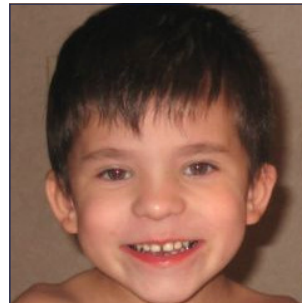
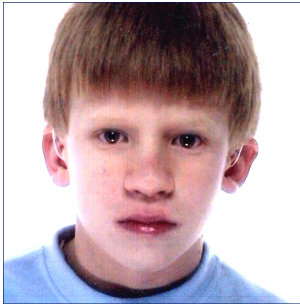


*Unique*TM

17q21.31 microdeletions



17q21.31 microdeletions

A 17q21.31 microdeletion is a very rare genetic condition in which a tiny piece is missing from one of the 46 chromosomes. The tiny missing bit increases the possibility of developmental and speech delay and learning difficulties. But there is quite a lot of individual variation.

Chromosomes are the structures in the nucleus of the body's cells that carry genetic information, telling the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. Each chromosome has a short (p) arm and a long (q) arm.

Looking at chromosome 17

You can't see chromosomes with a naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. Even if you magnify the chromosomes as much as possible, to about 850 times life size, a chromosome 17 with a microdeletion at q21.31 looks normal. The missing bit can only be found using molecular techniques such as FISH or microarrays.

Technologies such as FISH (fluorescence in situ hybridisation, a technique that reveals the chromosomes in fluorescent colour), MLPA (multiplex ligation-dependent probe amplification) or microarrays - a tool for analysing thousands of different DNA sequences at the same time - can focus in on particular segments of chromosomes and show whether specific genes are present or not.

The missing piece in 17q21.31 microdeletions includes four or five known genes and part of a sixth. The missing genes include *MAPT*, which plays a role in the functioning of the brain and the central nervous system. We do not yet know whether it is losing just a single gene such as *MAPT* or losing more of these genes that creates the difficulties that people with the 17q21.31 microdeletion syndrome face.

Sources and key references

The information in this leaflet is drawn from six key publications about the 17q21.31 microdeletion syndrome. The leaflet also draws on *Unique's* database of members with a 17q21.31 microdeletion.

Phenotypic Expansion and Further Characterisation of the 17q21.31 Microdeletion Syndrome
Tan TY et al *Journal of Medical Genetics* doi: 10.1136/jmg.2008.065391

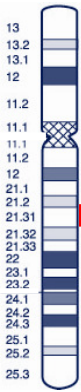
Clinical and molecular delineation of the 17q21.31 microdeletion syndrome Koolen DA et al
Journal of Medical Genetics doi: 10.1136/jmg.2008.058701

A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism Koolen D A et al *Nature Genetics* Sep. 2006 38(9) 999-1001.

Microdeletion encompassing *MAPT* at chromosome 17q21.3 is associated with developmental delay and learning disability Shaw-Smith C et al *Nature Genetics* Sep. 2006 38(9): 1032-7.

Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome Sharp A J et al *Nature Genetics* Sep. 2006 38(9): 1038-42.

A 17q21.31 microdeletion encompassing the *MAPT* gene in a mentally impaired patient Varela MC et al *Cytogenetic and Genome Research* 2006 114(1): 89-92.



Chromosome 17

The red bar marks the approximate site of the 17q21.31 region with two of the missing genes. In people with a variant chromosome 17, the order of these genes is reversed.

Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken. You will almost certainly be given a **karyotype** for your child, which is a shorthand notation for their chromosome make-up. With a microdeletion, the karyotype could read something like this

46,XY,ish del(17)(q21.31q21.31)de novo

- 46 = The total number of chromosomes in your child's cells
- XY = The two sex chromosomes, XY for males; XX for females
- .ish = The analysis was by FISH
- del = A deletion, or material is missing
- (17) = The deletion is from chromosome 17
- (q21.31q21.31) = There are two breakpoints in the chromosome, both in band 17q21.31, indicating a very small deletion.
- de novo = The parents' chromosomes have been checked and no rearrangement found at 17q21.31. The deletion is very unlikely to be inherited and has occurred for the first time in this family with this child. (See also page 7)

Microarrays

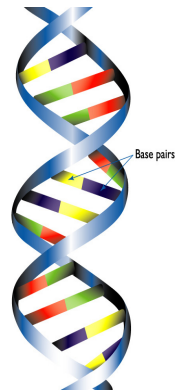
The report may read something like this

arr cgh 17q21.31 (B35:CHR17:41046729-41725780-)

Here a technology known as array-CGH (microarrays) has shown a deletion at 17q21.31. The first base pair (the chemicals in the DNA molecule that form the ends of the 'rungs' of its ladder-like structure, see diagram right) shown to be missing is number 41046729 counting from the top of the chromosome. The last base pair shown to be missing is 41725780. This means that about 679,000 base pairs are missing. This is usually expressed as 679 Kb (1 Kb = 1,000 base pairs). Everyone with the full syndrome is missing the same piece of about 500Kb but some are missing slightly more.

How common are 17q21.31 microdeletions?

17q21.31 microdeletions are rare. An estimated one baby in 16,000 has this chromosome disorder. The oldest people known to have the microdeletion are adults in their twenties but there must certainly be older people, still undiagnosed.



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

Most likely features



- Young babies are very floppy
- Young babies have difficulty feeding. Some need tube feeding for a time
- Babies hold their head up, sit, stand, move and walk late
- Children start speaking late and have difficulty making all the sounds of speech
- Children need support with learning
- Behaviour is typically friendly and pleasant
- Children and adults have recognisable facial features

■ **Young babies are very floppy**

Virtually all babies have low muscle tone (hypotonia), which makes them floppy to hold. This has many effects, including making it more difficult to suck effectively and later to speak clearly. Babies tend to have an open mouth and protruding tongue. Muscle tone improves with age but low tone can be persistent and lead to other effects, like a spinal curvature. Early intervention with physiotherapy and tone exercises is important.

■ **Young babies have difficulty feeding. Some need tube feeding**

At birth, babies may be unable to latch on and suck so weakly or feed so slowly that they cannot meet their own nutritional needs. Expressed breast milk and energy-enriched formula can be given through a naso-gastric tube passed through the nose until babies are strong and mature enough to feed direct from the breast or bottle.

“ She could not breastfeed or suck at birth. At first she took expressed breast milk from a spoon and was then bottle fed. At five, she still drinks from a baby’s bottle and is spoon fed. She gags and needs food that’s easy to chew and swallow, overfilling her mouth and choking if not regulated. Although tall, she is thin and still takes a malnutrition supplement. ”

■ **Babies hold their head up, sit, stand, move and walk late**

Control of whole body movement (gross motor skills) usually develops slowly and later than expected in children without a chromosome disorder. Some children walk before their second birthday, others not until their fourth or fifth year. Early intervention with physiotherapy, occupational therapy and other approaches such as aquatherapy and hippotherapy is important. Children may need special seating, walking aids, special footwear and a wheelchair for outdoors.

“ At 5 years, her hands are weak so she cannot use normal scissors and finds it hard to hold pencils. She uses handled bottles, special scissors, foam-padded pencils and curved easy-grip cutlery. ”

“ At 13 years, he still uses special cutlery and curly laces as he cannot tie them or undo jeans buttons. Apart from that he can generally dress himself although his clothes are often on back-to-front. He had an operation to fuse two bones in the foot when he was six and now walks independently. ”

■ **Children start speaking late and have difficulty making speech sounds**

Recognisable words may not be heard until a child is 2 to 6 years old and in some children even later. Before this, children communicate using gestures, body or facial

expression or vocal noises. Some children learn some sign language. Progress to phrases and sentences is possible for some. Children cannot make all the sounds of speech because they have difficulty organising and making facial movements. This is called oromotor dyspraxia and is believed to be a marked feature of the syndrome.

“ She has difficulty with all speech sounds and vocalises the ends of words, saying for example, ee for daddy. She communicates by signing, pushing and pulling, making gestures, vocal noises, touching, kissing, giving hugs and stroking hair. She understands more than she can convey ” - 5 years

“ He now speaks in sentences with some grammatical errors but has a lisp ” - 13 years

■ **Children need support with learning. Some children are taught in mainstream schools, others do better in a special school**

Children usually need learning support. A moderate learning disability is common, but there is individual variation. Researchers and *Unique* families suggest a developmental and learning quotient of around 50 in early childhood, implying that a child is operating at approximately the maturity of a child half their age. This means that for most children, special education will give the most supportive environment.

“ He is the strongest reader in the class at his special school. He downloads scripts from the internet and has read parts of Harry Potter books and Dr Who ” - 13 years

■ **Behaviour is typically friendly and pleasant**

Parents report that their children have good social skills: they are friendly, co-operative and like to make others laugh. Some have a tendency to develop ‘fixations’ on items like foods or favourite films. Some children also have sensory issues.

■ **Children and adults have recognisable facial features. A pear-shaped nose is common**

Children and adults may look more like others with a 17q21.31 microdeletion than like other members of their family. Some children have silvery hair which usually darkens with age. Eyes are typically blue. Children have a tubular or pear-shaped nose with a bulbous tip that becomes more obvious with age. Other common features include a high forehead; upslanting eyes, sometimes with tiny skinfolds at the inner corners; and large ears. In time, the face may lengthen and features lose their delicacy.

“ All I see is my unique son with a smile as bright as the sun and that is all that matters to me ”



Recognisable facial features in different children: at birth (left); 3 years (centre); and 10 years (right).

Growth

Some babies are born small and light for dates. In the early days, when feeding is difficult, growth may falter but it usually normalises. In time, some children catch up, but others remain short compared with other family members and a few are extremely short.

Medical concerns

Boys are commonly born with undescended testicles and these may need a small surgical operation to anchor them down. One baby in three has an anomaly of the kidneys or urinary system, including kidney reflux (where urine flushes back from the bladder towards the kidneys); duplex kidney (where all or part of the kidney and its drainage system forms in duplicate); and hydronephrosis (where the kidneys are swollen). Around a quarter are born with a hole in the heart, which may resolve naturally, with medication or be corrected by surgery; other heart problems have included a patent ductus arteriosus (a persisting fetal structure); pulmonary stenosis (where a thickened valve decreases blood flow to the lungs) and a bicuspid aortic valve (where the valve that regulates blood flow from the heart to the aorta has only two flaps instead of three), in one case with dilation of the base of the aorta.

Three babies in four were born either with very loose joints or with clicky or dislocated hips, requiring stabilisation to improve the development of the hip joint. Two children had joint dislocations, one repeatedly of the elbow, the other of the knee. Three babies had a split in the roof of the mouth and some a hollowed chest. Two babies were born with craniosynostosis (premature fusion of some of the bones of the skull) and one had her skull reshaped surgically. The same child has glycogen storage disease type O, a very rare liver disorder.

Children and adults are generally healthy. Seizures occur in more than half of the children but these usually seem to be well controlled with medication and some children outgrow them. Brain scans in more than one in three showed wide ventricles (the fluid-filled spaces in the brain) or unusual features of the corpus callosum, the broad band of nerve fibres that links the two sides of the brain. A squint (strabismus) and long sight are also common and at least one child had cataracts removed from both eyes. Hearing appears usually to be normal, but a slight hearing loss in both ears has been found in children with repeated ear infections and a mild-to-moderate mixed conductive and sensory loss has been found in another child.

Hands and feet

Unusual features of the hands and feet are common in people with a chromosome disorder. Most are cosmetic - such as having long, slender fingers - but talipes (club foot) has occurred, where the feet need repositioning to make walking easier. A teenager and an adult each developed hallux valgus where the big toe tilts towards the smaller toes and a bony 'bunion' appears on the inside of the foot. Wearing comfortable wide-fitting shoes and padding the bony lump may deal with any discomfort. If that is not sufficient, a chiropodist can advise and if necessary, the joint can be corrected. These two individuals also developed pes cavus (an excessively high arch). A further boy had flat and painful feet and had successful surgery (subtalar arthrodesis) to fuse bones in the heel. As a teenager he walks independently and wears shaped insoles to relieve pain.

Skin and teeth

Dry skin complaints occur, including eczema, keratosis pilaris (rough goose-flesh like skin) and ichthyosis (dry, thickened, scaly skin). Teeth in some children are small and widely spaced; in

others both milk and adult teeth are missing and enamel defects have been reported, making high quality dental care important.

How did this happen?

17q21.31 microdeletions usually occur out of the blue for no obvious reason. The genetic term for this is *de novo* (*dn*) and on a blood test at first sight, both parents appear to have normal chromosomes.

On closer examination, it is very likely that one parent will turn out to have a variant chromosome 17. In a variant chromosome 17, a small piece at 17q21.31 about twice as large as the microdeletion has broken out, flipped 180 degrees and been reinserted into the chromosome. This is known as an inversion. People with the variant chromosome 17 are entirely healthy and develop normally. In some parts of the world – Iceland, Europe and the Middle East – one person in five has a variant chromosome 17. These variants are so common that scientists think the variant chromosome 17 has given carriers some advantage in evolution, but no-one knows what this advantage might be.

But while people with a variant chromosome 17 are very common in some parts of the world, people with 17q21.31 microdeletions seem to be very rare. So something else unusual must have happened to cause the deletion and no one knows yet what this is.

The general theory of what has caused the microdeletion involves a mistake that occurs when the parents' sperm or egg cells are formed. At one point in the formation, all the chromosomes including the two chromosome 17s pair up and swap segments. To pair up precisely, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. However, throughout the chromosomes there are many DNA sequences that are so similar that it is thought that mispairing can occur, especially in people with the variant chromosome 17. The 17q21.31 region contains a number of large and complex but similar DNA sequences and it is quite likely that when they run in the opposite direction to normal, as they do on the variant chromosome 17, they can cause a mismatch. Although no-one has ever seen this happen, it is believed that when the exchange of genetic material, known as 'crossing over', occurs after mismatching, it is unequal, excising a length of the chromosome.

What is certain is that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary, workplace or lifestyle factors are known to cause 17q21.31 microdeletions. There is nothing that either parent did before or during pregnancy that caused the microdeletion.

Could this happen again?

The risk of having another affected child is almost certainly very low indeed. *Unique* has just one member family (out of 30) with two children with the 17q21.31 microdeletion, and they are believed to be the first to be identified. However, your genetics centre should be able to offer counselling before you have another pregnancy and if you already have a child with the microdeletion, prenatal diagnosis will be possible if that is what you choose.

Will my child have similarly affected children?

Adults with this deletion may form close relationships and want to have children. In each pregnancy, someone with the deletion is likely to have a 50 per cent risk of passing it on and a 50 per cent chance of having a child without it. A baby who inherits the deletion is likely to be affected but we haven't known about the syndrome for long enough to be certain of the range of possible effects or how obvious they would be.



Support and Information

**Rare Chromosome Disorder
Support Group,
PO Box 2189,
Caterham,
Surrey CR3 5GN,
UK**

Tel/Fax: +44(0)1883 330766

info@rarechromo.org

www.rarechromo.org

Email support group: **familyofchromosome17disorders@yahoo.com**

Website: **www.chromol7.com**

Support group in Europe

www.chromol7europe.webs.com

Unique lists other organisations' message boards and websites to help families looking for information. This does not imply that we endorse the content or have a responsibility for it.

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 and has been reviewed by Dr Serena Nik-Zainal, Clinical Genetics,

Addenbrooke's Hospital, Cambridge and by *Unique's* chief medical advisor, Professor Maj Hultén, Professor of Medical Genetics, University of Warwick, 2007.

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