Koolen-De Vries Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK24676/

SummaryClinical 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.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.

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DiagnosisNo consensus clinical diagnostic criteria for Koolen-de Vries syndrome (KdVS) have been published.Suggestive FindingsKdVS 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 affectedANDNeonatal/childhood hypotonia and feeding difficultiesEpilepsyDysmorphic facial features (See Clinical Description and Figure 1.)HypermetropiaCongenital heart anomaliesCongenital renal/urologic anomaliesHypermobility of the joints and/or joint dislocation/dysplasiaDeformities of the spine and/or feetFigure 1. Photographs of eight individuals with a 17q21.31 deletion 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 DiagnosisThe 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]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 1When 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

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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 episignature 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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

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[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.
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Suggestive FindingsKdVS 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 affectedANDNeonatal/childhood hypotonia and feeding difficultiesEpilepsyDysmorphic facial features (See Clinical Description and Figure 1.)HypermetropiaCongenital heart anomaliesCongenital renal/urologic anomaliesHypermobility of the joints and/or joint dislocation/dysplasiaDeformities of the spine and/or feetFigure 1. Photographs of eight individuals with a 17q21.31 deletion 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).

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Hypermetropia

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

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Establishing the DiagnosisThe 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]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 1When 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 2When 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

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10.Karyotype (to detect structural variants)Rare 111. 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

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Molecular Genetic Testing Used in Koolen-de Vries Syndrome

Gene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method
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Clinical CharacteristicsClinical DescriptionKoolen-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 FeaturesView in own windowFeatureFrequencyVery common 1Common 2Less common 3Occasional 4CommentsDistinctive facial features●See Dysmorphic craniofacial features after this table.Developmental delay / intellectual disability●Particularly in areas of speech & language delayHypotonia●Neonatal/childhoodStructural brain anomalies●Incl ventriculomegaly, corpus callosum anomalies, Arnold-Chiari type I malformation, & intraventricular hemorrhageJoint hypermobility●Incl joint dislocation/dysplasiaSeizures/epilepsy●Friendly/amiable disposition●Visual impairment●Hypermetropia, strabismus, congenital cataract, optic atrophyCongenital heart defects●VSD, ASD, bicuspid aortic valve, cardiomyopathy, aortic root dilatationGenitourinary anomalies●Cryptorchidism, hypospadias, hydronephrosis/VUR, renal duplicationFeeding difficulties●Musculoskeletal anomalies●Long fingers, pes

planus, pes cavus, calcaneovalgus deformity, scoliosis/kyphosis, pectus anomaliesAnxiety●ADHD●Hearing impairment●Most commonly conductive, although sensorineural hearing loss has been reportedTracheo-/laryngomalacia●Integument●Multiple nevi, fair hair, hemangioma, café au lait maculesBased on data from the Human Disease Genes websiteADHD = attention-deficit/hyperactivity disorder; ASD = atrial septal defect; VSD = ventriculoseptal defect; VUR = vesicoureteral reflux1. Present in more than 75% of affected individuals2. Present in 50%-75% of affected individuals3. Present in 25%-49% of affected individuals4. Present in 10-24% of affected individualsDysmorphic craniofacial features that may suggest KdVS include:Upslanted palpebral fissuresBlepharophimosisEpicanthusPtosisPear-shaped noseBulbous noseLarge/protruding earsThe 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:VentriculomegalyAplasia/hypoplasia of the corpus callosumHydrocephalusArnold-Chiari malformationIntraventricular hemorrhageInfrequent findings (present in fewer than 10% of reported individuals) may include the following:Sacral dimpleDural ectasiaSpina bifidaPineal cystCervical spinal canal stenosisMusculoskeletal. Joint hypermobility is common. Affected individuals may also experience joint dislocations. Other findings can include:Long, slender fingersPersistence of the fetal fingertip padsHypoplasia of the hand musclesPes planusPes cavusCalcaneovalgus deformityCongenital hip dislocationScoliosis/kyphosisPectus anomalies, including pectus excavatum or pectus carinatumSlender buildSpondylolisthesis (infrequently)Craniosynostosis (infrequently), most commonly sagittal, but metopic has also been observedCongenital 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 neviOther pigmentary skin abnormalities, such as vitiligo and café au lait maculesHemangiomaEczemaIchthyosis/hyperkeratosisHair abnormalities, such as fair hair and/or alopeciaNeoplasia. 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 CorrelationsGenotype-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].PenetrancePenetrance 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.NomenclatureThe 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.PrevalenceThe 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.

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Present in 50%-75% of affected individuals

Present in 25%-49% of affected individuals

Present in 10-24% of affected individuals

Upslanted palpebral fissures

Blepharophimosis

Epicanthus

Ptosis

Pear-shaped nose

Bulbous nose

Large/protruding ears

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.

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.

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

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

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.

Genotype-Phenotype CorrelationsGenotype-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].

PenetrancePenetrance 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.

NomenclatureThe 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.

PrevalenceThe 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) DisordersNo 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 DiagnosisThe 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 SyndromeView in own windowGene / GeneticMechanismDisorderMOIClinical CharacteristicsComment22q11.2 deletion
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ADWide 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.Deletions, maternal UPD, imprinting errors w/in PWCR 1Prader-Willi syndrome (PWS)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 UBE3AAngelman syndrome (AS)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. 3 Speech delay in children w/AS remains far more severe. 4

BRAF

KRAS

MAP2K1

MAP2K2

Cardiofaciocutaneous syndrome (CFC)ADVariable 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.

FMR1

Fragile X syndrome (See FMR1 Disorders.)XLIn 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 & seizuresOveractivity, impulsivity, & challenging behavior are more common in fragile X syndrome than in KdVS.

KAT6B

KAT6B disorders (incl genitopatellar syndrome & Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome)ADBroad phenotypic spectrum w/variable expressivity; DD/ID; hypotonia; genital abnormalities; & skeletal abnormalitiesSevere ID, immobile mask-like facies, & abnormalities of thyroid structure or function are assoc w/KAT6B disorders. Skeletal issues are more common in

KAT6B disorders than in KdVS.

KAT8

KAT8-related intellectual disability (Li-Ghorgani-Weisz-Hubshman syndrome)(OMIM 618974)ADDD/ID, epilepsy, & other developmental anomalies w/variable facial dysmorphismsStriking facial resemblance between KdVS & KAT8-related ID in some affected persons

WAC

WAC-related intellectual disability

ADVariable 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-linked1. 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]

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Morgan et al [2018a]

Grieco et al [2018]

ManagementEvaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Assessment of growth parameters to identify those w/failure to thriveConsider investigation of growth hormone deficiency in persons w/short stature.

Gastrointestinal/

Feeding

Feeding assessmentAssess for sucking & swallowing difficulties & need for feeding therapy in infancy.

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Neurologic

Brain imaging studies in persons w/microcephaly &/or seizureConsideration of Chiari malformation type 1 in those w/suggestive symptoms (headache, neck pain, cerebellar signs, or muscle weakness) 1EEG if seizures are suspectedReferral to neurologist for seizure disorder mgmt

Neurobehavioral/

Psychiatric

Neuropsychiatric evalFor persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD

Eyes

Ophthalmologic evalTo assess for hypermetropia, strabismus, congenital cataract, &/or optic atrophy, which may require referral for subspecialty care &/or low vision services

Hearing

Audiologic examTo assess for hearing loss

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of: Gross motor & fine motor skillsJoint hypermobility, pes planus, calcenovalgus deformity, scoliosis/kyphosis, pectus anomaliesMobility, ADL, & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Cardiovascular

Cardiac eval to incl echocardiogramFor possible heart anomalies incl septal defects & aortic dilatation

Genitourinary

Physical exam for hypospadias & cryptorchidism in malesRenal ultrasound examVoiding cystourethrogram, if indicated

Evaluate for ureteral reflux & other renal findings.

Integument

Full skin examTo assess for hemangiomas & multiple nevi

Respiratory

Upper airway evalIn infants & children w/signs or symptoms suspicious of tracheo-/laryngomalacia

Genetic counseling

By genetics professionals 2To inform affected persons & their families re nature, MOI, & implications of KdVS to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral;Information & resources for sibs of persons w/KdVS.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy1. Terrone et al [2012]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurseTreatment of ManifestationsThere 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 SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Feeding issues & motor delay related to hypotonia

Early intervention / feeding therapy / physiotherapyNasogastric tube feeding may be required for neonates w/severe feeding issues.

Growth hormone deficiency

Growth hormone therapy per endocrinologist

Developmental delay / Intellectual disability

See Developmental Delay / Intellectual Disability Management Issues.

Seizures

Standardized treatment w/ASM by experienced neurologistMany ASMs may be

effective 1Education of parents/caregivers 2

Eyes

OphthalmologistRefractive errors, strabismusOphthalmic subspecialistMore complex findings (e.g., cataract, retinal dystrophy)Low vision servicesChildren: through early intervention programs &/or school districtAdults: low vision clinic &/or community vision services / OT / mobility services

Hearing loss

Standard mgmt per audiologist/otolaryngologist

Scoliosis / Hip dislocation / Positional deformities of feet

Standard orthopedic care

Cardiac, renal, urologic, & other medical issues

Standard mgmt of specific issue

Cryptorchidism

Treatment by urologist, if indicated

Multiple nevi

Regular checkup by dermatologist if multiple nevi are present.

Family/Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Ongoing assessment of need for palliative care involvement &/or home nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy1. 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 IssuesChildren 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 ConcernsChildren 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.SurveillanceTo 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 SyndromeView in own windowSystem/ConcernEvaluationFrequency

Constitutional

Measurement of growth parametersEval of nutritional status & safety of oral intake

At each visit

Development

Monitor developmental progress & educational needs.

Neurologic

Monitor those w/seizures as clinically indicated.Assess for new manifestations such as seizures, changes in tone.

Neurobehavioral/

Psychiatric

Assessment for anxiety, ADHD, & ASD

Musculoskeletal

Physical medicine, OT/PT assessment of mobility, self-help skills

Family/Community

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).

Integument

Full skin exam in those w/lighter skin tones or skin types who are at greater risk for developing melanomaAnnually

Ophthalmologic involvement

Ophthalmologic evalPer treating ophthalmologistLow vision servicesPer treating clinicians

Hearing

Audiologic evalAnnually, or as clinically indicatedADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapyEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic

counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Assessment of growth parameters to identify those w/failure to thriveConsider investigation of growth hormone deficiency in persons w/short stature.

Gastrointestinal/

Feeding

Feeding assessmentAssess for sucking & swallowing difficulties & need for feeding therapy in infancy.

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Neurologic

Brain imaging studies in persons w/microcephaly &/or seizureConsideration of Chiari malformation type 1 in those w/suggestive symptoms (headache, neck pain, cerebellar signs, or muscle weakness) 1EEG if seizures are suspectedReferral to neurologist for seizure disorder mgmt

Neurobehavioral/

Psychiatric

Neuropsychiatric evalFor persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD

Eyes

Ophthalmologic evalTo assess for hypermetropia, strabismus, congenital cataract, &/or optic atrophy, which may require referral for subspecialty care &/or low vision services

Hearing

Audiologic examTo assess for hearing loss

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of: Gross motor & fine motor skillsJoint hypermobility, pes planus, calcenovalgus deformity, scoliosis/kyphosis, pectus anomaliesMobility, ADL, & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Cardiovascular

Cardiac eval to incl echocardiogramFor possible heart anomalies incl septal defects & aortic dilatation

Genitourinary

Physical exam for hypospadias & cryptorchidism in malesRenal ultrasound examVoiding cystourethrogram, if indicated

Evaluate for ureteral reflux & other renal findings.

Integument

Full skin examTo assess for hemangiomas & multiple nevi

Respiratory

Upper airway evalIn infants & children w/signs or symptoms suspicious of tracheo-/laryngomalacia

Genetic counseling

By genetics professionals 2To inform affected persons & their families re nature, MOI, &

implications of KdVS to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral;Information & resources for sibs of persons w/KdVS.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy1. Terrone et al [2012]

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

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System/ConcernEvaluationComment

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Upper airway evalIn infants & children w/signs or symptoms suspicious of tracheo-/laryngomalacia

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Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral;Information & resources for sibs of persons w/KdVS.

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Eval for early intervention / special education

Gross motor & fine motor skills

Joint hypermobility, pes planus, calcenovalgus deformity, scoliosis/kyphosis, pectus anomalies

Mobility, ADL, & need for adaptive devices

Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Physical exam for hypospadias & cryptorchidism in males

Renal ultrasound exam

Voiding cystourethrogram, if indicated

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Terrone et al [2012]

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Treatment of ManifestationsThere 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 SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Feeding issues & motor delay related to hypotonia

Early intervention / feeding therapy / physiotherapyNasogastric tube feeding may be required for neonates w/severe feeding issues.

Growth hormone deficiency

Growth hormone therapy per endocrinologist

Developmental delay / Intellectual disability

See Developmental Delay / Intellectual Disability Management Issues.

Seizures

Standardized treatment w/ASM by experienced neurologistMany ASMs may be effective 1Education of parents/caregivers 2

Eyes

OphthalmologistRefractive errors, strabismusOphthalmic subspecialistMore complex findings (e.g., cataract, retinal dystrophy)Low vision servicesChildren: through early intervention programs &/or

school districtAdults: low vision clinic &/or community vision services / OT / mobility services

Hearing loss

Standard mgmt per audiologist/otolaryngologist

Scoliosis / Hip dislocation / Positional deformities of feet

Standard orthopedic care

Cardiac, renal, urologic, & other medical issues

Standard mgmt of specific issue

Cryptorchidism

Treatment by urologist, if indicated

Multiple nevi

Regular checkup by dermatologist if multiple nevi are present.

Family/Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Ongoing assessment of need for palliative care involvement &/or home nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy1. 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 IssuesChildren 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

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Hearing loss

Standard mgmt per audiologist/otolaryngologist

Scoliosis / Hip dislocation / Positional deformities of feet

Standard orthopedic care

Cardiac, renal, urologic, & other medical issues

Standard mgmt of specific issue

Cryptorchidism

Treatment by urologist, if indicated

Multiple nevi

Regular checkup by dermatologist if multiple nevi are present.

Family/Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Ongoing assessment of need for palliative care involvement &/or home nursingConsider involvement in adaptive sports or Special Olympics.

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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.

Treatment of Manifestations in Individuals with Koolen-de Vries Syndrome

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Gross motor dysfunction

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Integument

Full skin exam in those w/lighter skin tones or skin types who are at greater risk for developing melanomaAnnually

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

Therapies Under InvestigationSearch 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, 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 InheritanceKoolen-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 TestingOnce 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.

Mode of InheritanceKoolen-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).

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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:

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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].

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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.

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:

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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

Koolen-de Vries Syndrome Foundation

Enriching lives through education, awareness and research.

Phone: 833-721-KDVS

www.kdvsfoundation.org

Chromosome Disorder Outreach Inc.

Phone: 561-395-4252Email: info@chromodisorder.org

www.chromodisorder.org

MedlinePlus

Intellectual Disability

Unique: Understanding Rare Chromosome and Gene Disorders

United KingdomPhone: +44 (0) 1883 723356Email: info@rarechromo.org

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

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MedlinePlus

Intellectual Disability

Unique: Understanding Rare Chromosome and Gene Disorders

United Kingdom

Phone: +44 (0) 1883 723356

Email: info@rarechromo.org

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 GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

KANSL1

17q21.31

KAT8 regulatory NSL complex subunit 1

KANSL1 @ LOVD

KANSL1

KANSL1

Not applicable

17q21.31Not applicableData 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) View in own window

610443KOOLEN-DE VRIES SYNDROME; KDVS

612452KAT8 REGULATORY NSL COMPLEX, SUBUNIT 1; KANSL1Molecular PathogenesisDe 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+/- 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].

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Chapter NotesAuthor NotesRadboudumc Center of Expertise: rare congenital developmental disordersAcknowledgmentsThe 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 History2 February 2023 (ma) Comprehensive update posted live13 June 2019 (ma) Comprehensive update posted live20 November 2012 (me) Comprehensive update posted live26 January 2010 (me) Review posted live28 August 2009 (dak) Original submission

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