this means there is an extra copy of a tiny piece of chromosome 16 near the middle of the chromosome at a place called p13.11. The extra piece is usually so tiny it is often called a microduplication.

Chromosome 16 is one of the 23 pairs of chromosome in the cells of the body that carry genetic material. 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 top part of the chromosome down to the indent on the diagram is the short arm of chromosome 16 and is known as the "p" arm. The bottom bit is the longer "q" arm.



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.

When a particular chromosome disorder gives a similar, consistent pattern of problems in affected individuals it is called a syndrome. Recently a new 16p13.11 microduplication syndrome has been described. The features associated with 16p13.11 microduplication syndrome are believed to be caused by the presence of three copies of the genes in this region instead of the normal two copies.

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

Why did this happen?

Recent research has shown that 16p13.11 is a so-called "hotspot" for structural rearrangements. While some cases of 16p13.11 microduplications are *de novo* (dn),

meaning new, and are caused when both parents have "normal" chromosomes and there is 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, it is believed that the vast majority of children inherit the microduplication from their often mildly or seemingly unaffected parents. Although there is some evidence to suggest that in *de novo* cases there is a bias towards more boys than girls being affected, others have not found such a bias. More research is therefore required to confirm this.

You may read or hear the terms "incomplete penetrance" and "variable expressivity" in relation to 16p13.11 microduplications (see blue box). 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.

Can it happen again?

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.

The possibility of having another pregnancy with a 16p13.11 microduplication depends on the parents' chromosomes. If both parents have normal chromosomes on a blood test, the possibility of having another child with a 16p13.11 microduplication is almost certainly no higher than anyone else's (less than a one percent risk). However, there is a very small possibility that the duplication occurred during the formation of the

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.

egg or sperm cells in a parent (germline mosaicism). When this occurs there is a tiny chance that parents with apparently normal chromosomes could have another affected pregnancy.

In families where the microduplication has been inherited from a parent the possibility of having another child with the microduplication rises to about 50 percent in each pregnancy. Your genetics centre should be able to offer counselling before you have another pregnancy. Prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

What are the main features of 16p13.11 microduplication syndrome?

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; however, what is clear is that the affect on a carrier of a 16p13.11 microduplication can range from "silent", meaning there are no obvious unusual features, to being much more obvious and severe, even within the same family.

The most common features are:

- Some degree of learning difficulty. Children may need support with learning. While some children don't have any learning difficulty, 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. The amount of support needed by each child will therefore vary, although most benefit from supportive services for special needs. Several children have dyslexia, for which they require extra support.

- A developmental delay. While gross motor skills including rolling over, sitting, crawling and walking are often unaffected, one of the first signs may be a delay in reaching these milestones. A number of children suffer from poor coordination or "clumsiness". Mobility is often affected by abnormal muscle tone and some children are described as having high tone (hypertonia) or more commonly low tone (hypotonia). Babies with low muscle tone at birth feel floppy to hold and have obvious head lag. Low muscle tone generally improves with maturity but may still be present in adults. Regular physiotherapy helps, and the use of orthotics such as support boots may also help increase mobility.

> "He walks, runs and climbs, but can be clumsy" – *5 years*

- Behaviour and emotional disorders In general children with a 16p13.11 microduplication are happy and affectionate. Alongside this, one of the most common features of 16p13.11 microduplications are behavioural and emotional disorders. The most common of these, certainly among members of *Unique*, are an autism spectrum

disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD). A diagnosis can be extremely helpful in accessing services and tailoring educational and behavioural therapy to meet the specific needs of a child with autism or ADHD.

ASDs include autism and Asperger's disorder and are associated with impaired social skills, problems with communicating, and a need to carry out repetitive and restrictive behaviours.

ADHD is characterised by restlessness, a short attention span and impulsivity. There is also an association between ADHD and problems with sleeping and excessive weight gain.

It has also been proposed that duplications of 16p13.11 increase the risk of 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.

A number of other behavioural concerns have been mentioned in the medical literature and among *Unique* families including: depression; a vulnerability to frustration, which is common among children with a communication difficulty; extreme sensitivity to touch and a small minority who succumb to temper tantrums, aggression and anxiety-related 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*

Behavioural and emotional disorders show a male bias in the general population, meaning boys and men are more likely to be affected than girls and women. There is evidence to suggest that this male bias is also seen for cases of autism and schizophrenia associated with 16p13.11 microduplications.

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.

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 although one study has called into question a role for *NDE1*.

- Speech delay in some children. For children with a 16p13.11 microduplication there is often a delay in acquiring speech and language skills. Many *Unique* children experienced a delay and several are described as non-verbal. There are also a few cases where children have experienced regression in their level of speech. There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. Where a speech delay is suspected, parental concerns should be acted on early to ensure home or school-based therapy is provided. Speech therapy can prove extremely effective.

Other less common features include:

> “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*

- Problems with feeding - Feeding difficulties do not appear to be a consistent feature but there are a number of cases of babies and children who were very fussy eaters. Several babies experienced acid reflux. Where feeding difficulties were linked to a ‘failure to thrive’, where there is poor weight gain and physical growth failure over a period of time, a few children have needed a nasogastric tube (where a tube is inserted through the nose that delivers nutrition directly to the stomach) for several weeks or months. Other children benefit from seeing a dietician. There are several cases of chronic constipation that required treatment, including the use of laxatives. Several children are described as having food intolerances and allergies.

- Heart conditions/defects - In a few cases a heart defect has been identified in babies with a 16p13.11 microduplication. These include one baby with a 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 expected to resolve by itself. One baby with 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). A baby boy had hypoplastic left heart syndrome where the left lower pumping chamber (left ventricle) of the heart does not develop properly meaning it is much smaller than usual affecting blood flow through the heart.

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, leading researchers involved in the study to suggest that the 16p13.11 microduplication increases the risk of developing TAAD. A subsequent study noted a number of other carriers affected by TAAD.

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 MYH11 gene is located at 16p13.11 and has been suggested as an important candidate gene for predisposition to TAAD.

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.

- Seizures - Seizures (epilepsy) appear to affect some of those with a 16p13.11 microduplication. *Unique* has six members who have experienced seizures ranging from an isolated incident to more serious, ongoing incidents that required treatment with anti-epileptic medicine. In one case, a boy who experienced numerous seizures throughout childhood was treated with several anti-epileptic drugs before a successful treatment was found that left him seizure-free.

- Skeletal abnormalities - Several children suffer from scoliosis, where there is a sideways spinal curvature. These cases were generally described as mild. Underlying the curve may be abnormalities of muscle tone and in some cases the bones of the spine (vertebrae) may be fused together or incorrectly formed. The curvature can be treated with physiotherapy and exercises, or a support brace may be needed. If the curve becomes marked it is possible to straighten the spine using rods

Hyperflexible joints – Seven children who are members of *Unique* and a number of children in the medical literature have extremely loose, hypermobile joints. This means they can move their limbs into positions others find impossible. While this may cause no problems, hypermobility is sometimes associated with pain and stiffness in the joints and muscles, joints that dislocate (come out of position) easily and injuries including sprains. *Unique* members report that their children with hypermobile joints are prone to falling over easily when tired and suffer from fatigue.

Abnormalities of the skull - 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).

Other abnormalities - One baby was born with a sunken chest (pectus excavatum). Another 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).

- Problems with the eyes and eyesight - Several children have eye problems. Two children registered with *Unique* are long-sighted, which in one case is described as severe. One child has astigmatism (the cornea - the clear cover over the iris and pupil - is abnormally curved, which makes objects appear blurred) and several children have a squint (where the eye turns inwards, outwards, upwards or downwards), which in one case improved following surgery on the eye muscles. One child had nystagmus, where there is a continual uncontrolled movement of the eyes.

- Abnormalities of the brain, kidneys, urinary or genital systems – Information is limited, but several cases of abnormalities of the brain associated with 16p13.11 microduplications have been detected by MRI. These incidents are sporadic and there doesn't appear to be a consistent feature. These abnormalities include several cases of myelination delay, a small corpus callosum (the bundle of nerve

fibres that links the left and right hemispheres of the brain), a cyst (fluid-filled sac) on the brain and one case of more complex abnormalities.

Two babies had an inguinal hernia, where fatty tissue or a part of the bowel, such as the intestine, pokes through into the groin at the top of the inner thigh. In one case this was in conjunction with an umbilical hernia where the weakness that leads to the protrusion is near the belly button.

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

One boy had a horseshoe-shaped kidney where the two kidneys are fused together at the lower end. There are at least four other cases in the medical literature of individuals with a 16p13.11 microduplication where there have been disorders of the urogenitary system, including a person who had only one kidney (unilateral renal agenesis) and two brothers with chronic renal disease; however, it was not possible to say for definite that these were caused by the duplication alone.

Two children registered with *Unique* have a cleft palate where there is a split or gap in the upper lip, the roof of the mouth or occasionally both. A cleft occurs if, early in pregnancy, the separate parts of the developing baby's face don't join together properly. This happens in ~1 in 700 births and is the most common congenital problem relating to the face. Surgery is the most common treatment. Depending on the type of cleft, children may also require speech and language therapy and orthodontic treatment for their teeth.

Several children are described has having a tremor. Tremors occur when there is an uncontrollable shake or tremble of part of the body. Although there is no cure for a tremor, medication can help in many cases.

- Unusually formed hands or feet - Several children and adults have unusually shaped hands and feet. These include several cases of polydactyly (one or more extra digits); one child with large, puffy hands with small nails; another child with deep creases in the palms and an incurving fifth finger (clinodactyly); and a futher 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).

Adults with 16p13.11 microduplications

An ever-increasing number of adults with 16p13.11 microduplications have been reported in the medical literature and *Unique* has at least 12 adult members with the microduplication. Many 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. A number of adult members of *Unique* live an independent life having successfully completed their schooling and gone on to work in a variety of occupations, including nursing and management.

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Notes

Inform Network Support

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The information in this leaflet is drawn partly from published medical literature. This quick read guide was reviewed by Dr Francisco Barros , Fundacion Publica Galega de Medicina Xenomica Edif. Consultas planta -2, Hospital Clinico Universitario 15,707 Santiago de Compostela, Spain.
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