



## Koolen-de Vries Syndrome

Synonym: KdVS

David A Koolen, MD, PhD,<sup>1</sup> Angela Morgan, Prof, PhD,<sup>2,3</sup> and Bert BA de Vries, MD, PhD<sup>1</sup>

Created: January 26, 2010; Updated: February 2, 2023.

### Summary

#### Clinical characteristics

Koolen-de Vries syndrome (KdVS) is characterized by congenital malformations, developmental delay / intellectual disability, neonatal/childhood hypotonia, epilepsy, dysmorphisms, and behavioral features. Psychomotor developmental delay is noted in all individuals from an early age. The majority of individuals with KdVS function in the mild-to-moderate range of intellectual disability. Other findings include speech and language delay (100%), epilepsy (~33%), congenital heart defects (25%-50%), renal and urologic anomalies (25%-50%), and cryptorchidism. Behavior in most is described as friendly, amiable, and cooperative.

#### Diagnosis/testing

The diagnosis of KdVS is established in a proband who has either a heterozygous 500- to 650-kb deletion at chromosome 17q21.31 that includes *KANSL1* or a heterozygous intragenic pathogenic variant in *KANSL1*. Note: The 17q21.31 deletion cannot be identified by analysis of G-banded chromosomes or other cytogenetic banding techniques.

#### Management

*Treatment of manifestations:* Supportive care, ideally through a multidisciplinary team of specialists, to improve quality of life, maximize function, and reduce complications is recommended. Speech therapy to support early feeding challenges and communication development; physiotherapy for gross and fine motor delays; educational programs directed to specific disabilities identified. Growth hormone therapy is indicated for those with growth hormone deficiency. Routine treatment of vision issues / strabismus; hearing loss; cardiac, renal, and urologic issues; epilepsy; scoliosis, hip dislocation, and positional deformities of the feet; multiple nevi.

**Author Affiliations:** 1 Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands; Email: david.koolen@radboudumc.nl; Email: bert.devries@radboudumc.nl. 2 Murdoch Children's Research Institute, Victoria, Australia; Email: angela.morgan@mcri.edu.au. 3 Department of Audiology and Speech Pathology, University of Melbourne, Melbourne, Australia; Email: angela.morgan@mcri.edu.au.

*Surveillance:* At each visit: measurement of growth parameters; evaluation of nutritional status and safety of oral intake; monitoring of developmental progress and educational needs; assessment for new manifestations, such as seizures and changes in tone; behavioral assessment; assessment of mobility and self-help skills. Annual full skin examination in those with lighter skin tones or skin types who are at greater risk for developing melanoma. Ophthalmology and hearing evaluations annually or as clinically indicated.

## Genetic counseling

KdVS, caused by a heterozygous deletion at chromosome 17q21.31 or a heterozygous intragenic *KANSL1* pathogenic variant, is an autosomal dominant disorder. Almost all affected individuals represent simplex cases (i.e., a single affected individual in the family). The recurrence risk for future pregnancies is slightly greater than that of the general population because of the possibility of germline mosaicism in one of the parents. Once the KdVS-related genetic alteration has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

## Diagnosis

No consensus clinical diagnostic criteria for Koolen-de Vries syndrome (KdVS) have been published.

## Suggestive Findings

KdVS **should be considered** in probands with the following clinical and family history findings.

### Clinical findings

- Mild-to-moderate developmental delay or intellectual disability in which speech and language development is particularly affected

AND

- Neonatal/childhood hypotonia and feeding difficulties
- Epilepsy
- Dysmorphic facial features (See Clinical Description and Figure 1.)
- Hypermetropia
- Congenital heart anomalies
- Congenital renal/urologic anomalies
- Hypermobility of the joints and/or joint dislocation/dysplasia
- Deformities of the spine and/or feet

**Family history.** Because KdVS is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family).

## Establishing the Diagnosis

The diagnosis of KdVS **is established** in a proband with typical clinical findings and of any of the following (see Table 1):

- A heterozygous deletion at chromosome 17q21.31 that includes *KANSL1* (~60% of affected individuals). The 17q21.31 deletion is typically 500 to 650 kb in size (hg19: chr17:43700000-44250000) and is flanked by segmental duplications.
- A heterozygous intragenic pathogenic (or likely pathogenic) variant in *KANSL1* (~40% of affected individuals)
- Haploinsufficiency of *KANSL1* due to chromosome rearrangements [Moreno-Igoa et al 2015]



**Figure 1.** Photographs of eight individuals with a 17q21.31 deletion

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *KANSL1* variant of uncertain significance does not establish or rule out the diagnosis. (3) A characteristic epigenetic signature for KdVS has been established and may aid in the determination of the clinical significance of uncertain variants (see Further Testing to Consider).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (chromosomal microarray analysis, single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of KdVS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the phenotypic findings suggest the diagnosis of KdVS, molecular genetic testing approaches can include **chromosomal microarray analysis (CMA)**, **single-gene testing**, or use of a **multigene panel**.

- **CMA** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *KANSL1*) that cannot be detected by sequence analysis. If no DNA copy variant is detected by CMA, the next step is to perform either **single-gene testing** or a **multigene panel**.
- **Single-gene testing.** Sequence analysis of *KANSL1* is performed to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, gene-targeted deletion/duplication analysis to detect exon-level deletions or duplications that could have been missed on CMA could be considered.
- **An intellectual disability multigene panel** that includes *KANSL1* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of this condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Option 2

When the diagnosis of KdVS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Note: Some exome sequencing platforms also provide information on DNA copy number variants (CNVs); genome sequencing frequently includes information on DNA CNVs. As such, exome sequencing with CNV analysis or genome sequencing could be considered as a first-line test for KdVS.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

## Further Testing to Consider

**Epigenetic signature analysis / methylation array.** A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with KdVS [Aref-Eshghi et al 2020, Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore clarify the diagnosis in individuals with: (1) convincing findings of KdVS but in whom no 17q21.31 deletion or pathogenic variant in *KANSL1* has been identified via sequence analysis or genomic testing; or (2) suggestive findings of KdVS and a *KANSL1* variant of uncertain clinical significance identified by molecular genetic testing. The data from the epigenetic signature analysis must be interpreted carefully. A positive result on the methylation array is insufficient for diagnosis without clinical findings consistent with KdVS. For an introduction to epigenetic signature analysis click [here](#).

**Karyotype.** If a 17q21.31 deletion is not identified on CMA and an intragenic pathogenic variant in *KANSL1* has not been identified on either a multigene panel or comprehensive genomic testing (exome or genome sequencing), additional options for testing include karyotype. A chromosome translocation with a 17q21.31 breakpoint that disrupted *KANSL1* has been observed in one case report [Moreno-Igoa et al 2015].

**Table 1.** Molecular Genetic Testing Used in Koolen-de Vries Syndrome

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>KANSL1</i>	CMA <sup>3, 4, 5</sup>	~60% <sup>6</sup>
	Sequence analysis <sup>7</sup>	~40% <sup>8</sup>
	Gene-targeted deletion/duplication analysis <sup>9</sup>	See footnote 10.
	Karyotype (to detect structural variants)	Rare <sup>11</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *KANSL1*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 17q21.31 region. CMA designs in current clinical use target the 17q21.31 region.

4. Many affected individuals are identified by a genome-wide CMA screen for deletions/duplications that includes probe coverage of *KANSL1*. It is too early to ascertain the frequency of the 17q21.31 deletion that contains *KANSL1* and a *KANSL1* pathogenic sequence variant. Given the fact that the chromosome locus involved is flanked by segmental duplications, predisposing the locus to undergo deletion, it is likely that the recurrent 17q21.31 deletion that includes *KANSL1* occurs more frequently than intragenic pathogenic *KANSL1* sequence variants [Koolen et al 2006, Koolen et al 2012b, Zollino et al 2012, Zollino et al 2015, Koolen et al 2016].

5. To date, testing in all unaffected parents from whom the deleted chromosome 17 originated has shown a 900-kb inversion involving chromosome 17q21.31. The frequency of this inversion (also referred to as the H2 lineage) in these parents is significantly greater than the ~20% frequency of the inversion found in the European population as a whole [Stefansson et al 2005] ( $p < 10^{-5}$ , Pearson's chi-square test) [Koolen et al 2008]. Testing for the inversion is not routinely indicated (see Molecular Genetics).

6. Koolen et al [2006], Sharp et al [2006], Shaw-Smith et al [2006]. CMA testing is appropriate to define breakpoints of large deletions; however, intragenic deletions in *KANSL1* may not be detected by this method. Note: To date, all *KANSL1* intragenic deletions reported have been identified through CMA analysis.

7. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

8. Koolen et al [2012b], Zollino et al [2012], Zollino et al [2015], Koolen et al [2016]

9. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

10. Gene-targeted methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined. *KANSL1* gene-targeted deletion/duplication analysis could be considered if CMA and sequence analysis are not diagnostic, as smaller, atypical deletions encompassing part of *KANSL1* have been reported [Cooper et al 2011, Dubourg et al 2011, Kitsiou-Tzeli et al 2012, Koolen et al 2012b].

11. Moreno-Igoa et al [2015]

## Clinical Characteristics

### Clinical Description

Koolen-de Vries syndrome (KdVS) has a clinically recognizable phenotype that includes neonatal/childhood hypotonia, developmental delay / intellectual givdisability, dysmorphisms (see Figure 1), speech and language delays, congenital malformations, and behavioral features. To date, more than 200 individuals have been identified with KdVS [Koolen et al 2006, Sharp et al 2006, Koolen et al 2008, Grisart et al 2009, Tan et al 2009, Koolen et al 2012b, Zollino et al 2012, Zollino et al 2015, Koolen et al 2016, Morgan et al 2018a, Myers et al 2017, Amenta et al 2022, St John et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.



**Table 2.** Koolen-de Vries Syndrome: Frequency of Select Features

Feature	Frequency				Comments
	Very common <sup>1</sup>	Common <sup>2</sup>	Less common <sup>3</sup>	Occasional <sup>4</sup>	
Distinctive facial features	●				See <b>Dysmorphic craniofacial features</b> after this table.
Developmental delay / intellectual disability	●				Particularly in areas of speech & language delay
Hypotonia		●			Neonatal/childhood
Structural brain anomalies		●			Incl ventriculomegaly, corpus callosum anomalies, Arnold-Chiari type I malformation, & intraventricular hemorrhage
Joint hypermobility		●			Incl joint dislocation/dysplasia
Seizures/epilepsy			●		
Friendly/amiable disposition			●		
Visual impairment			●		Hypermetropia, strabismus, congenital cataract, optic atrophy
Congenital heart defects			●		VSD, ASD, bicuspid aortic valve, cardiomyopathy, aortic root dilatation
Genitourinary anomalies			●		Cryptorchidism, hypospadias, hydronephrosis/VUR, renal duplication
Feeding difficulties			●		
Musculoskeletal anomalies			●		Long fingers, pes planus, pes cavus, calcaneovalgus deformity, scoliosis/kyphosis, pectus anomalies
Anxiety				●	
ADHD				●	
Hearing impairment				●	Most commonly conductive, although sensorineural hearing loss has been reported
Tracheo-/laryngomalacia				●	
Integument				●	Multiple nevi, fair hair, hemangioma, café au lait macules

Based on data from the [Human Disease Genes website](#)

ADHD = attention-deficit/hyperactivity disorder; ASD = atrial septal defect; VSD = ventriculoseptal defect; VUR = vesicoureteral reflux

1. Present in more than 75% of affected individuals
2. Present in 50%-75% of affected individuals
3. Present in 25%-49% of affected individuals
4. Present in 10-24% of affected individuals

**Dysmorphic craniofacial features** that may suggest KdVS include:

- Upslanted palpebral fissures
- Blepharophimosis
- Epicanthus
- Ptosis

- Pear-shaped nose
- Bulbous nose
- Large/protruding ears

The nose can have a high nasal bridge, a broad nasal root, long columella, and underdeveloped and/or thick alae nasi. The facial characteristics change with age. In infancy the facial gestalt is mostly characterized by hypotonia with an "open mouth" appearance. With increasing age there is usually elongation of the face and broadening of the chin, and the "tubular" or "pear" shape of the nose may become more apparent.

**Developmental delay / intellectual disability.** Psychomotor delay is noted in all affected individuals from an early age. The level of developmental delay varies significantly. The majority of individuals with KdVS function in the mild-to-moderate range of intellectual disability.

- **Communication disorder** is a core feature of KdVS, with a common speech and language phenotype seen. This includes an overriding "double hit" of oral hypotonia and apraxia in infancy and preschool, associated with severely delayed speech development [Morgan et al 2018a]. St John et al [2023] defined speech, language, and functional/adaptive behavior in 81 individuals with KdVS.
  - First words occur on average between ages 2.5 and 3.5 years.
  - **Childhood apraxia of speech (CAS)** is common in the preschool years, and speech development is effortful even when supported with intensive therapy.
 

Augmentative (e.g., sign language) or alternative (e.g., communication devices) communication may alleviate frustration for the child and promote communication development.

Overall, however, speech prognosis is positive, with CAS improving markedly around age eight to 12 years. At this time, the dysarthric element of speech is more apparent with a slow rate and monotone presentation.
  - **Stuttering** has been described in 76.6% of verbal individuals and follows a unique trajectory of late onset and fluctuating presence [St John et al 2023].
  - **Receptive and expressive language** abilities are commensurate, but literacy skills remain a relative weakness.
  - **Social competence**, successful behavioral/emotional control, and coping skills are areas of relative strength, while communication difficulties affect daily living skills as an area of comparative difficulty.

**Hypotonia** with poor sucking and slow feeding can be evident in the neonatal period and during childhood. Feeding difficulties may require hospitalization and/or nasogastric tube feeding in some neonates. Beyond infancy and into the preschool years, many children experience issues chewing difficult, lumpy, or solid textures [Morgan et al 2018a].

**Epilepsy**, including generalized seizures and unilateral clonic seizures, is noted in approximately 33% of affected individuals. The epilepsy phenotypic spectrum in KdVS is broad; however, most individuals have focal seizures, with some having a phenotype resembling the self-limited focal epilepsies of childhood [Myers et al 2017].

- The typical epilepsy phenotype of KdVS involves childhood-onset focal seizures that are prolonged and have prominent autonomic features.
- Multifocal epileptiform discharges are the typical EEG pattern.

**Neurobehavioral/psychiatric manifestations.** In many affected individuals, behavior is described as friendly, amiable, and cooperative, with or without frequent laughing. However, behavioral findings including attention-

deficit/hyperactivity disorder have been reported [Koolen et al 2008, Tan et al 2009, Koolen et al 2016]. A subset of affected individuals have autism and/or anxiety.

**Growth.** Short stature is not one of the most common clinical features of the syndrome. However, El Chehadeh-Djebbar et al [2011] reported a child with a 17q21.31 deletion, short stature (4 SD below the mean), complete growth hormone deficiency, and gonadotropic deficiency [El Chehadeh-Djebbar et al 2011]. Brain MRI showed partial pituitary stalk interruption, expanding the phenotypic spectrum of the syndrome.

**Ophthalmologic involvement** in individuals with this condition include hypermetropia, strabismus, congenital cataract, and optic atrophy.

**Hearing impairment.** A minority of affected individuals experience recurrent otitis media.

### **Neuroimaging/other neurodevelopmental features**

- **Brain MRI.** Structural brain abnormalities may be universal, including signs of abnormal neuroblast migration and abnormal axonal guidance. Affected individuals have been described as having:
  - Ventriculomegaly
  - Aplasia/hypoplasia of the corpus callosum
  - Hydrocephalus
  - Arnold-Chiari malformation
  - Intraventricular hemorrhage
- Infrequent findings (present in fewer than 10% of reported individuals) may include the following:
  - Sacral dimple
  - Dural ectasia
  - Spina bifida
  - Pineal cyst
  - Cervical spinal canal stenosis

**Musculoskeletal.** Joint hypermobility is common. Affected individuals may also experience joint dislocations. Other findings can include:

- Long, slender fingers
- Persistence of the fetal fingertip pads
- Hypoplasia of the hand muscles
- Pes planus
- Pes cavus
- Calcaneovalgus deformity
- Congenital hip dislocation
- Scoliosis/kyphosis
- Pectus anomalies, including pectus excavatum or pectus carinatum
- Slender build
- Spondylolisthesis (infrequently)
- Craniosynostosis (infrequently), most commonly sagittal, but metopic has also been observed

**Congenital heart defects** mainly include septal heart defects; however, cardiac valve disease, aortic root dilatation, and pulmonary stenosis have also been described.

**Renal and urologic anomalies** include vesicoureteral reflux, hydronephrosis, pyelectasis, and duplex renal system. Cryptorchidism has been reported in the majority of males. A minority of affected individuals experience recurrent urinary tract infection.



**Respiratory.** Some affected individuals experience recurrent respiratory infections. There is no known immune deficiency described in affected individuals that can explain this finding. Tracheo-/laryngomalacia has also been reported in a relatively small number of affected individuals.

#### **Other associated features reported infrequently (fewer than 10% of known affected individuals)**

- **Endocrinology.** In addition to at least one affected individual with growth hormone deficiency, other reported hormonal issues include hypothyroidism, precocious puberty, and primary adrenal insufficiency.
- **Integument.** A myriad of skin findings have been described, typically in a few individuals each, including [Wright et al 2011, Zollino et al 2015, Koolen et al 2016]:
  - Multiple nevi
  - Other pigmentary skin abnormalities, such as vitiligo and café au lait macules
  - Hemangioma
  - Eczema
  - Ichthyosis/hyperkeratosis
  - Hair abnormalities, such as fair hair and/or alopecia
- **Neoplasia.** It is unclear if individuals with this condition have an increased risk above the general population risk of developing a malignancy. Infrequent malignancies in affected individuals have included melanoma and testicular neoplasms. Individuals with KdVS who have lighter skin tones or skin types who are at greater risk for developing melanoma should be evaluated annually to assess ectodermal findings and cutaneous changes (see Management). Currently, there is no consensus tumor screening protocols that have been proposed or published for individuals with KdVS.

**Life span.** Longitudinal data are insufficient to determine life expectancy, although survival into adulthood is typical. One reported individual is alive at age 63 years [Farnè et al 2022].

## **Genotype-Phenotype Correlations**

Genotype-phenotype correlations in KdVS have not been demonstrated. Notably, the clinical features of affected individuals with atypical deletions and those with pathogenic variants in *KANSL1* are in keeping with the phenotype seen in individuals with a classic 17q21.31 deletion [Zollino et al 2015, Koolen et al 2016].

## **Penetrance**

Penetrance is 100%. Clinical features of KdVS are apparent in all individuals with a deletion of or a pathogenic variant in *KANSL1*, although the extent and severity of clinical findings vary among individuals.

## **Nomenclature**

The disorder was first recognized following chromosomal microarray analysis among large cohorts of unselected individuals with intellectual disability [Koolen et al 2006, Sharp et al 2006, Shaw-Smith et al 2006]. The identification of individuals with a similar phenotype and a *de novo* *KANSL1* pathogenic variant [Koolen et al 2012b, Zollino et al 2012] led OMIM to assign the name "Koolen-de Vries syndrome" to the condition.

## **Prevalence**

The prevalence of KdVS is unknown. The authors estimate the prevalence of the 17q21.31 deletion to be 1:55,000 individuals [Koolen et al 2016]. The prevalence of individuals with a pathogenic sequence variant in *KANSL1* cannot be determined with precision owing to the limited number of such affected individuals identified thus far. Preliminary data suggest that pathogenic *KANSL1* sequence variants may be as frequent as deletions, but more studies are needed to determine an unbiased prevalence.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with deletion of the genes located within the 17q21.31 chromosome locus or with pathogenic variants in *KANSL1*. Besides the recurrent classic 17q21.31 microdeletion, several atypical 17q21.31 deletions have been described in children with clinical features typically associated with the classic 17q21.31 microdeletion [Cooper et al 2011, Dubourg et al 2011, Kitsiou-Tzeli et al 2012, Koolen et al 2012b]. All these atypical deletions encompass at least *KANSL1*.

**Duplication of 17q21.31** (OMIM 613533). Persons with a reciprocal duplication of the region deleted in Koolen-de Vries syndrome differ phenotypically from those with the 17q21.31 deletion. The reciprocal duplication has been found in a female with severe psychomotor developmental delay, microcephaly, facial dysmorphisms, abnormal digits, and hirsutism [Kirchhoff et al 2007] and in four individuals with mild psychomotor developmental delay and behavioral findings [Grisart et al 2009].

***MAPT***. Pathogenic gain-of-function variants in *MAPT*, the gene encoding microtubule-associated protein tau, have been identified in individuals diagnosed with frontotemporal dementia with parkinsonism-17 (FTDP-17). These variants result in pathogenic deposits of hyperphosphorylated tau. This is in contrast to the haploinsufficiency of *MAPT* in Koolen-de Vries syndrome due to a deletion of 17q21.31 that includes *KANSL1* and *MAPT*. Therefore, individuals who have the 17q21.31 deletion are not at an increased risk for FTDP-17 or related tauopathies.

## Differential Diagnosis

The most common findings in Koolen-de Vries syndrome (KdVS) – developmental delay and childhood hypotonia – are common and relatively nonspecific indications for molecular cytogenetic analysis. However, the concurrent finding of characteristic facial dysmorphic features, epilepsy, hypermetropia, congenital heart defects, renal or urologic anomalies, cryptorchidism, and/or distinctive friendly/amiable behavior may prompt specific consideration of the diagnosis of KdVS. See Table 3 for other diagnoses that may be considered in individuals with developmental delay, childhood hypotonia, and additional findings overlapping those observed in KdVS.

**Table 3.** Selected Disorders with Developmental Delay, Childhood Hypotonia, and Concurrent Findings Similar to Koolen-de Vries Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Clinical Characteristics	Comment
22q11.2 deletion	<a href="#">22q11.2 deletion syndrome</a>	AD	Wide range of highly variable features; major clinical manifestations incl CHD (esp conotruncal malformations), palatal abnormalities, immune deficiency, characteristic facial features, & learning difficulties.	KdVS may be considered in persons who tested negative for deletion of 22q11.2.

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Clinical Characteristics	Comment
Deletions, maternal UPD, imprinting errors w/in PWCR <sup>1</sup>	<a href="#">Prader-Willi syndrome (PWS)</a>	See footnote 1.	Severe hypotonia & feeding difficulties in early infancy, followed in later infancy / early childhood by excessive eating & gradual development of morbid obesity (unless eating is externally controlled); DD/ID; distinctive behavioral phenotype (w/temper tantrums, stubbornness, manipulative behavior, & obsessive-compulsive characteristics)	Behavior issues & sleep disturbances are more common in PWS than in KdVS.
Disruption of maternally imprinted <i>UBE3A</i>	<a href="#">Angelman syndrome (AS)</a>	See footnote 2.	Severe DD/ID; severe speech impairment; gait ataxia &/or tremulousness of limbs; unique behavior w/apparent happy demeanor incl frequent laughing, smiling, & excitability; microcephaly & seizures are common.	Research shows that prognosis for speech in persons w/KdVS is positive; apraxia resolves, & although dysarthria persists, most children are intelligible by mid-to-late childhood. <sup>3</sup> Speech delay in children w/AS remains far more severe. <sup>4</sup>
<i>BRAF</i> <i>KRAS</i> <i>MAP2K1</i> <i>MAP2K2</i>	<a href="#">Cardiofaciocutaneous syndrome (CFC)</a>	AD	Variable findings incl dysmorphic craniofacial features, cardiac issues, skin & hair abnormalities, hypotonia, eye abnormalities, GI dysfunction, seizures, & varying degrees of neurocognitive delay; polyhydramnios is present in vast majority of cases.	Cutaneous features are more common in CFC. CFC & KdVS are further distinguished by differences in facial dysmorphisms.
<i>FMR1</i>	Fragile X syndrome (See <a href="#">FMR1 Disorders.</a> )	XL	In males, DD/ID w/behavioral issues; ASD in 50%-70% of affected persons; characteristic craniofacial features that become more obvious w/age; medical issues incl hypotonia & seizures	Overactivity, impulsivity, & challenging behavior are more common in fragile X syndrome than in KdVS.
<i>KAT6B</i>	<a href="#">KAT6B disorders</a> (incl genitopatellar syndrome & Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome)	AD	Broad phenotypic spectrum w/ variable expressivity; DD/ID; hypotonia; genital abnormalities; & skeletal abnormalities	Severe ID, immobile mask-like facies, & abnormalities of thyroid structure or function are assoc w/ <i>KAT6B</i> disorders. Skeletal issues are more common in <i>KAT6B</i> disorders than in KdVS.
<i>KAT8</i>	<a href="#">KAT8-related intellectual disability (Li-Ghorgani-Weisz-Hubshman syndrome)</a> (OMIM 618974)	AD	DD/ID, epilepsy, & other developmental anomalies w/ variable facial dysmorphisms	Striking facial resemblance between KdVS & <i>KAT8</i> -related ID in some affected persons

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Clinical Characteristics	Comment
WAC	WAC-related intellectual disability	AD	Variable degrees of DD/ID; behavioral abnormalities incl anxiety, ADHD, &/or ASD are observed in majority of older children & adults. Most infants have significant but nonspecific features at birth such as neonatal hypotonia & feeding issues.	Epilepsy is less common in WAC-related ID than in KdVS.

AD = autosomal dominant; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CHD = congenital heart defect; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; PWCR = Prader-Willi critical region; UPD = uniparental disomy; XL = X-linked

1. PWS is caused by an absence of expression of imprinted genes in the paternally derived PWS/Angelman syndrome (AS) region (i.e., 15q11.2-q13) of chromosome 15 by one of several genetic mechanisms (paternal deletion, maternal uniparental disomy 15, and rarely an imprinting defect). The risk to the sibs of a proband with PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.

2. The risk to sibs of a proband with Angelman syndrome depends on the genetic mechanism leading to the loss of *UBE3A* function.

3. Morgan et al [2018a]

4. Grieco et al [2018]

## Management

### Evaluations Following Initial Diagnosis

To establish the clinical consequences in an individual diagnosed with Koolen-de Vries syndrome (KdVS), the evaluations in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis of Koolen-de Vries Syndrome

System/Concern	Evaluation	Comment
<b>Constitutional</b>	Assessment of growth parameters to identify those w/failure to thrive	Consider investigation of growth hormone deficiency in persons w/short stature.
<b>Gastrointestinal/ Feeding</b>	Feeding assessment	Assess for sucking & swallowing difficulties & need for feeding therapy in infancy.
<b>Development</b>	Developmental assessment	<ul style="list-style-type: none"> <li>To incl motor, adaptive, cognitive, &amp; speech/language eval</li> <li>Eval for early intervention / special education</li> </ul>
<b>Neurologic</b>	Brain imaging studies in persons w/ microcephaly &/or seizure	Consideration of Chiari malformation type 1 in those w/ suggestive symptoms (headache, neck pain, cerebellar signs, or muscle weakness) <sup>1</sup>
	EEG if seizures are suspected	Referral to neurologist for seizure disorder mgmt
<b>Neurobehavioral/ Psychiatric</b>	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
<b>Eyes</b>	Ophthalmologic eval	To assess for hypermetropia, strabismus, congenital cataract, &/or optic atrophy, which may require referral for subspecialty care &/or low vision services
<b>Hearing</b>	Audiologic exam	To assess for hearing loss

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: <ul style="list-style-type: none"> <li>Gross motor &amp; fine motor skills</li> <li>Joint hypermobility, pes planus, calcaneovalgus deformity, scoliosis/kyphosis, pectus anomalies</li> <li>Mobility, ADL, &amp; need for adaptive devices</li> <li>Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> </ul>
<b>Cardiovascular</b>	Cardiac eval to incl echocardiogram	For possible heart anomalies incl septal defects & aortic dilatation
<b>Genitourinary</b>	<ul style="list-style-type: none"> <li>Physical exam for hypospadias &amp; cryptorchidism in males</li> <li>Renal ultrasound exam</li> <li>Voiding cystourethrogram, if indicated</li> </ul>	Evaluate for ureteral reflux & other renal findings.
<b>Integument</b>	Full skin exam	To assess for hemangiomas & multiple nevi
<b>Respiratory</b>	Upper airway eval	In infants & children w/signs or symptoms suspicious of tracheo-/laryngomalacia
<b>Genetic counseling</b>	By genetics professionals <sup>2</sup>	To inform affected persons & their families re nature, MOI, & implications of KdVS to facilitate medical & personal decision making
<b>Family support &amp; resources</b>		Assess need for: <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>Social work involvement for parental support;</li> <li>Home nursing referral;</li> <li>Information &amp; resources for sibs of persons w/KdVS.</li> </ul>

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Terrone et al [2012]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

There is no cure for Koolen-de Vries syndrome.

**Supportive care** to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Treatment of Manifestations in Individuals with Koolen-de Vries Syndrome

Manifestation/Concern	Treatment	Considerations/Other
<b>Feeding issues &amp; motor delay related to hypotonia</b>	Early intervention / feeding therapy / physiotherapy	Nasogastric tube feeding may be required for neonates w/severe feeding issues.
<b>Growth hormone deficiency</b>	Growth hormone therapy per endocrinologist	
<b>Developmental delay / Intellectual disability</b>	See Developmental Delay / Intellectual Disability Management Issues.	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
<b>Seizures</b>	Standardized treatment w/ASM by experienced neurologist	<ul style="list-style-type: none"> <li>Many ASMs may be effective <sup>1</sup></li> <li>Education of parents/caregivers <sup>2</sup></li> </ul>
<b>Eyes</b>	Ophthalmologist	Refractive errors, strabismus
	Ophthalmic subspecialist	More complex findings (e.g., cataract, retinal dystrophy)
	Low vision services	<ul style="list-style-type: none"> <li>Children: through early intervention programs &amp;/or school district</li> <li>Adults: low vision clinic &amp;/or community vision services / OT / mobility services</li> </ul>
<b>Hearing loss</b>	Standard mgmt per audiologist/otolaryngologist	
<b>Scoliosis / Hip dislocation / Positional deformities of feet</b>	Standard orthopedic care	
<b>Cardiac, renal, urologic, &amp; other medical issues</b>	Standard mgmt of specific issue	
<b>Cryptorchidism</b>	Treatment by urologist, if indicated	
<b>Multiple nevi</b>	Regular checkup by dermatologist if multiple nevi are present.	
<b>Family/Community</b>	<ul style="list-style-type: none"> <li>Ensure appropriate social work involvement to connect families w/local resources, respite, &amp; support.</li> <li>Coordinate care to manage multiple subspecialty appointments, equipment, medications, &amp; supplies.</li> </ul>	<ul style="list-style-type: none"> <li>Ongoing assessment of need for palliative care involvement &amp;/or home nursing</li> <li>Consider involvement in adaptive sports or <a href="#">Special Olympics</a>.</li> </ul>

ASM = anti-seizure medication; OT = occupational therapy

1. One affected infant with seizures had a partial response to levetiracetam, but complete control was achieved when topiramate was added to the anti-seizure regimen [Paolo et al 2021].

2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see [Epilepsy Foundation Toolbox](#).

## Developmental Delay / Intellectual Disability Management Issues

Children with KdVS require early, intensive speech motor and language therapy, with targeted literacy and social language interventions as developmentally appropriate.

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States (US); standard recommendations may vary from country to country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

**Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

**Ages 5-21 years**



- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

**All ages.** Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

## Motor Dysfunction

### Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment as needed (e.g., walkers, bath chairs, orthotics, adaptive strollers).

**Fine motor dysfunction.** Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

**Oral motor dysfunction** should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

**Communication issues.** Consider evaluation for alternative means of communication (e.g., [augmentative and alternative communication](#) [AAC]) used alongside verbal therapies for individuals who have expressive language difficulties. Intensive verbal speech therapy approaches for childhood apraxia of speech are recommended in the early years [Morgan et al 2018b, St John et al 2023], and literacy, dysarthria, and social skill therapies are required in the school years.

## Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications when necessary.

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 6 are recommended.

**Table 6.** Recommended Surveillance for Individuals with Koolen-de Vries Syndrome

System/Concern	Evaluation	Frequency
<b>Constitutional</b>	<ul style="list-style-type: none"> <li>Measurement of growth parameters</li> <li>Eval of nutritional status &amp; safety of oral intake</li> </ul>	At each visit
<b>Development</b>	Monitor developmental progress & educational needs.	
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>Monitor those w/seizures as clinically indicated.</li> <li>Assess for new manifestations such as seizures, changes in tone.</li> </ul>	
<b>Neurobehavioral/ Psychiatric</b>	Assessment for anxiety, ADHD, & ASD	
<b>Musculoskeletal</b>	Physical medicine, OT/PT assessment of mobility, self-help skills	
<b>Family/Community</b>	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	
<b>Integument</b>	Full skin exam in those w/lighter skin tones or skin types who are at greater risk for developing melanoma	Annually
<b>Ophthalmologic involvement</b>	Ophthalmologic eval	Per treating ophthalmologist
	Low vision services	Per treating clinicians
<b>Hearing</b>	Audiologic eval	Annually, or as clinically indicated

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Koolen-de Vries syndrome (KdVS), caused by a heterozygous deletion at chromosome 17q21.31 or a heterozygous intragenic *KANSL1* pathogenic variant, is an autosomal dominant disorder. Almost all affected individuals represent simplex cases (i.e., a single affected individual in the family).

## Risk to Family Members

### Parents of a proband

- To date, all reported intragenic *KANSL1* pathogenic variants and almost all reported 17q21.31 deletions have been *de novo* in the proband.
- Evaluation of the parents by testing that will detect the 17q21.31 deletion or intragenic *KANSL1* pathogenic variant present in the proband is recommended to confirm their genetic status and to allow reliable recurrence risk counseling. FISH analysis in the parents to evaluate for a balanced insertion and/or translocation may also be considered.
- All unaffected parents tested to date from whom a deleted chromosome 17 originated have shown a 900-kb inversion involving chromosome 17q21.31. This inversion (also referred to as the H2 lineage) is enriched in Europeans, and carriers are predisposed to the 17q21.31 deletion (see Molecular Genetics).

Note: Testing for the 17q21.31 inversion polymorphism in parents is not recommended for recurrence risk assessment because it does not provide additional information that is of clinical use. The inversion is common in northern European populations, and although it seems to be a necessary factor for the deletion to occur, many other factors are important given the fact that the 17q21.31 deletion is relatively rare.

- If the 17q21.31 deletion or intragenic *KANSL1* pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* genetic alteration.
  - The proband inherited a genetic alteration from a parent with germline (or somatic and germline) mosaicism. Somatic and (presumed) germline mosaicism for a 17q21.31 deletion has been identified in at least two parents [Koolen et al 2012a].

Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a genetic alteration that is present in the germ cells only.
- Theoretically, a parent could have a balanced chromosome rearrangement involving 17q21.31 resulting in a 17q21.31 deletion in an affected child; balanced chromosome rearrangements in parents involving 17q21.31 have not been reported to date.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If the parents are clinically unaffected and the 17q21.31 deletion or intragenic *KANSL1* pathogenic variant detected in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of:
  - Parental germline mosaicism [Koolen et al 2012a];
  - A balanced chromosome rearrangement involving 17q21.31 (not reported, but theoretically possible).

### Offspring of a proband

- Individuals who have the 17q21.31 deletion or an intragenic *KANSL1* pathogenic variant have a 50% chance of transmitting the genetic alteration to each child.
- To date, one individual diagnosed with KdVS has been known to reproduce [Author, personal observation].

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has a KdVS-related genetic alteration or, theoretically, a balanced chromosomal rearrangement, the parent's family members may be at risk.

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of a child with KdVS.

## Prenatal Testing and Preimplantation Genetic Testing

Once the KdVS-related genetic alteration has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Kool Kid Alliance**  
[www.koolkidalliance.com](http://www.koolkidalliance.com)
- **Koolen-de Vries Syndrome Foundation**  
*Enriching lives through education, awareness and research.*  
**Phone:** 833-721-KDVS  
[www.kdvsfoundation.org](http://www.kdvsfoundation.org)
- **Chromosome Disorder Outreach Inc.**  
**Phone:** 561-395-4252  
**Email:** [info@chromodisorder.org](mailto:info@chromodisorder.org)  
[chromodisorder.org](http://chromodisorder.org)
- **MedlinePlus**  
[Intellectual Disability](#)
- **Unique: Understanding Rare Chromosome and Gene Disorders**  
United Kingdom

**Phone:** +44 (0) 1883 723356

**Email:** [info@rarechromo.org](mailto:info@rarechromo.org)

[rarechromo.org](http://rarechromo.org)

- **GenIDA Registry: Genetically Determined Intellectual Disabilities and Autism Spectrum Disorders**

*A website for Patients, Families and Professionals*

France

[GenIDA](#)

- **Human Disease Gene Website Series - Registry**

**Email:** [info@humandiseasegenes.com](mailto:info@humandiseasegenes.com)

[Koolen-de Vries syndrome](#)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.** Koolen-de Vries Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">KANSL1</a>	17q21.31	<a href="#">KAT8 regulatory NSL complex subunit 1</a>	<a href="#">KANSL1 @ LOVD</a>	<a href="#">KANSL1</a>	<a href="#">KANSL1</a>
<i>Not applicable</i>	17q21.31	Not applicable			

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Koolen-de Vries Syndrome ([View All in OMIM](#))

<a href="#">610443</a>	KOOLEN-DE VRIES SYNDROME; KDVS
<a href="#">612452</a>	KAT8 REGULATORY NSL COMPLEX, SUBUNIT 1; KANSL1

## Molecular Pathogenesis

*De novo* pathogenic variants in *KANSL1* were identified in children with clinical features that are in keeping with the phenotype seen in individuals with a classic 17q21.31 deletion, demonstrating that *KANSL1* is the primary gene involved in this deletion syndrome [Koolen et al 2012b, Zollino et al 2012].

*KANSL1* encodes KAT8 regulatory NSL complex subunit 1 (KANSL1), the longer isoform of which (NP\_001180395.1) has 1,105 amino acids. KANSL1 is a scaffold protein of the nonspecific lethal complex that contains the histone acetyltransferase MOF, which acetylates histone H4 on lysine 16 (H4K16ac) to facilitate transcriptional activation [Mendjan et al 2006].

H4K16ac activates the expression of a broad set of genes including several autophagy-related genes [Füllgrabe et al 2013]. Autophagy is a catabolic process important for the clearance of protein aggregates and damaged organelles within the cell, which is essential for cell homeostasis and survival. Autophagy is essential in neurons, not only for cell homeostasis but also for regulation of development and function [Shehata et al 2012, Tang et al 2014].

Studies in mice have shown that heterozygous loss of *Kansl1* leads to changes in gene expression related to synaptic transmission and to a decrease in basal synaptic transmission and plasticity [Arbogast et al 2017], but the underlying cellular mechanisms remain unknown.

Linda et al [2022] reported that KANSL1 deficiency leads to increased oxidative stress and autophagosome formation in iPSCs and iNeurons. In neurons, increased reactive oxygen species (ROS)-activated autophagy reduced neuronal synaptic connectivity and activity. The observed neuronal phenotype could be rescued by treatment with apocynin, an antioxidant that reduced oxidative stress and autophagosome accumulation. These findings were supported by the study of Li et al [2022], in which *KANSL1* was identified as an essential gene for autophagy using siRNA screening. *Kansl1*<sup>+/-</sup> mice exhibit impairment in the autophagic clearance of damaged mitochondria and accumulation of reactive oxygen species, thereby resulting in defective neuronal and cardiac function.

**Laboratory technical considerations.** Genetic testing of the 17q21.31 genomic region is challenging. The mapping and interpretation of the deletion breakpoints are confounded by the structural complexity and genomic variation of the 17q21.31 locus [Koolen et al 2016]. Two haplotypes exist, in direct (H1) and inverted (H2) orientation [Stefansson et al 2005]. The H2 haplotype is enriched in Europeans, and those with this haplotype are predisposed to the 17q21.31 deletion [Koolen et al 2006, Sharp et al 2006, Koolen et al 2008, Zody et al 2008]. However, the frequency of *de novo* 17q21.31 deletions in those with the H2 inversion is low, and other as yet poorly understood factors are likely to be important in the generation of the deletion.

The 17q21.31 inversion polymorphism (H2 haplotype) and the copy number polymorphism clusters encompassing exons 1-3 of *KANSL1* contribute to difficulties in single nucleotide variant calling, such as loss-of-function variant "artifacts" in *KANSL1* [Koolen et al 2016]. The detection of a truncating variant in exons 1-3 of *KANSL1* is not sufficient to make a diagnosis of KdVS. In these cases, a compatible clinical phenotype and variant analysis of parental samples is of the utmost importance to verify that the possibly pathogenic variant occurred *de novo*.

**Mechanism of disease causation.** Loss of function. The 17q21.31 deletion is typically 500 to 650 kb in size (hg19: chr17:43700000-44250000) and is flanked by segmental duplications that mediate nonallelic homologous recombination [Itsara et al 2012].

## Chapter Notes

### Author Notes

Radboudumc Center of Expertise: [rare congenital developmental disorders](#)

### Acknowledgments

The authors gratefully acknowledge the [KdVS Foundation](#), other support groups and the parents/caregivers for their participation in research and for their generous sharing of information.

### Revision History

- 2 February 2023 (ma) Comprehensive update posted live
- 13 June 2019 (ma) Comprehensive update posted live
- 20 November 2012 (me) Comprehensive update posted live
- 26 January 2010 (me) Review posted live
- 28 August 2009 (dak) Original submission



## References

### Literature Cited

- Amenta S, Frangella S, Marangi G, Lattante S, Ricciardi S, Doronzio PN, Orteschi D, Veredice C, Contaldo I, Zampino G, Gentile M, Scarano E, Graziano C, Zollino M. Adult phenotype in Koolen-de Vries/*KANSL1* haploinsufficiency syndrome. *J Med Genet.* 2022;59:189-95. PubMed PMID: 33361104.
- Arbogast T, Iacono G, Chevalier C, Afinowi NO, Houbaert X, van Eede MC, Laliberte C, Birling MC, Linda K, Meziane H, Selloum M, Sorg T, Nadif Kasri N, Koolen DA, Stunnenberg HG, Henkelman RM, Kopanitsa M, Humeau Y, De Vries BBA, Hérault Y. Mouse models of 17q21.31 microdeletion and microduplication syndromes highlight the importance of *Kansl1* for cognition. *PLoS Genet.* 2017;13:e1006886. PubMed PMID: 28704368.
- Aref-Eshghi E, Kerkhof J, Pedro VP, Groupe DI. France, Barat-Houari M, Ruiz-Pallares N, Andrau JC, Lacombe D, Van-Gils J, Fergelot P, Dubourg C, Cormier-Daire V, Rondeau S, Lecoquierre F, Saugier-Weber P, Nicolas G, Lesca G, Chatron N, Sanlaville D, Vitobello A, Faivre L, Thauvin-Robinet C, Laumonnier F, Raynaud M, Alders M, Mannens M, Henneman P, Hennekam RC, Velasco G, Francastel C, Ulveling D, Ciolfi A, Pizzi S, Tartaglia M, Heide S, Héron D, Mignot C, Keren B, Whalen S, Afenjar A, Bienvenu T, Campeau PM, Rousseau J, Levy MA, Brick L, Kozenko M, Balci TB, Siu VM, Stuart A, Kadour M, Masters J, Takano K, Kleefstra T, de Leeuw N, Field M, Shaw M, Gecz J, Ainsworth PJ, Lin H, Rodenhiser DI, Friez MJ, Tedder M, Lee JA, DuPont BR, Stevenson RE, Skinner SA, Schwartz CE, Genevieve D, Sadikovic B. Evaluation of DNA methylation epigenatures for diagnosis and phenotype correlations in 42 mendelian neurodevelopmental disorders. *Am J Hum Genet.* 2020;106:356-70. PubMed PMID: 32109418.
- Cooper GM, Coe BP, Girirajan S, Rosenfeld JA, Vu TH, Baker C, Williams C, Stalker H, Hamid R, Hannig V, Abdel-Hamid H, Bader P, McCracken E, Niyazov D, Leppig K, Thiese H, Hummel M, Alexander N, Gorski J, Kussmann J, Shashi V, Johnson K, Rehder C, Ballif BC, Shaffer LG, Eichler EE. A copy number variation morbidity map of developmental delay. *Nat Genet.* 2011;43:838-46. PubMed PMID: 21841781.
- Dubourg C, Sanlaville D, Doco-Fenzy M, Le Caignec C, Missirian C, Jaillard S, Schluth-Bolard C, Landais E, Boute O, Philip N, Toutain A, David A, Edery P, Moncla A, Martin-Coignard D, Vincent-Delorme C, Mortemousque I, Duban-Bedu B, Drunat S, Beri M, Mosser J, Odent S, David V, Andrieux J. Clinical and molecular characterization of 17q21.31 microdeletion syndrome in 14 French patients with mental retardation. *Eur J Med Genet.* 2011;54:144-51. PubMed PMID: 21094706.
- El Chehadeh-Djebbar S, Callier P, Masurel-Paulet A, Bensignor C, Méjean N, Payet M, Ragon C, Durand C, Marle N, Mosca-Boidron AL, Huet F, Mugneret F, Faivre L, Thauvin-Robinet C. 17q21.31 microdeletion in a patient with pituitary stalk interruption syndrome. *Eur J Med Genet.* 2011;54:369-73. PubMed PMID: 21397059.
- Farnè M, Bernardini L, Capalbo A, Cavarretta G, Torres B, Sanchini M, Fini S, Ferlini A, Bigoni S. Koolen-de Vries syndrome in a 63-year old woman: report of the oldest patient and review of the adult phenotype. *Am J Med Genet A.* 2022;188:692-707. PubMed PMID: 34665525.
- Füllgrabe J, Lynch-Day MA, Heldring N, Li W, Struijk RB, Ma Q, Hermanson O, Rosenfeld MG, Klionsky DJ, Joseph B. The histone H4 lysine 16 acetyltransferase hMOF regulates the outcome of autophagy. *Autophagy.* 2013;9:1621-3. PubMed PMID: 23934085.
- Grieco JC, Bahr RH, Schoenberg MR, Conover L, Mackie LN, Weeber EJ. Quantitative measurement of communication ability in children with Angelman syndrome. *J Appl Res Intellect Disabil.* 2018;31:e49-e58. PubMed PMID: 27990716.

- Grisart B, Willatt L, Destrée A, Fryns JP, Rack K, de Ravel T, Rosenfeld J, Vermeesch JR, Verellen-Dumoulin C, Sandford R. 17q21.31 microduplication patients are characterised by behavioural problems and poor social interaction. *J Med Genet.* 2009;46:524-30. PubMed PMID: 19502243.
- Itsara A, Vissers LE, Steinberg KM, Meyer KJ, Zody MC, Koolen DA, de Ligt J, Cuppen E, Baker C, Lee C, Graves TA, Wilson RK, Jenkins RB, Veltman JA, Eichler EE. Resolving the breakpoints of the 17q21.31 microdeletion syndrome with next-generation sequencing. *Am J Hum Genet.* 2012;90:599-613. PubMed PMID: 22482802.
- Kirchhoff M, Bisgaard AM, Duno M, Hansen FJ, Schwartz M. A 17q21.31 microduplication, reciprocal to the newly described 17q21.31 microdeletion, in a girl with severe psychomotor developmental delay and dysmorphic craniofacial features. *Eur J Med Genet.* 2007;50:256-63. PubMed PMID: 17576104.
- Kitsiou-Tzeli S, Frysira H, Giannikou K, Syrmou A, Kosma K, Kakourou G, Leze E, Sofocleous C, Kanavakis E, Tzetis M. Microdeletion and microduplication 17q21.31 plus an additional CNV, in patients with intellectual disability, identified by array-CGH. *Gene.* 2012;492:319-24. PubMed PMID: 22037486.
- Koolen DA, Dupont J, de Leeuw N, Vissers LE, van den Heuvel SP, Bradbury A, Steer J, de Brouwer AP, Ten Kate LP, Nillesen WM, de Vries BB, Parker MJ. Two families with sibling recurrence of the 17q21.31 microdeletion syndrome due to low-grade mosaicism. *Eur J Hum Genet.* 2012a;20:729-33. PubMed PMID: 22293690.
- Koolen DA, Kramer JM, Neveling K, Nillesen WM, Moore-Barton HL, Elmslie FV, Toutain A, Amiel J, Malan V, Tsai AC, Cheung SW, Gilissen C, Verwiel ET, Martens S, Feuth T, Bongers EM, de Vries P, Scheffer H, Vissers LE, de Brouwer AP, Brunner HG, Veltman JA, Schenck A, Yntema HG, de Vries BB. Mutations in the chromatin modifier gene *KANSL1* cause the 17q21.31 microdeletion syndrome. *Nat Genet.* 2012b;44:639-41. PubMed PMID: 22544363.
- Koolen DA, Pfundt R, Linda K, Beunders G, Veenstra-Knol HE, Conta JH, Fortuna AM, Gillessen-Kaesbach G, Dugan S, Halbach S, Abdul-Rahman OA, Winesett HM, Chung WK, Dalton M, Dimova PS, Mattina T, Prescott K, Zhang HZ, Saal HM, Hehir-Kwa JY, Willemsen MH, Ockeloen CW, Jongmans MC, Van der Aa N, Failla P, Barone C, Avola E, Brooks AS, Kant SG, Gerkes EH, Firth HV, Öunap K, Bird LM, Masser-Frye D, Friedman JR, Sokunbi MA, Dixit A, Splitt M; DDD Study, Kukulich MK, McGaughran J, Coe BP, Flórez J, Nadif Kasri N, Brunner HG, Thompson EM, Geçiz J, Romano C, Eichler EE, de Vries BB. The Koolen-de Vries syndrome: a phenotypic comparison of patients with a 17q21.31 microdeletion versus a *KANSL1* sequence variant. *Eur J Hum Genet.* 2016;24:652-9. PubMed PMID: 26306646.
- Koolen DA, Sharp AJ, Hurst JA, Firth HV, Knight SJ, Goldenberg A, Saugier-veber P, Pfundt R, Vissers LE, Destrée A, Grisart B, Rooms L, Van der Aa N, Field M, Hackett A, Bell K, Nowaczyk MJ, Mancini GM, Poddighe PJ, Schwartz CE, Rossi E, De Gregori M, Antonacci-Fulton LL, McLellan MD 2nd, Garrett JM, Wiechert MA, Miner TL, Crosby S, Ciccone R, Willatt L, Rauch A, Zenker M, Aradhya S, Manning MA, Strom TM, Wagenstaller J, Krepischi-Santos AC, Vianna-Morgante AM, Rosenberg C, Price SM, Stewart H, Shaw-Smith C, Brunner HG, Wilkie AO, Veltman JA, Zuffardi O, Eichler EE, de Vries BB. Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. *J Med Genet.* 2008;45:710-20. PubMed PMID: 18628315.
- Koolen DA, Vissers LE, Pfundt R, de Leeuw N, Knight SJ, Regan R, Kooy RF, Reyniers E, Romano C, Fichera M, Schinzel A, Baumer A, Anderlid BM, Schoumans J, Knoers NV, van Kessel AG, Sistermans EA, Veltman JA, Brunner HG, de Vries BB. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. *Nat Genet.* 2006;38:999-1001. PubMed PMID: 16906164.
- Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet

- C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dymont D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation epigenatures expand and refine the epigenetic landscapes of mendelian disorders. *HGG Adv*. 2021;3:100075. PubMed PMID: 35047860.
- Li T, Lu D, Yao C, Li T, Dong H, Li Z, Xu G, Chen J, Zhang H, Yi X, Zhu H, Liu G, Wen K, Zhao H, Gao J, Zhang Y, Han Q, Li T, Zhang W, Zhao J, Li T, Bai Z, Song M, He X, Zhou T, Xia Q, Li A, Pan X. Kansl1 haploinsufficiency impairs autophagosome-lysosome fusion and links autophagic dysfunction with Koolen-de Vries syndrome in mice. *Nat Commun*. 2022;13:931. PubMed PMID: 35177641.
- Linda K, Lewerissa EI, Verboven AHA, Gabriele M, Frega M, Klein Gunnewiek TM, Devilee L, Ulferts E, Hommersom M, Oudakker A, Schoenmaker C, van Bokhoven H, Schubert D, Testa G, Koolen DA, de Vries BBA, Nadif Kasri N. Imbalanced autophagy causes synaptic deficits in a human model for neurodevelopmental disorders. *Autophagy*. 2022;18:423-42. PubMed PMID: 34286667.
- Mendjan S, Taipale M, Kind J, Holz H, Gebhardt P, Schelder M, Vermeulen M, Buscaino A, Duncan K, Mueller J, Wilm M, Stunnenberg HG, Saumweber H, Akhtar A. Nuclear pore components are involved in the transcriptional regulation of dosage compensation in *Drosophila*. *Mol Cell*. 2006;21:811-23. PubMed PMID: 16543150.
- Moreno-Igoa M, Hernández-Charro B, Bengoa-Alonso A, Pérez-Juana-del-Casal A, Romero-Ibarra C, Nieva-Echebarria B, Ramos-Arroyo MA. KANSL1 gene disruption associated with the full clinical spectrum of 17q21.31 microdeletion syndrome. *BMC Med Genet*. 2015;16:68. PubMed PMID: 26293599.
- Morgan AT, Haafte LV, van Hulst K, Edley C, Mei C, Tan TY, Amor D, Fisher SE, Koolen DA. Early speech development in Koolen de Vries syndrome limited by oral praxis and hypotonia. *Eur J Hum Genet*. 2018a;26:75-84. PubMed PMID: 29225339.
- Morgan AT, Murray E, Liégeois FJ. Interventions for childhood apraxia of speech. *Cochrane Database Syst Rev*. 2018b;5:CD006278. PubMed PMID: 29845607.
- Myers KA, Mandelstam SA, Ramantani G, Rushing EJ, de Vries BB, Koolen DA, Scheffer IE (2017) The epileptology of Koolen-de Vries syndrome: electro-clinico-radiologic findings in 31 patients. *Epilepsia*. 58:1085-94. PubMed PMID: 28440867.
- Paolo P, Matteo F, Rossella L, Anna M, Rosario C, Paola G, Cristiano T, Giorgio R. Koolen-de Vries syndrome: preliminary observations of topiramate efficacy. *Child Neurol Open*. 2021;8:2329048X211019183.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-24. PubMed PMID: 25741868.
- Sharp AJ, Hansen S, Selzer RR, Cheng Z, Regan R, Hurst JA, Stewart H, Price SM, Blair E, Hennekam RC, Fitzpatrick CA, Segreaves R, Richmond TA, Guiver C, Albertson DG, Pinkel D, Eis PS, Schwartz S, Knight SJ, Eichler EE. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. *Nat Genet*. 2006;38:1038-42. PubMed PMID: 16906162.
- Shaw-Smith C, Pittman AM, Willatt L, Martin H, Rickman L, Gribble S, Curley R, Cumming S, Dunn C, Kalaitzopoulos D, Porter K, Prigmore E, Krepischi-Santos AC, Varela MC, Koiffmann CP, Lees AJ, Rosenberg C, Firth HV, de Silva R, Carter NP. Microdeletion encompassing MAPT at chromosome 17q21.3 is associated with developmental delay and learning disability. *Nat Genet*. 2006;38:1032-7. PubMed PMID: 16906163.

- Shehata M, Matsumura H, Okubo-Suzuki R, Ohkawa N, Inokuchi K. Neuronal stimulation induces autophagy in hippocampal neurons that is involved in AMPA receptor degradation after chemical long-term depression. *J Neurosci*. 2012;32:10413-22. PubMed PMID: 22836274.
- Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, Barnard J, Baker A, Jonasdottir A, Ingason A, Gudnadottir VG, Desnica N, Hicks A, Gylfason A, Gudbjartsson DE, Jonsdottir GM, Sainz J, Agnarsson K, Birgisdottir B, Ghosh S, Olafsdottir A, Cazier JB, Kristjansson K, Frigge ML, Thorgeirsson TE, Gulcher JR, Kong A, Stefansson K. A common inversion under selection in Europeans. *Nat Genet*. 2005;37:129-37. PubMed PMID: 15654335.
- St John M, van Reyk O, Koolen DA, de Vries BBA, Amor DJ, Morgan AT. Expanding the speech and language phenotype in Koolen-de Vries syndrome: late onset and periodic stuttering a novel feature. *Eur J Hum Genet*. 2023;31:531-40. PubMed PMID: 36529818.
- Tan TY, Aftimos S, Worgan L, Susman R, Wilson M, Ghedia S, Kirk EP, Love D, Ronan A, Darmanian A, Slavotinek A, Hogue J, Moeschler JB, Ozmore J, Widmer R, Bruno D, Savarirayan R, Peters G. Phenotypic expansion and further characterisation of the 17q21.31 microdeletion syndrome. *J Med Genet*. 2009;46:480-9. PubMed PMID: 19447831.
- Tang P, Hou H, Zhang L, Lan X, Mao Z, Liu D, He C, Du H, Zhang L. Autophagy reduces neuronal damage and promotes locomotor recovery via inhibition of apoptosis after spinal cord injury in rats. *Mol Neurobiol*. 2014;49:276-87. PubMed PMID: 23954967.
- Terrone G, D'Amico A, Imperati F, Carella M, Palumbo O, Gentile M, Canani RB, Melis D, Romano A, Parente I, Riccitelli M, Del Giudice E. A further contribution to the delineation of the 17q21.31 microdeletion syndrome: central nervous involvement in two Italian patients. *Eur J Med Genet*. 2012;55:466-71. PubMed PMID: 22659270.
- Wright EB, Donnai D, Johnson D, Clayton-Smith J. Cutaneous features in 17q21.31 deletion syndrome: a differential diagnosis for cardio-facio-cutaneous syndrome. *Clin Dysmorphol*. 2011;20:15-20. PubMed PMID: 21084979.
- Zody MC, Jiang Z, Fung HC, Antonacci F, Hillier LW, Cardone MF, Graves TA, Kidd JM, Cheng Z, Abouelleil A, Chen L, Wallis J, Glasscock J, Wilson RK, Reily AD, Duckworth J, Ventura M, Hardy J, Warren WC, Eichler EE. Evolutionary toggling of the MAPT 17q21.31 inversion region. *Nat Genet*. 2008;40:1076-83. PubMed PMID: 19165922.
- Zollino M, Marangi G, Ponzi E, Orteschi D, Ricciardi S, Lattante S, Murdolo M, Battaglia D, Contaldo I, Mercuri E, Stefanini MC, Caumes R, Edery P, Rossi M, Piccione M, Corsello G, Della Monica M, Scarano F, Priolo M, Gentile M, Zampino G, Vijzelaar R, Abdulrahman O, Rauch A, Oneda B, Deardorff MA, Saitta SC, Falk MJ, Dubbs H, Zackai E. Intragenic KANSL1 mutations and chromosome 17q21.31 deletions: broadening the clinical spectrum and genotype-phenotype correlations in a large cohort of patients. *J Med Genet* 2015;52:804-14. PubMed PMID: 26424144.
- Zollino M, Orteschi D, Murdolo M, Lattante S, Battaglia D, Stefanini C, Mercuri E, Chiurazzi P, Neri G, Marangi G. Mutations in KANSL1 cause the 17q21.31 microdeletion syndrome phenotype. *Nat Genet*. 2012;44:636-8. PubMed PMID: 22544367.

## License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No

further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: [admasst@uw.edu](mailto:admasst@uw.edu).