Support and Information

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On Facebook there are various groups:
Koolen de Vries Syndrome - 17q21.31 Microdeletion Syndrome Support Group
or
Chromosome 17 Disorders
or
Chromo 17 Europe - Koolen-De Vries Syndrome/17th Chromosome conditions
Also:
www.17q21.com or www.17q21.net Website for the 17q21.31 research project led by Dr David Koolen
www.chromo17europe.webs.com
http://health.groups.yahoo.com/group/familyofchromosome17disorders
Yahoo group for any chromosome 17 syndrome started in US by mother of a child with a 17q21.31 microdeletion

Unique lists other organisations’ message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.

This 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. The information is believed to be the best available at the time of publication. It was compiled by Unique and reviewed by Dr David Koolen, Department of Human Genetics, Nijmegen, Netherlands.

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Previously known as 17q21.31 microdeletion syndrome

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Koolen-De Vries syndrome

Koolen-De Vries syndrome [you pronounce Vries as ‘freeze’] is a rare genetic condition caused by the loss of part of chromosome 17 (17q21.31 microdeletion) including the gene called KANSL1, or by a change in the KANSL1 gene. These genetic changes cause developmental delay, learning difficulties and possibly some health concerns as well. But individuals vary, both in the degree to which they are affected and in other effects.

The KANSL1 gene is found on the long arm of chromosome 17. 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. The 23rd pair are the sex chromosomes: XX for females and XY for males. Each chromosome has a short (p) arm and a long (q) arm. KANSL1 is found at a place on the long arm of chromosome 17 called 17q21.31. Until 2012 Koolen-De Vries syndrome was called 17q21.31 microdeletion syndrome.

Chromosome 17q and genetic testing

You can’t see chromosomes with the 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. Each band contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the ‘rungs’ of its ladder-like structure and make up genes.

A technique known as microarray comparative genomic hybridization (array CGH) can show the loss of tiny amounts of DNA from a chromosome or a change in a particular gene. Using this technique, laboratory geneticists can see whether the 17q21.31 region including the KANSL1 gene is missing. Another technique known as FISH can also be used to show that DNA is missing, but these techniques do not show tiny changes in the KANSL1 gene. A technique known as DNA sequence analysis is used to identify small changes in the KANSL1 gene at the base pair level.

The KANSL1 gene is found between base pair 44,107,282-44,302,733 on chromosome 17. These numbers are from Human Genome build 19. The human genome is updated as more information is found; each new version is called a ‘build’. In each build, the base pair numbers may change slightly. In February 2013, hg19 is the newest build. Confusingly, hg19 is also sometimes called Genome Reference Consortium human genome 37, GRCh37. In the previous build hg18, KANSL1 was found between base pairs 41,463,129–41,658,510.

Sources

The information in this guide is drawn from information on the www.17q21 website; from articles in the medical literature; and from Unique’s database (Varela 2006; El-Chehadeh-Djebbar 2011; Wright 2011; Terrone 2012; Unique). With the first-named author and publication date you can look for abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). When this updated guide was compiled, Unique had 51 members with Koolen-De Vries syndrome.
Genes

It has been shown that a change in *KANSL1* is sufficient to cause Koolen-De Vries syndrome. The 17q21.31 region that is missing in most individuals with Koolen-De Vries syndrome contains at least four other genes, *CRHR1*, *SPPL2C*, *MAPT*, and *STH*. The role of these genes in the syndrome is not known. *KANSL1* is expressed in all human tissues, including the central nervous system. The KANSL1 protein acts together with other proteins in a complex known as the NSL complex, which is highly conserved in evolution. This means that the protein complex was already present in other, less complex organisms such as fruit fly (Drosophila), indicating that it has important functions. The NSL complex contains, among other proteins, the acetyltransferase KAT8, which influences gene expression by modifying the proteins that package and order the DNA (histones). In other words, *KANSL1* and the NSL complex are important for controlling the function of the genetic DNA code. The complex allows (or doesn’t allow) the information in particular pieces of DNA to be turned into action.

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Genetic test results

Koolen-De Vries syndrome is diagnosed on the basis of a genetic test. A microarray [array CGH] test result may look something like this:

46,XX.arr 17q21.31(43,568,123-44,236,497)x1 [hg19]

- **46**: The number of chromosomes in each cell
- **XX**: The two sex chromosomes: XX for females, XY for males
- **arr**: The genetic test was by array CGH
- **17q21.31**: The missing DNA is in the region known as 17q21.31
- **(43,568,123-44,236,497)x1**: DNA is missing between base pairs 43,568,123 and 44,236,497. Take the first long number from the second, and you get 668,374. This is the number of base pairs missing, approximately 0.67Mb. 1Mb is one million base pairs.
- **[hg19]**: The base pair numbers refer to the human genome build 19.

A FISH test result may look something like this:

46,XY.ish del (17)(q21.31q21.31)(RP11-656014 and RP5-843B9)dn

- **46**: The number of chromosomes in each cell
- **XY**: The two sex chromosomes: XY for males, XX for females
- **.ish**: The test used fluorescence in situ hybridisation to check the number of copies of particular sections of the chromosome
- **del**: Some material was found to be missing
- **(17)(q21.31q21.31)**: Both the start and end points of the missing material were in the chromosome band called 17q21.31
- **(RP11-656014 and RP5-843B9)**: The codes for the particular sections of chromosome 17 that the FISH test was looking for
- **dn**: Short for Latin *de novo*, a genetic change that has not been inherited but has arisen ‘anew’.

DNA sequence analysis may look something like this:

A heterozygote pathogenic mutation in the *KANSL1* gene (NM_1193466.1): c.985_986del (p.(Leu329fs)).
What should happen after diagnosis?

After someone is diagnosed with Koolen-De Vries syndrome, it’s recommended that they have a range of further tests, so long as they are relevant. These tests are designed to show whether or not they are affected by various features of the syndrome and, if so, how mildly or severely.

The tests include: a developmental evaluation; feeding assessment; speech and language testing; hearing test; kidney ultrasound; heart evaluation. If a child’s head is unusually small [microcephaly] and/or they have had seizures, a brain scan is recommended; if seizures are suspected, an EEG (electroencephalogram/ recording of the electrical activity of the brain) and referral to a neurologist. If a child is markedly short for their age, a test for growth hormone shortage is suggested.

How did this happen?

In almost all families, the person with Koolen-De Vries syndrome is the only one with loss of the 17q21.31 region or a change in KANSL1. This suggests that it is a new event and has occurred out of the blue. The genetic term for this is de novo (dn). The only way to be certain is for both parents to have a genetic test themselves.

When you examine the DNA of parents of a child with Koolen-De Vries syndrome caused by loss of the 17q21.31 region, one or both parents will be found to have a variant chromosome 17. In this chromosome 17, a small piece about one and a half times as large as the missing piece is flipped 180 degrees. 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. They are so common that scientists think the variant chromosome has given them some advantage in evolution.

But while people with a variant chromosome 17 are very common in some parts of the world, people with 17q21.31 microdeletions causing Koolen-De Vries syndrome seem to be very rare. So something else quite unusual must have happened to cause the deletion and despite plausible theories no one knows for certain what this is.

What is certain is that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary or lifestyle factors are known to cause Koolen-De Vries syndrome. There is nothing that either parent did before or during pregnancy that caused it.

Can it happen again?

It is extremely unusual to have more than one child with Koolen-De Vries syndrome, but it cannot be ruled out. Your genetics centre can counsel you on your personal risk of it happening again. In a family with one affected child, prenatal testing of any future pregnancies is technically possible, and your genetic specialist can discuss this with you.

In just two families identified so far, two children with Koolen-De Vries syndrome have been born. When this has happened, the cause has been a very small proportion of cells with loss of the 17q21.31 region in one of the parents. Geneticists call this mosaicism, and it can affect any cells in the body, or just the cells that go to make up the mother’s eggs or the father’s sperm. In both the families we know about, the mother had a small proportion of cells missing the 17q21.31 region, but it could just as well have been the father. Both mothers developed normally and had no reason to suspect mosaicism until they had two affected children.

Parents of one affected child may wish to be tested for mosaicism, and your genetics centre will tell you whether this is possible. If it is, parents will have a blood test and possibly a buccal swab as well to collect cells from inside the cheek. If these tests confirm mosaicism, parents may choose prenatal testing in any future pregnancies.
Medical concerns

Many children and adults do not have any important birth defects. However, baby boys are commonly (more than 70%) born with the testicles not yet descended into the scrotum. The testicles may come down naturally in time; if they don’t, they can be brought down and fixed in a short surgical operation.

When you examine the brain of people with Koolen-De Vries syndrome using an MRI or CT scan, in more than half of cases some kind of structural anomaly is found. Most commonly, in around 1 in 3, the fluid-filled ventricles of the brain are enlarged. Slightly less common, but still affecting more than 1 in 4 people, is a complete or partial failure of the development of the broad band of nervous tissue that connects the two hemispheres of the brain (agenesis/ dysgenesis of corpus callosum). Your paediatrician or neurologist will interpret the implications of your child’s brain scan for you.

Around 4 babies in 10 are born with a heart problem. This is most commonly a hole between the upper chambers of the heart (atrial septal defect, ASD), or the lower chambers (ventricular septal defect/ VSD). Problems with the valves that regulate blood flow through the heart have also been seen. The approach to the problem depends on its severity and can include monitoring and surgical correction.

Around one baby in 3 has a problem with their kidneys or urinary system. The problems seen include enlarged kidneys (hydronephrosis); kidney reflux, where urine backflows from the bladder and can reach the kidneys, potentially causing scarring; enlargement of the part of the kidney where urine collects (pyelectasis); and a duplication of part of the kidneys and their drainage system. Some babies also have repeated urinary tract infections, and may be prescribed protective antibiotic treatment.

One baby in 5 is born with clicky or dislocated hips, requiring immobilisation, sometimes in a brace or plaster, to improve the development of the hip joint. Almost as many are born with, or develop, a spinal curve. The curve may be sideways (scoliosis), forwards (kyphosis) or backwards (lordosis). Monitoring, physiotherapy, and in some cases bracing or surgery may be needed.

Unusual features of the hands and feet are common in people with a chromosome disorder. Many of these features are just cosmetic or an effect of low muscle tone, and almost 1 in 3 babies is born with a positional foot deformity, where the feet need repositioning to make walking easier.

Health and well being

While children and adults with Koolen-De Vries syndrome are generally healthy, seizures are common. However, they are usually easy to control with medication and some children have outgrown them.

Repeated infections, including chest infections, are often troublesome in pre-schoolers, but usually ease by the age of 5 years.

Around 1 in 3 people with the syndrome have unusually long sight, which needs to be corrected with glasses, while a further 1 in 3 have a squint (strabismus), which will usually also need correction. Unique’s records suggest that short sight is also common.

Most likely features of Koolen-De Vries syndrome

- Young babies are floppy
- Young babies have difficulty feeding. They may 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. Some children are taught in mainstream schools, others do better in a special school
- Children and adults are generally friendly and cooperative
- Children and adults have recognisable facial features, especially a pear-shaped nose with a bulbous tip and a long face. The typical facial features may not be seen in babies and young children.

- Young babies are very floppy
- 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.

- Muscle tone improves with age but low tone can be persistent and may lead to other effects, like a spinal curvature (scoliosis). Early intervention with physiotherapy and tone exercises is important.

- Young babies have difficulty feeding. They may need tube feeding for a time

At birth, babies may be unable to latch on or suck so weakly 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 they 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 main nutrition 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. Most children walk by their second birthday, one or two not until their fourth year. Almost 2 in 3 children have unusually bendy joints, which contributes to the difficulties that they face in controlling their body movements.

Early intervention with physiotherapy, occupational therapy and other approaches such as aquatherapy is important. Children may need special seating, walking aids, special footwear and a wheelchair for outdoors.

Fine motor skills (using and co-ordinating the hands) are also affected, and a child’s hands may be particularly weak. One child in three has underdeveloped hand muscles.

“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.”
Children start speaking late and have difficulty making all the sounds of speech
Speech and language are particularly affected. Expressive language (speaking) seems to be more affected than receptive language (understanding).
Recognisable words are rarely heard until a child is 2 to 5 years old. Before this, children communicate using gestures, body or facial expression or vocal noises. Some children learn a limited sign language, and many use picture systems and computer touch screens to help communication. Progress to short phrases may be possible by the teenage years.
Children cannot make all the sounds of speech because they have difficulty making and organising facial movements. This is called oromotor dyspraxia and is 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

Children need support with learning. Some children are taught in mainstream schools, others do better in a special school
Children benefit from early intervention and learning support, although the amount of support they need varies a lot between individuals. So far, we believe that most people with the syndrome have a mild to moderate level of learning disability, but in some it is more marked. At least one adult has achieved average grades in several national school examinations.

Children and adults are generally friendly and cooperative
Children and adults with Koolen-De Vries syndrome are typically well-behaved, sociable, friendly, happy and loving. As in any group of people with a developmental condition, difficulties have been reported, including autism spectrum disorders, difficulties concentrating, anxiety and passivity, but these reports are heavily outweighed by the reports of delightful behaviour.
“She is empathetic and caring, strong-willed, loving, kind, brave, does not give in, and mostly happy.”

Children and adults have recognisable facial features, although these are less easy to see in babies and young children
Children and adults may look more like others with Koolen-De Vries syndrome than like other members of their family.
Typically, children and adults have a prominent nose with a broad tip, often called ‘pear-shaped’ or tubular. Other common features are a high or broad forehead; a long face; small folds of skin across the inner corner of the eyes, which may slant upwards; large ears that may stick out; and a narrow or high roof to the mouth. Hair may be an unusual colour or texture for the family; and the eyes may be pale or blue. In time, facial features may lose their delicacy.

Growth
More than a quarter of babies are born small and light for dates. However, head size is often large relative to weight and length. In the early days, when feeding is difficult, growth may falter but it usually normalises. In time, growth may catch up, but at least 1 in 5 children are short compared with other family members and some are extremely short.