

Support and Information



Rare Chromosome Disorder Support Group,

The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants.

If you can, please make a donation via our website at

www.rarechromo.org/donate

Please help us to help you!

Facebook and internet groups:

<https://kdvsfoundation.org/>

KdVS foundation educates, increases awareness and promotes research for the support and enrichment of individuals living with Koolen-de Vries Syndrome and their families.

www.17q21.com or www.17q21.net

Website for the 17q21.31 research project led by Dr David Koolen

www.facebook.com/groups/KoolenDeVriesSyndrome/

Parents blog: <http://emily17q.blogspot.co.uk/>

Europe: www.facebook.com/groups/171438096379820/

USA Kool Kid alliance (public facebook group):

www.facebook.com/groups/420842758111942/about/

Chromosome 17 disorders:

www.facebook.com/pages/Chromosome-17-Disorders/221075181258226

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. Versions 1.1 and 1.2 reviewed by Professor Marcella Zollino, Institute of Medical Genetics, Catholic University, Rome, Italy.

2013 Version 1 (PM). 2015 Version 1.1 (PM). 2018 Version 1.2 (AP)

Copyright © Unique 2020

Rare Chromosome Disorder Support Group
Registered in England and Wales

Charity Number 1110661
Company Number 5460413



Koolen-de Vries syndrome



**May also be known as: KANSL1 haploinsufficiency syndrome
or: KANSL1-related intellectual disability syndrome**

Previously known as 17q21.31 microdeletion syndrome

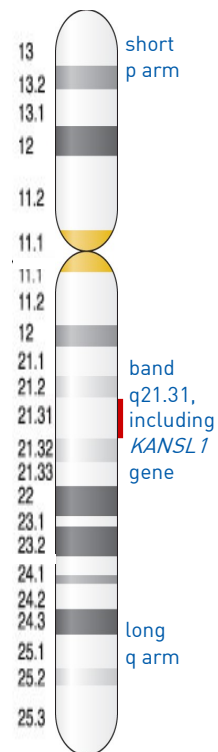
rarechromo.org

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 [Zollino 2012; Koolen 2012]. These genetic changes cause developmental delay, learning difficulties and possibly some health issues but the degree to which individuals are affected varies.

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 *KANSL1* 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.

The coding parts of a gene are called exons. When a deletion only involves exons 1-3 of *KANSL1* no clinical effects may be found.

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. 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.



So far, no-one with Koolen-de Vries syndrome is known to have had children of their own. One reason is that older people with the syndrome may not have had the newer genetic tests and so remain undiagnosed. Another reason is that adults with learning disabilities are less likely to have children than adults without learning disabilities. We do not yet know whether Koolen-De Vries syndrome affects fertility.

When this guide was published, Unique's oldest member with Koolen-De Vries syndrome was aged 32 years. The oldest known people with the syndrome are adults in their thirties, but there are certainly older people, not yet diagnosed.

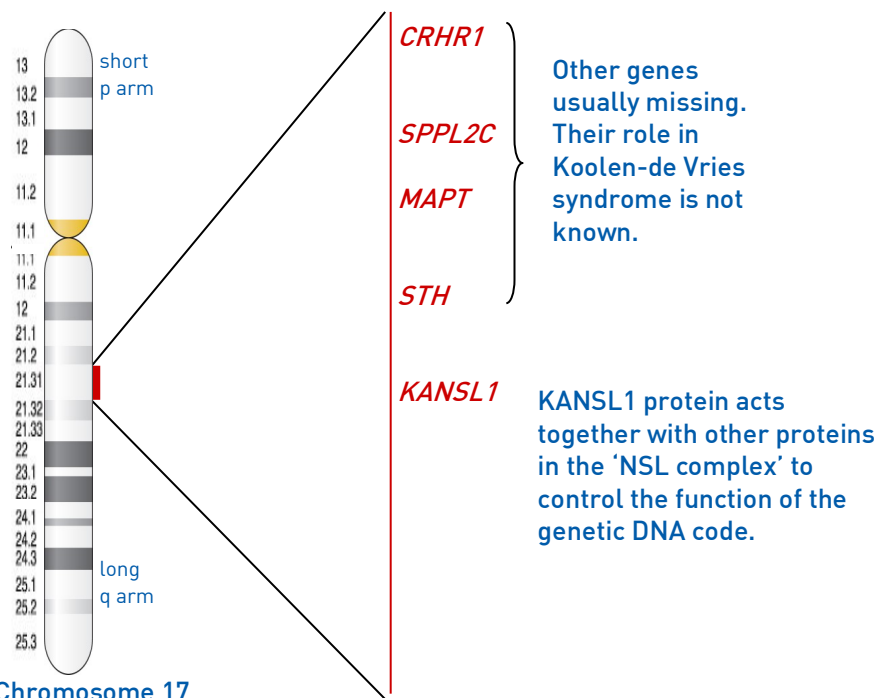


call this mosaicism, and it can affect any cells in the body, or just the cells that go to make up the mother's eggs or the father's sperm. In both the families we know about, the mother had a small proportion of cells missing the 17q21.31 region, but it could just as well have been the father. Both 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.

Genes

It has been shown that a change in *KANSL1* is sufficient to cause Koolen-de Vries syndrome (Zollino 2015; Koolen 2015). 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.



Koolen-De Vries syndrome is rare. It's estimated that one in 55,000 people have this condition however not all children with learning difficulties are offered a genetic test so many children may remain undiagnosed.



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. X1 denotes one copy, 2 copies are expected since there are two copies of chromosome 17
[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 genetic test was by fluorescence *in situ* hybridisation
Del Del denotes *deletion*; some material was found to be missing
(17) The material was missing from chromosome 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) FISH codes for the altered sections of chromosome 17
Dn Denotes *de novo*, the genetic change has not been inherited but has arisen 'anew'.

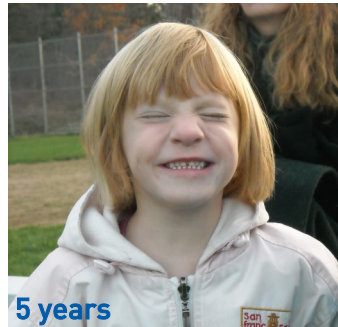
DNA sequence analysis may look something like this:

A heterozygous pathogenic mutation in the *KANSL1* gene (NM_1193466.1): c.985_986del (p.[Leu329fs]).
heterozygous one copy out of the two gene copies is affected
pathogenic causes an 'outcome' to individuals
mutation change in DNA sequence
KANSL1 name of gene that has been altered
NM_1193466.1 reference sequence number for the *KANSL1* gene
c.985_986del the mutation is a *deletion* between base pair numbers 985 and 986 of the gene's coding sequence
p.[Leu329fs] genes code for amino acids which form proteins. The protein sequence has been altered, the first amino acid to have been altered is *Leucine* at protein sequence number 329. The alteration is a *frame shift* which means every amino acid after Leu329 has been affected.

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 is recommended. If a child is markedly short for their age, a test for growth hormone shortage is suggested.



Gene change [mutation] or deletion. What difference does it make?

It is too early to know for sure all the differences between children with Koolen-de Vries caused by a deletion and those where it's caused by a gene mutation. Many people with the deletion have been studied and reported in medical journals, but far fewer with a *KANSL1* gene mutation. So far it seems that in most respects there are no general differences between the two groups (Zollino 2015; Koolen 2015). But early research studies are starting to suggest some differences: one study suggested that heart problems might be more common in those with a deletion, while having an unusually large head could be especially common in those with a gene mutation [Zollino 2015]. Mouse models of both 17q21.31 deletions and *KANSL1* mutations are being studied and may help increase knowledge of potential differences as well as roles of other genes included in 17q21.31 deletions (Arbogast 2017).

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. Hearing difficulties, either from transient or permanent hearing loss, affect around one person in 4, and are correctable with hearing aids or tubes (Zollino 2015; Koolen 2015).

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 might 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



Medical concerns

Many children and adults do not have any important birth defects. However, baby boys are commonly 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. Hypospadias has also been seen, where the hole normally at the end of the penis is on the underside instead.

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). Subependymal heterotopias have also been seen, where grey matter appears in the wrong part of the brain. Your paediatrician or neurologist will interpret the implications of your child's brain scan for you. One baby was born with the bony plates of the skull fused too early, limiting brain growth. This child also had developmental damage to the structure of the eye and its neurological connections [Zollino 2015].

Around half of all children experience seizures, most often febrile seizures in babies under one [Zollino 2015; Koolen 2015]. Only one case of seizures uncontrolled by drugs has been reported [Zollino 2015]. A recent study of epilepsy in children and adults with Koolen-de Vries syndrome identified focal impaired awareness seizures (an electrical disturbance in a localised part of one hemisphere of the brain that affects a person's consciousness) as the most frequent seizure type, usually with an effect on the autonomic nervous system (e.g. heart rate, blood pressure, sweating), (Myers 2017).

Around 4 babies in 10 with a deletion [not a gene change] 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) or a persistent ductus arteriosus [PDA] where a shortcut for bloodflow around the body fails to close naturally around the time of birth. 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.

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.

■ Some 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 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. 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) may 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.

One researcher found excellent response to speech therapy, with useful speech developing by 4 years and only one person (with a large deletion) not able to speak [Zollino 2015]. Another researcher mentions early combined oral hypotonia (decreased muscle tone of the mouth) and oral apraxia (difficulty connecting speech messages from the brain to the mouth to make accurate movements necessary for word formation) can occur but apraxia can resolve in later childhood. Early, intensive speech motor and language therapy is recommended (Morgan 2018). Children's difficulties making all the sounds of speech because they have difficulty making and organising facial movements is also called oromotor dyspraxia (or apraxia) 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 benefit from 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, most people with the syndrome have a mild to moderate level of learning disability, though in a few probably mostly with a deletion rather than a gene change, it can be more marked. Two children, one with a deletion and one a gene change - mutation - have learning abilities within low normal ranges. 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; a long philtrum [the upper lip between nose and mouth]; sparse eyebrows; and a narrow or high roof to the mouth. There may be gaps between the teeth. 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

A third to a half of babies are born small and light for dates (Zollino 2015; Koolen 2015). However, head size is often large relative to weight and length - more common in those with a gene change than a deletion [Zollino 2015]. 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.