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Koolen-de Vries Syndrome

Synonym: KdVS

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Summary

Clinical characteristics

Koolen-de Vries syndrome (KdVS) is characterized by developmental delay / intellectual disability, neonatal/childhood hypotonia, dysmorphisms, congenital malformations, 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 (71% of males). Behavior in most is described as friendly, amiable, and cooperative.

Diagnosis/testing

The diagnosis of Koolen-de Vries syndrome 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: Physiotherapy for gross and fine motor delays; speech therapy to support early feeding challenges and communication development; educational programs directed to specific disabilities identified. Routine treatment of: vision issues / strabismus; hearing loss; cardiac, renal, and urologic problems; epilepsy; scoliosis, hip dislocation, and positional deformities of the feet; multiple nevi.

Surveillance: Routine ophthalmologic examinations for hypermetropia and strabismus; monitoring for progressive spine deformities; routine monitoring for other medication complications depending on the organ system involved.

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Genetic counseling

Koolen-de Vries syndrome, caused by a deletion at 17q21.31 or a pathogenic variant in *KANSL1*, is inherited in an autosomal dominant manner; to date almost all cases result from a *de novo* deletion or *KANSL1* pathogenic variant. Thus, most affected individuals represent simplex cases (i.e., a single occurrence in a family). The recurrence risk for future pregnancies is low (probably <1%) but greater than that of the general population because of the possibility of germline mosaicism in one of the parents. Prenatal testing is technically feasible, but the likelihood of recurrence in families who have had an affected child is low.

Diagnosis

Suggestive Findings

Koolen-de Vries syndrome (KdVS) **should be suspected** in individuals presenting with mild-to-moderate developmental delay or intellectual disability in which speech and language development is particularly affected, in combination with additional clinical findings.

Additional clinical findings

- 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

Establishing the Diagnosis

The diagnosis of Koolen-de Vries syndrome **is established** in a proband with typical clinical findings and detection of any of the following (see Table 1):

- A heterozygous deletion at chromosome 17q21.31 that includes *KANSL1* (~95% of affected individuals) [Koolen et al 2006, Sharp et al 2006, Shaw-Smith et al 2006]. The 17q21.31 deletion is typically 500- to 650-kb in size (hg19: chr17:43,700,000-44,250,000) and is flanked by segmental duplications.
- A heterozygous intragenic pathogenic variant in *KANSL1* (~5% of affected individuals) [Koolen et al 2012b, Zollino et al 2012, Zollino et al 2015, Koolen et al 2016].
- Haploinsufficiency of *KANSL1* due to chromosome rearrangements [Moreno-Igoa et al 2015].

Molecular genetic testing approaches can include a combination of **chromosomal microarray (CMA)**, **single-gene testing**, a **multigene panel**, and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing).

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. CMA is recommended first because deletions are identified in ~95% of probands (see Table 1). The ability to determine the size of the deletion depends on the type of microarray used and the density of probes in the 17q21.31 region.

If chromosomal microarray does not identify the cause of the individual's features, gene-targeted testing, which requires that the clinician to determine which gene(s) are likely involved, or genomic testing may be considered. Because the phenotype of KdVS is broad, individuals with the distinctive findings described in Suggestive

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

Findings may 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 other genomic testing (see Option 2).

Option 1

If a chromosome 17q21.31 deletion is not identified on CMA, testing options include the following:

- **Single-gene testing.** Sequence analysis of *KANSL1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications that may have been missed on CMA.
- An **intellectual disability multigene panel** that includes *KANSL1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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 the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

If a 17q21.31 deletion is not identified on CMA and an intragenic pathogenic variant has not been identified on either a multigene panel or comprehensive genomic testing (genomic sequencing and exome array), 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 [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KANSL1	CMA [3, 4]	~95% [5]
	Sequence analysis [6]	~5%
	Gene-targeted deletion/duplication analysis [7]	See footnote 8
	Karyotype (to detect structural variants)	Rare [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. The majority of affected individuals are identified by a genome-wide CMA screen for deletions/duplications that includes probe coverage of *KANSL1*. The ability to size the deletion depends on the type of microarray used and the density of probes in the 17q21.31 region. It is too early to ascertain the frequency of the 17q21.31 microdeletion and a *KANSL1* pathogenic 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 microdeletion occurs more frequently.
4. 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).
5. 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.
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. 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].
9. 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 disability, dysmorphisms (Figure 1), speech and language delays, congenital malformations, and behavioral features (Table 2). Males and females are affected equally.

Table 2. Features of Koolen-de Vries Syndrome

Frequency	Feature
Very common (>75% of individuals)	• Distinctive facial features (see **Dysmorphic craniofacial features** following table) • Hypotonia (neonatal/childhood) • Developmental delay / intellectual disability • Speech & language delay • Friendly/amiable disposition

Table 2. continued from previous page.

Frequency	Feature

Common (50%-75%)	• Structural brain anomalies
	  ◦ Ventriculomegaly
	  ◦ Aplasia/hypoplasia of corpus callosum
	  ◦ Hydrocephalus
	  ◦ Arnold-Chiari type I malformation
	  ◦ Intraventricular hemorrhage
	• Joint hypermobility &/or joint dislocation/dysplasia

Less common (25%-50%)	• Seizures
	• Visual impairment
	  ◦ Hypermetropia
	  ◦ Strabismus
	  ◦ Congenital cataract
	  ◦ Optic atrophy
	• Abnormality of the heart
	  ◦ Ventricular septal defect
	  ◦ Atria septal defect
	  ◦ Bicuspid aortic valve
	  ◦ Cardiomyopathy
	  ◦ Aortic dilatation
	• Renal & urogenital anomalies
	  ◦ Cryptorchidism
	  ◦ Hydronephrosis / vesicoureteral reflux
	  ◦ Renal duplication
	  ◦ Fetal pyelectasis
	• Hypospadias
	• Feeding difficulties
	• Long fingers
	• *Pes planus* / *pes cavus* / calcaneovalgus deformity

Occasional (10%-25%)	• Anxiety • Attention-deficit/hyperactivity disorder • Hearing impairment • Scoliosis/kyphosis • Tracheo-/laryngeomalacia • Pectus excavatum/carinatum • Slender build • Multiple nevi • Fair hair
Infrequent (<10%)	• Autistic behavior • Craniosynostosis • Sacral dimple • Spondylolisthesis • Dural ectasia • Spina bifida • Pineal cyst • Cervical spinal canal stenosis • Recurrent urinary tract infections • Recurrent respiratory infections • Recurrent otitis media • Eczema • Hypopigmentation of the skin / vitiligo • Alopecia • Café au lait spots • Ichthyosis/hyperkeratosis • Growth hormone deficiency

Table 2. continued from previous page.

Frequency	Feature
	• Hypothyroidism • Precocious puberty • Primary adrenal insufficiency • Melanoma • Testicular neoplasm • Hemangioma

Clinical information based on data entered in the HDG website Series

Dysmorphic craniofacial features that may suggest KdVS:

- Upslanted palpebral fissure
- 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 form of the nose may become more apparent.

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 problems chewing difficult, lumpy, or solid textures [Morgan et al 2018a].

Psychomotor developmental delay is noted in all 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].
  - First words occur between ages 2.5 and 3.5 years on average.
  - Childhood apraxia of speech (CAS) is common in these 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 is present in a handful of cases (17%), and has been noted in adolescence only.
- Receptive and expressive language abilities are typically commensurate (79%), both being severely affected relative to peers.
- Children are reported as sociable with a desire to communicate; in some individuals (36%) social skill impairments appear with increasing age and increasing social demands.

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.
- Structural brain abnormalities may be universal, including signs of abnormal neuroblast migration and abnormal axonal guidance (see Table 2).

Other common findings (see Table 2) include dental anomalies, slender long fingers, persistence of the fetal fingertip pads, hypoplasia of the hand muscles, slender lower limbs, joint hypermobility, hip dislocation, and positional deformities of the feet. In addition, multiple nevi, other pigmentary skin abnormalities, and hair abnormalities have been reported [Wright et al 2011, Zollino et al 2015, Koolen et al 2016].

- **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.
- **Scoliosis** is the most commonly observed spine anomaly; lordosis and kyphosis have also been reported and sometimes require surgery [Koolen et al 2008, Tan et al 2009].
- **Behavior.** In the vast majority of individuals, behavior is described as friendly, amiable, and cooperative, with or without frequent laughing. However, behavior problems, including attention-deficit/hyperactivity disorder, have been reported [Koolen et al 2008, Tan et al 2009, Koolen et al 2016].

Growth. Short stature is not one of the most common clinical features of the syndrome. However, El Chehadeh-Djebbar et al [2011] reported on a child with a 17q21.31 deletion, short stature (-4 SD), 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.

Life span. Longitudinal data are insufficient to determine life expectancy, although survival into adulthood is typical.

Genotype-Phenotype Correlations

Genotype-phenotype correlations in KdVS have not been shown. 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 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 Koolen-de Vries syndrome is unknown. The authors estimate the prevalence of the 17q21.31 deletion at 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.

Koolen-de Vries syndrome occurs with equal frequency in males and females [Koolen et al 2008].

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*.

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 retardation and behavior problems [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. 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 friendly/amiable behavior may prompt specific consideration of the diagnosis of Koolen-de Vries syndrome. See Table 3 for other diagnoses with developmental delay and intellectual disability that may be considered in affected individuals.

Table 3. Disorders with Developmental Delay and Intellectual Disability to Consider in the Differential Diagnosis of Koolen-de Vries Syndrome (KdVS)

Disorder	Gene / Genetic Mechanism	MOI	Features of Differential Diagnosis Disorder	
			Additional features overlapping w/ KdVS	Distinguishing from KdVS
Deletion 22q11.2 [1] (velocardiofacial syndrome)	22q11.2 deletion	AD [2]	• Long face, narrow palpebral fissures, prominent tubular nose w/ bulbous nasal tip • Ventricular septal defects • Slender hands & digits	• Neonatal hypocalcemia • T-lymphocyte dysfunction • Epilepsy less common

Table 3. continued from previous page.

Disorder	Gene / Genetic Mechanism	MOI	Features of Differential Diagnosis Disorder	
			Additional features overlapping w/ KdVS	Distinguishing from KdVS
Prader-Willi syndrome	Abnormal parent-specific imprinting w/in Prader-Willi critical region	See footnote 3	• Severe neonatal/childhood hypotonia • Seizures • Strabismus • Upslanting palpebral fissures • Cryptorchidism • Blonde to light brown hair	• Childhood hyperphagia • Central obesity • Behavior problems & sleep disturbances more common than in KdVS
Fragile X syndrome	Genetic alteration in *FMR1*	XL	Facial gestalt (adult males w/KdVS may show some coarsening & elongation w/↑ age)	Overactivity, impulsivity, & challenging behavior more common
Angelman syndrome	Disruption of maternally imprinted *UBE3A*	See footnote 4	• Speech & language delay • Feeding problems &/or muscle hypotonia in infancy • Epilepsy	• Microcephaly & seizures common • Gait ataxia &/or tremulous limbs • Inappropriate happy demeanor • More marked & persistent speech delay beyond preschool years (rarely phrase-level speech) [5]
Cardiofaciocutaneous syndrome	*BRAF* [6] *MAP2K1* *MAP2K2* *KRAS*	AD [2]	• Nevi & other pigmentary skin abnormalities • Congenital heart anomalies	• Postnatal short stature • Coarse facies; fine & brittle hair • Cardiac abnormalities more frequent
WAC-related ID	*WAC*	AD [2]	• Neonatal/childhood hypotonia • Language & motor DD • Congenital abnormalities of urogenital system	Epilepsy less common

Table 3. continued from previous page.

Disorder	Gene / Genetic Mechanism	MOI	Features of Differential Diagnosis Disorder	
			Additional features overlapping w/ KdVS	Distinguishing from KdVS
Say-Barber-Biesecker variant of Ohdo syndrome (see *KAT6B*-Related Disorders)	*KAT6B*	AD [2]	• Neonatal hypotonia & feeding difficulties • Blepharophimosis; bulbous nose • Cryptorchidism	• Immobile mask-like face • Patellar hypoplasia/ agenesis • Lacrimal duct anomalies • Hearing loss • Thyroid anomalies

AD = autosomal dominant; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked
1. KdVS may be considered in individuals who tested negative for deletion of 22q11.2.
2. Typically *de novo*
3. The risk to 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.
4. The risk to sibs of a proband with Angelman syndrome depends on the genetic mechanism leading to the loss of *UBE3A* function.
5. Research shows that prognosis for speech in individuals with KdVS is positive; apraxia resolves, and although dysarthria persists, most children are intelligible by mid-to-late childhood [Morgan et al 2018a]. Speech delay in children with Angelman syndrome remains far more severe [Grieco et al 2018], however, there is little published information on communication in individuals with Angelman syndrome.
6. 75% of individuals with cardiofaciocutaneous syndrome have a pathogenic variant in *BRAF*. Three other genes known to be associated with CFC syndrome are: *MAP2K1* and *MAP2K2* (~25%), and *KRAS* (<2%).

Management

Evaluations Following Initial Diagnosis

To establish the clinical consequences in an individual diagnosed with Koolen-de Vries syndrome (KdVS), the following evaluations are recommended if they have not already been completed.

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

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth parameters to identify those w/ failure to thrive	Consider investigation of growth hormone deficiency in individuals w/short stature.
Eyes	Ophthalmology evaluation	
ENT/Mouth	Audiologic examination	
Cardiovascular	Cardiac evaluation	For possible heart anomalies incl septal defects & aortic dilatation
Gastrointestinal/ Feeding	Feeding assessment	Asses for sucking & swallowing difficulties & need for feeding therapy in infancy.
Genitourinary	• Renal ultrasound examination • Voiding cystourethrogram, if indicated	Evaluate for ureteral reflux & other renal problems.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Developmental assessment	To incl motor, speech/language evaluation, general cognitive, & vocational skills
	Neuropsychiatric evaluation	Screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
	Brain imaging studies in individuals w/microcephaly &/or seizure	Consideration of a Chiari malformation type 1 in those w/ suggestive symptoms (headache, neck pain, cerebellar signs, or muscle weakness) [1]
	EEG if seizures are suspected	Referral to neurologist for seizure disorder management
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder

1. Terrone et al [2012]

Treatment of Manifestations

Treatment includes routine medical care by a pediatrician or other primary physician and the following.

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

Manifestation/ Concern	Treatment	Considerations/Other
Feeding problems & motor delay related to hypotonia	Early intervention / feeding therapy / physiotherapy	Nasogastric tube feeding may be required for neonates w/severe feeding issues.
Vision issues / strabismus	Standard management for visual problems as directed by ophthalmologist	
Hearing loss	Standard management	
Cardiac, renal, urologic, & other medical issues	Standard management of specific issue	
Cryptorchidism	Treatment by urologist, if indicated	
Seizures	Standard treatment / routine antiepileptic drugs under care of neurologist	
Speech & language	• Speech production requires intensive motor speech treatment in preschool yrs. • Language development requires focused intervention & augmentative (sign language) or alternative (communication device) support until oral speech & language develops. • Feeding abilities – support development of chewing. • Early sound awareness to support literacy development • In older children, work on social skill development.	
Scoliosis / Hip dislocation / Positional deformities of the feet	Standard orthopedic care	
Multiple nevi	Regular checkup by dermatologist if multiple nevi present	

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.

Developmental Disability / 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.

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. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

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] 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

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

System/Concern	Evaluation	Frequency
Constitutional	Ongoing pediatric care	
Eyes	Ophthalmology evaluation due to ↑ risk for hypermetropia & strabismus	Routine intervals
Cardiovascular	Monitoring as needed	
Genitourinary	Monitoring as needed	
Musculoskeletal	Monitoring for spine deformities/scoliosis	Routine intervals until growth is complete
Neurologic	Specialized neurologic care for individuals w/epilepsy	
Miscellanous/ Other	Monitor developmental progress & educational needs	

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 in the US and EU Clinical Trials Register 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Koolen-de Vries syndrome (KdVS), caused by a heterozygous deletion at 17q21.31 or a heterozygous intragenic *KANSL1* pathogenic variant, is inherited in an autosomal dominant manner. 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. FISH analysis in the parents to evaluate for a balanced insertion and/or translocations may also be considered. Note: Testing for the 17q21.31 inversion polymorphism is not recommended (see Molecular Genetics).
- If the 17q21.31 deletion or intragenic *KANSL1* pathogenic variant cannot be identified in the leukocyte DNA of either parent, the most likely explanation is that the genetic alteration is *de novo* in the proband. Another possible explanation is germline and/or somatic and germline mosaicism in a parent. Somatic and (presumed) germline mosaicism for a 17q21.31 deletion has been identified in at least two parents [Koolen et al 2012a].
- 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, the risk to sibs is low (probably <1%) but greater than that of the general population because the parents may have one of the following:
  - 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 a *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, his or her 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 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the KdVS-related genetic alteration has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

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**
  P.O. Box 928
  Arden NC 28704
  www.koolkidalliance.com
- **Supporting Families with Koolen-de Vries Syndrome**
  Enriching lives through education, awareness and research.
  P.O. Box 470218
  Fort Worth TX 76147
  Phone: 833-721-KDVS
  www.supportingkdvs.org
- **Chromosome Disorder Outreach (CDO)**
  PO Box 724
  Boca Raton FL 33429-0724
  Phone: 561-395-4252 (Family Helpline)
  Email: info@chromodisorder.org
  www.chromodisorder.org
- **Medline Plus**
  Intellectual Disability
- **My46 Trait Profile**
  Koolen-De Vries syndrome
- **Unique: The Rare Chromosome Disorder Support Group**
  G1 The Stables
  Station Road West
  Oxted Surrey RH8 9EE
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org; rarechromo@aol.com
  www.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

  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
KANSL1	17q21.31	KAT8 regulatory NSL complex subunit 1	KANSL1 @ LOVD	KANSL1	KANSL1
Not applicable	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)

610443	KOOLEN-DE VRIES SYNDROME; KDVS
612452	KAT8 REGULATORY NSL COMPLEX, SUBUNIT 1; KANSL1

17q21.31 Deletion

The 17q21.31 deletion is typically 500 to 650 kb in size (hg19: chr17:43,700,000-44,250,000) and is flanked by segmental duplications that mediate nonallelic homologous recombination [Itsara et al 2012]. 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 carriers are predisposed to the 17q21.31 microdeletion [Koolen et al 2006, Sharp et al 2006, Koolen et al 2008, Zody et al 2008]. The frequency of *de novo* 17q21.31 microdeletions in carriers of the H2 inversion is low, and other as-yet poorly understood factors are likely to be important in the generation of the deletion.

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

KANSL1

Gene structure. *KANSL1* has several transcript variants. The longest, NM_001193466.1, has 15 exons. For a detailed summary of gene, transcript, and protein information see Table A, **Gene**.

Pathogenic variants. To date, all pathogenic *KANSL1* variants reported are truncating variants. [Koolen et al 2012b, Zollino et al 2012, Zollino et al 2015, Koolen et al 2016].

Table 7. Selected *KANSL1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.916C>T	p.Gln306Ter	NM_001193466.1 NP_001180395.1
c.1816C>T	p.Arg606Ter	
c.1652+1G>A	See footnote 1	
c.2785_2786delAG	p.Arg929GlyfsTer44	
c.1867_1870del	p.Ile623AlafsTer6	
c.985_986del	p.Leu329GlufsTer22	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Splice-site variant resulting in skipping of exon 6, causing a frameshift and premature termination of the *KANSL1* mRNA [Koolen et al 2012b]

The 17q21.31 inversion polymorphism (H2 haplotype) and the copy number polymorphism clusters encompassing exons 1–3 of KANSL1 contribute to difficulties in SNV calling, such as loss-of-function variant "artefacts" 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, next to a compatible clinical phenotype, variant analysis of the parental samples is of the utmost importance to verify that the possibly pathogenic variant occurred *de novo*.

Normal gene product. *KANSL1* encodes KAT8 regulatory NSL complex subunit 1, 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].

Abnormal gene product. 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. H4K16ac is known to be essential for the regulation of autophagy, a process controlling degradation and recycling of proteins and shown to play a role in synapse development and function. Disruption in autophagy can therefore lead to impairments in neuronal development and synaptic transmission and could play an essential role in the pathophysiology of KdVS.

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Chapter Notes

Author Notes

Radboudumc Center of Expertise Rare Congenital Developmental Disorders Website

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- 20 November 2012 (me) Comprehensive update posted live
- 26 January 2010 (me) Review posted live
- 28 August 2009 (dak) Original submission

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