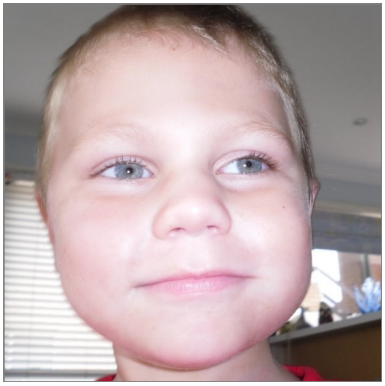
Understanding Chromosome & Gene Disorders

16p13.11 microduplications



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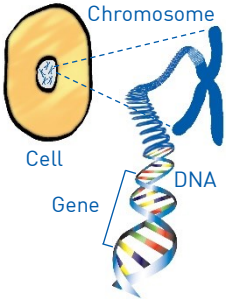
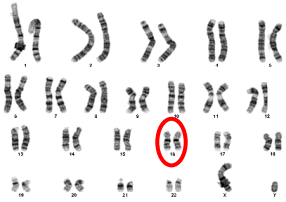
What is a 16p13.11 microduplication?

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

Background on chromosomes

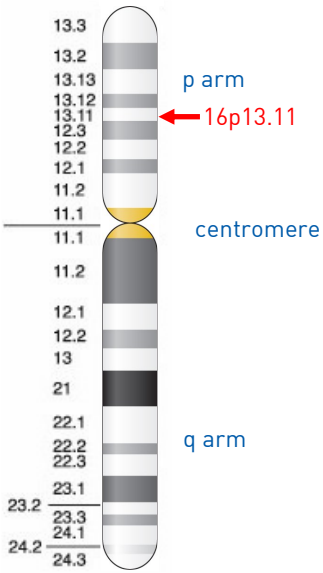
Our bodies are made up of trillions of cells. Most of these cells contain a set of around 20,000 genes that carry the set of instructions that tell the body how to develop, grow and function. Genes are carried in structures called chromosomes, which consist of a complex chemical called DNA. Chromosomes (and hence genes) usually come in pairs, one inherited from the mother and one from the father. A typical cell in the body has 46 chromosomes that are numbered 1 to 22, approximately from largest to smallest, apart from the sex chromosomes (usually two Xs for a girl and an X and a Y for a boy).





A male karyotype (XY sex chromosomes) with 46 chromosomes in total.

Chromosome 16 pair circled in red.



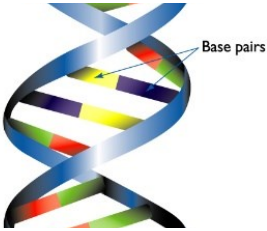
Looking at chromosome 16

Chromosomes can't be seen with the naked eye, but they can be stained so that each has a distinctive pattern of light and dark bands when viewed at about 1000 times life size under a light microscope. You can see these bands in the diagram opposite.

Each chromosome has a short (p) arm and a long (q) arm. The bands are numbered outwards starting from the point where the short and long arms meet (the centromere) (marked in yellow). A low number such as q11 is close to the centromere; this part of the arm that is fairly close to the centromere is called the proximal part. A higher number such as q23 is closer to the end of the chromosome, in the part referred to as distal. The term cen is used to indicate a location that is very close to the centromere, while ter (for terminal) indicates a location that is very close to the end of the p or q arm.

DNA has a ladder-like structure, with the ladder's rungs formed from chemicals known as base pairs. There are millions of base pairs in a chromosome so the numbers are usually shortened. One million base pairs is called a megabase, and written as 1Mb.

The size of the tiny extra bit of 16p13.11 is measured in base pairs. 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 in chromosome 16. Most people have a 16p13.11 microduplication that is between 1.1 Mb and 1.65Mb in size.



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 produce a report with the result 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

Are all people with a 16p13.11 microduplication affected in the same way?

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 effect on a carrier of a 16p13.11 microduplication can range from "silent", meaning there are no obvious unusual features, to an individual with significant learning needs and/or medical concerns.

You may read or hear the terms "incomplete penetrance" and "variable expressivity" in relation to 16p13.11 microduplications (see blue box on pg 4). 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 concerns, but many people with the microduplication have no apparent physical, learning or behavioural concerns.

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. It is likely to be a combination of other genetic variants across the genome as well as different environmental factors.

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.

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 issues and only discovered they carried the microduplication after their child was diagnosed.

The effect on development, health and behaviour of some genetic conditions ranges from being barely perceptible to being associated with significant learning needs and/or medical concerns. 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 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. An ever-increasing number of adults with

16p13.11 microduplications have been reported in the medical literature and *Unique* has at least 50 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. 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. Some adults with a 16p13.11 microduplication have developed adult-onset conditions, including a cardiovascular disorder called TAAD (Kuang 2011; Allach El Khattabi 2018; Hamad & Sherlaw-Sturrock 2023) (see page 8).

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 and one child was found to have inherited a 16p13.11 microduplication from both parents (Allach El Khattabi 2018; Hamad & Sherlaw-Sturrock 2023; Unique). However, in some cases the microduplication occurs when both parents have ordinary 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?

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 low. It is possible that the duplication occurred during the formation of the egg or sperm cells in a parent, meaning there could be more than one egg or sperm carrying the duplication (called germline mosaicism). When this occurs there is a tiny chance that parents with apparently unaffected 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 (1 in 2) 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.

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. Occasionally, unusual findings on ultrasound scans or reduced growth in the womb (intrauterine growth retardation (IUGR) were observed. One study of 206 pregnancies found that almost 1 in 10 babies were born prematurely (Hamad & Sherlaw-Sturrock 2023).

What are the main features of 16p13.11 microduplications?

The features associated with 16p13.11 microduplications are believed to be caused by the presence of three copies of the genes in this region instead of the normal two copies. Features vary, even between members of the same family, and they do not affect everyone. In any individual, when present, a feature can be more or less obvious.

Some degree of learning (intellectual) disability/learning difficulties

Children may need support with learning. While some children don't have any learning (intellectual) disability and/or learning difficulties, 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 mild to moderate learning disability. 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 (Hannes 2009; Nagamani 2010; Ramalingam 2011; Allach El Khattabi 2018; Arlsan 2022; Hamad & Sherlaw-Sturrock 2023; Unique).

Developmental delay

While gross motor skills, including rolling over, sitting, crawling and walking can be unaffected, one of the first signs may be a delay in reaching these milestones. A number of children suffer from poor coordination or "clumsiness". In a few children, mobility is affected by abnormal muscle tone, some children are described as having low tone (hypotonia) or less commonly increased tone (hypertonia). 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 (Hannes 2009; Nagamani 2010; Allach El Khattabi 2018; Hamad & Sherlaw-Sturrock 2023; Unique).

A delay in the development of hand use and hand-eye coordination (fine motor skills) may be observed and children may take longer to reach for and grab toys and hold a bottle or cup. Some children have occupational therapy to try to help overcome these difficulties (Unique).

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

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. 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 (Ullmann 2007; Hannes 2009; Nagamani 2010; Allach El Khattabi 2018; Arlsan 2022; Hamad & Sherlaw-Sturrock 2023; Unique).

"Challenging" behaviours & social, emotional & anxiety disorders

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.

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). ASDs are associated with impaired social skills, difficulties 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. A diagnosis can be extremely helpful in accessing services and tailoring educational and behavioural therapy to meet the specific needs of a child with ASD or ADHD.

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: 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; 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.

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 concerns 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 (Ullmann 2007; Hannes 2009; Nagamani 2010; Williams 2010; Ramalingam 2011; Allach El Khattabi 2018; Arslan 2022; Hamad & Sherlaw-Sturrock 2023; Unique).

"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*

Other less common features include:

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', meaning 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.

"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*

Heart conditions

Many babies with a 16p13.11 microduplication are born completely healthy. Others are born with a health condition present from birth, which can be quite minor or more serious.

In a few babies the heart is affected, with conditions including ventricular septal defect (VSD), where there is one or more holes in the wall between the two pumping chambers of the heart (ventricles); atrial septal defect (ASD), where there is a hole between the upper chambers of the heart; pulmonary stenosis, a narrowing of the pulmonary valve; and 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.

Aortic dilation and thoracic aortic aneurysm dissection (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.

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 the researchers involved to suggest that 16p13.11 microduplication increases the risk of developing TAAD (Kuang 2011). A subsequent study noted a number of other carriers affected by TAAD (Allach El Khattabi 2018), while, more recently, researchers focussing on the possible link between 16p13.11 microduplications and cardiac anomalies identified that persistent aortic dilatation was present in 8 of 104 individuals with a 16p13.11 microduplications who had an echocardiogram performed, including in two children (Hamad & Sherlaw-Sturrock 2023). Taken together, these studies have led researchers to propose that 16p13.11 microduplication is a susceptibility factor that increases the chance of developing aortic dilation but that other additional factors are likely to be required for dilatation to develop. Several studies identified a male bias towards developing aortic dilatation, which may suggest that male carriers of 16p13.11 microduplication are at higher risk of aortic complications.

It has been suggested that routine screening from childhood onwards of those with 16p13.11 microduplication is carried out, to identify and monitor cases of aortic dilation. Adult carriers of a 16p13.11 microduplication who have not been screened should have a scan to look at their aorta as a precaution, while taking steps to keep blood pressure under control is recommended to reduce the likelihood of any problems occurring. 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.

Seizures

Seizures (epilepsy) appear to affect some of those with a 16p13.11 microduplication. *Unique* has several members who have experienced seizures, ranging from an isolated incident to more serious, ongoing incidents that required treatment with anti -epileptic medicine (Hannes 2009; Nagamani 2010; Ramalingam 2011; Allach El Khattabi 2018; Arslan 2022; Hamad & Sherlaw-Sturrock 2023; Unique).

Skeletal anomalies

Several children suffer from scoliosis, where there is a sideways spinal curvature. These cases are 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 – Several 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.

Anomalies of the skull - Several babies have been born with microcephaly (an unusually small head), one of whom had a large soft forehead. A few have macrocephaly (an unusually large head). Cases of brachycephaly (a flat head) and craniosynostosis (an unusual head shape caused by premature fusing of the skull

bones) have also been reported.

Other anomalies - A few babies have been born with a sunken chest (pectus excavatum) or a tethered cord (the spinal cord is incorrectly attached to the tissues around the spine, meaning the spinal cord can't move freely, which limits movement). (Nagamani 2010; Hamad & Sherlaw-Sturrock 2023; Unique).

Eyes and vision

Some people with the microduplication have anomalies affecting their eyes or vision. These have included cases of long-sightedness (hyperopia), which in one case is described as severe; astigmatism (where the cornea - the clear cover over the iris and pupil - is curved unusually, which makes objects appear blurred); nystagmus (where there is a continual uncontrolled movement of the eyes); and several children have a squint (where the eye turns inwards, outwards, upwards or downwards), which we know in one case improved following surgery on the eye muscles (Hannes 2009; Arslan 2022; Hamad & Sherlaw-Sturrock 2023; Unique).

Hearing

Hearing appears to be generally unaffected, but a few children have experienced some degree of hearing loss. Some children are particularly prone to ear infections, which can be very painful and debilitating. These can sometimes lead to a build-up of sticky fluid in the middle ear (glue ear) that can cause temporary fluctuating conductive hearing loss. Glue ear usually resolves as children get older, when the ear tubes widen and become more vertical, resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, children may need a grommet (a small ventilation tube inserted into the eardrum), to reduce pressure in the middle ear. Treatment of ear infections with antibiotics may also be necessary (Hamad & Sherlaw-Sturrock 2023; Unique).

Anomalies of the brain, kidneys, urinary or genital systems

Information is limited, but several cases of anomalies 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 but have included 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 anomalies. Several *Unique* members have experienced migraines.

A few 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 had laryngomalacia (the larynx is particularly soft and limp) but it did 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 anomalies affecting 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. Your child's doctor may arrange an ultrasound scan of their kidneys to look for any anomalies.

Several children, including two children registered with *Unique,* had a cleft palate/lip (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 health condition present from birth 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.

(Hannes 2009; Nagamani 2010; Ramalingam 2011; Allach El Khattabi 2018; Arslan 2022; Hamad & Sherlaw-Sturrock 2023; Unique)

Hands & feet

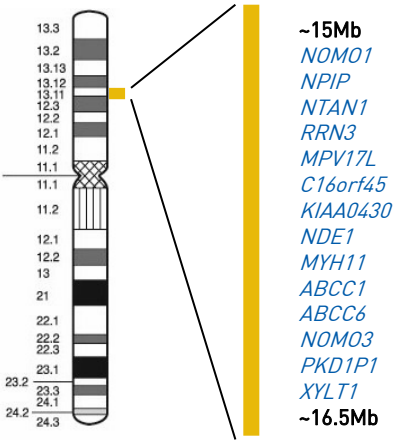
Some children and adults have unusually-shaped hands and feet. These include cases of polydactyly (one or more extra digits); flat feet (pes planus); small nails; deep creases in the palms; an incurving fifth finger (clinodactyly); arachnodactyly ('spider fingers', where the fingers are unusually long and slender); and large big toes with webbing between two of the toes (Hannes 2009; Nagamani 2010; Arslan 2022; Hamad & Sherlaw-Sturrock 2023; Unique).

Ongoing research involving 16p13.11

A 16p13.11 microduplication is tiny, so it can only be found using molecular techniques such as array CGH. These techniques can 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 13 OMIM genes. The most commonly shared duplicated genes are *ABCC1*, *ABCC6*, *NDE1* and *MYH11*.



Possible role of 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 that may be associated with a 16p13.11 microduplication (Williams 2010; Ingason 2011; Allach El Khattabi 2018; Arslan 2022; Hamad & Sherlaw-Sturrock 2023).

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; Arslan 2022; Hamad & Sherlaw-Sturrock 2023).

It has been suggested that disruption of the *ABCC1* gene may be related to the hearing loss experienced by a small number of individuals (Hamad & Sherlaw-Sturrock 2023)

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 (Fujitani 2017; Allach El Khattabi 2018; Arslan 2022; Hamad & Sherlaw-Sturrock 2023).

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 potentially 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.

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.

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Notes

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This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change.
The original guide was compiled by Unique in 2012 and reviewed by Dr Sandesh Nagamani, Texas Children's Hospial, USA; Dr Heather Mefford, University of Washington, USA; and Professor Maj Hultén, University of Warwick, UK. Further information was added in 2017 and reviewed by Dr Francisco Barros, Fundacion Publica Galega de Medicina Xenomica Edif. Consultas planta -2, Hospital Clinico Universitario 15,707 Santiago de Compostela, Spain. An additional update based on medical literature was carried out in 2024 and and reviewed by Dr Hannah Titheradge, Consultant in Clinical Genetics at Birmingham Women's and Children's NHS Foundation Trust, UK.

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Version 1.1 (SW)
Version 1.2 (CA/SW)
Version 2 (CA)

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