U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Abela L, Kurian MA. *KMT2B*-Related Dystonia. 2018 Apr 26 [Updated 2022 Sep 29]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

KMT2B-Related Dystonia

Synonyms: DYT28, DYT-KMT2B

Lucia Abela, MD, MSc[1] and Manju Ann Kurian, MA, MBBChir, PhD[1]

Created: April 26, 2018; Revised: September 29, 2022.

Summary

Clinical characteristics

KMT2B-related dystonia (DYT-*KMT2B*) is a complex childhood-onset (mean age 7 years) movement disorder described to date in 39 individuals. It is characterized by a progressive disease course evolving commonly from lower-limb focal dystonia into generalized dystonia with prominent cervical, cranial, and laryngeal involvement. Communication difficulties, secondary to articulation difficulties and low speech volume, are common. Bulbar dysfunction leads to impaired swallowing. Intellectual disability (ID) / developmental delay (DD) are commonly reported.

Additional findings can include eye movement abnormalities, skin changes, psychiatric comorbidities (attention-deficit/hyperactivity disorder, anxiety, depression, and obsessive-compulsive disorder), myoclonus, seizures, spasticity, and sensorineural hearing loss. Many affected individuals follow a similar disease course, though milder and atypical findings have been described.

Diagnosis/testing

The diagnosis of DYT-*KMT2B* is established in a proband with either a heterozygous pathogenic variant in *KMT2B* or a heterozygous interstitial deletion of 19q13.12 that includes a *KMTB2* whole-gene deletion.

Management

Treatment of manifestations:

- Dystonia: Although pharmacologic treatment with levodopa and other commonly used anti-dystonic agents generally does not result in long-term benefit for the majority of affected individuals, a trial of these agents is considered reasonable. One group observed a significant improvement of motor manifestations with an antimuscarinic (anticholinergic) agent. Bilateral globus pallidus interna deep brain stimulation results in substantial clinical improvement, particularly in younger individuals.

Author Affiliation: 1 Developmental Neurosciences Programme, UCL-Institute of Child Health, London, United Kingdom; Email: lucia.abela@ucl.ac.uk; Email: manju.kurian@ucl.ac.uk.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

- Other: Early initiation of physiotherapy and a tailored exercise program is advised as well as use of adaptive aids (e.g., ankle-foot orthoses, walkers) as necessary to support and maintain ambulation. Speech-language therapy is crucial to assist in feeding skills and communication. Nutrition specialists / dieticians are needed to assess calorie needs and reduce the risk of malnutrition. Address DD/ID issues through appropriate specialists/agencies.

Surveillance: Regular monitoring of weight and height in children, nutritional status, swallowing function, speech and language, adaptive functioning (ability to perform activities of daily living), orthopedic complications (hip dislocation and kyphoscoliosis), hearing, eye movements, skin, and psychiatric status.

Genetic counseling

DYT-*KMT2B* is inherited in an autosomal dominant manner. To date, ~84% of individuals have the disorder as the result of a *de novo KMT2B* pathogenic variant and ~16% have inherited the *KMT2B* variant (10% from an affected parent; 6% from a clinically asymptomatic parent). Each child of an individual with DYT-*KMT2B* has a 50% chance of inheriting the *KMT2B* pathogenic variant; reduced penetrance and intrafamilial clinical variability have been reported. Once the *KMT2B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No formal diagnostic criteria for DYT-*KMT2B* have been published to date.

Suggestive Findings

DYT-*KMT2B* **should be suspected** in individuals with the following findings.

Clinical Findings

Typical disease course [Zech et al 2016, Lange et al 2017, Meyer et al 2017, Zech et al 2017a, Zech et al 2017b]:

- Onset of dystonia usually within the first decade, but may be in the second decade or later
- Initial presentation:
  - In the majority, lower-limb dystonia (manifesting as toe-walking, abnormal gait, and balance difficulties)
  - In some, upper-limb dystonia, and less commonly, cervical or truncal dystonia
- With increasing age: prominent cervical, laryngeal, and/or cranial dystonia (manifesting as retrocollis, torticollis, dysarthria/anarthria, dysphonia, and difficulties in swallowing and chewing)
- Within two to 11 years of onset: evolution into generalized dystonia

Neuroimaging

Brain MRI abnormalities frequently reported in younger affected individuals (age range: 3-18 years) include subtle and symmetric hypointense lateral streaks in the external globus pallidus (Figure 1) on T_2-weighted, T_2*-weighted, susceptibility-weighted, and echo-planar b0-diffusion imaging data sets [Meyer et al 2017].

Note: This pattern may represent an age-dependent phenomenon as these features were often not evident in adults and may become less prominent over time. Indeed, in one individual such MR changes were less evident on MRI performed at age 17 years compared to neuroimaging performed at age 13 years.

DaTSCAN and **FDG-PET-CT scan** were normal in the three individuals evaluated with these methods.

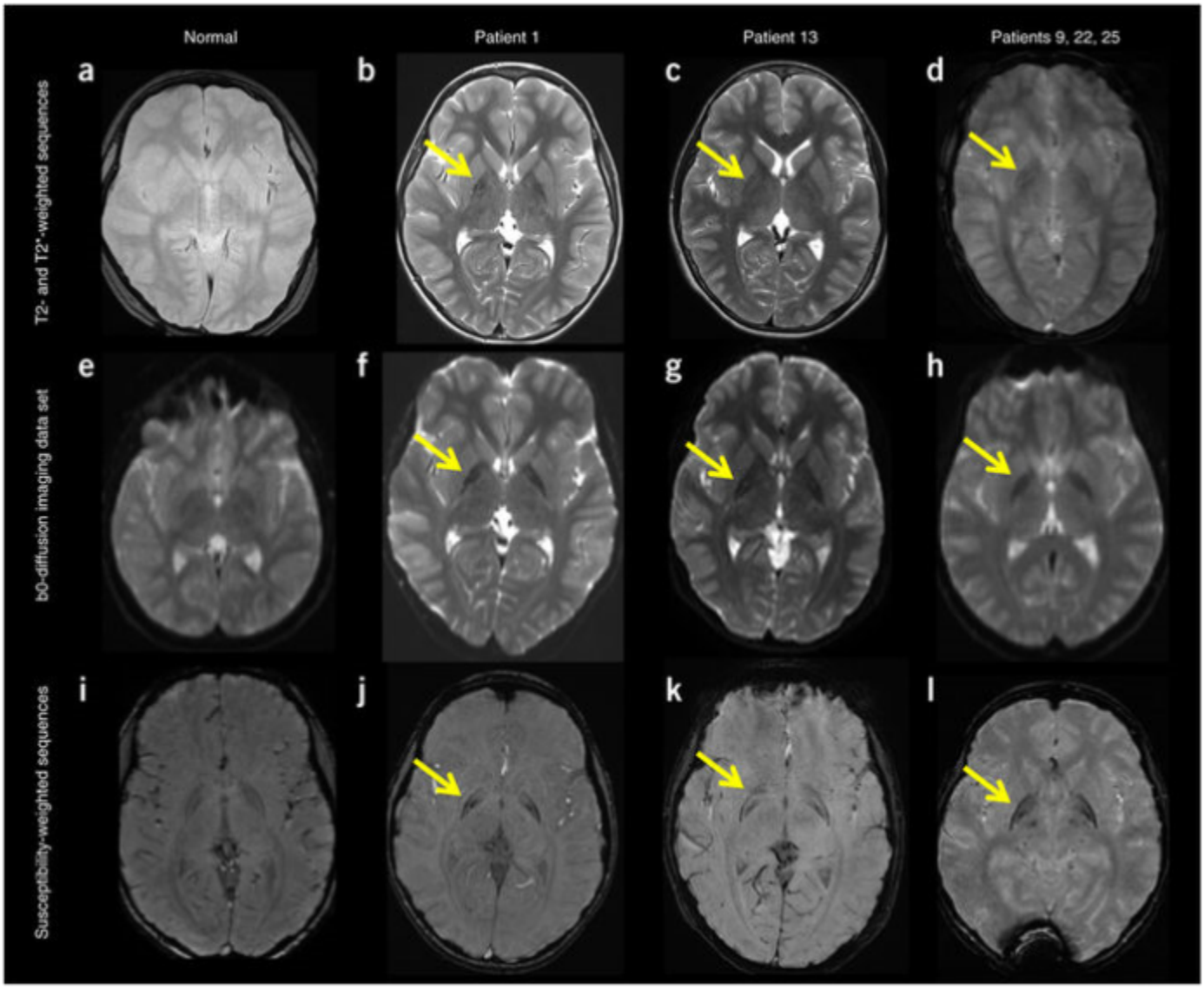

Figure 1. Radiologic MRI features of patients with *KMT2B* variants

a-l. T_2*-weighted (a, d) and T_2-weighted (b, c) images; echo-planar technique diffusion imaging data set images with *b* value of zero (e-h); susceptibility-weighted sequences (i-l)

a,e,i. Representative MR images from control patients for T_2*-weighted sequences (age 10 years, 2 months) (a), diffusion-weighted sequences (age 10 years, 4 months) (e), and susceptibility-weighted sequences (age 10 years, 8 months) (i), indicating normal appearances of basal ganglia.

Imaging abnormalities are indicated by yellow arrows and demonstrate subtle, bilateral hypointense lateral streaks in the external globus pallidus. Patient 1, age 9 years, 5 months (b,f,j); patient 13, age 11 years, 3 months (c,g,k); patient 9, age 15 years, 1 month (d); patient 22, age 13 years, 1 month (h); patient 25, age 16 years (l).

Reprinted from Meyer et al [2017]; Macmillan Publishers Ltd

Laboratory Findings

CSF analysis in 13 affected individuals showed the following minor perturbations of monoaminergic metabolites [Meyer et al 2017]:

- Marginal reduction of 5-hydroxyindoleacetic acid (5-HIAA) in three
- Mild elevation of 5-HIAA and tetrahydrobiopterin (BH4) in two others

Establishing the Diagnosis

The diagnosis of DYT-*KMT2B* **is established** in a proband with one of the following [Zech et al 2016, Lange et al 2017, Meyer et al 2017, Zech et al 2017a, Zech et al 2017b] (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant in *KMT2B* (26/36 probands reported to date)
- A heterozygous interstitial deletion of 19q13.12 that encompasses the entirety of *KMTB2* (10/36 probands reported to date)

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 section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *KMT2B* variant of uncertain significance does not establish or rule out the diagnosis.

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

Persons with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom a specific diagnosis has been elusive are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When the phenotypic and neuroimaging findings suggest the diagnosis of DYT-*KMT2B*, molecular genetic testing approaches can include **chromosomal microarray analysis (CMA)** (if not already performed) followed by gene-targeted testing (**single-gene testing** or a dystonia **multigene panel**):

- **CMA** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications of 19q13.12 (including *KMT2B*) that cannot be detected by sequence analysis.
- **Single-gene testing.** Sequence analysis of *KMT2B* 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.
- **A dystonia multigene panel** that includes *KMT2B* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the 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 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 phenotype is indistinguishable from many other inherited disorders with dystonia, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Exome array (when clinically available) may be considered if exome sequencing is not diagnostic, particularly when evidence supports autosomal dominant inheritance.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Epigenetic signature analysis / methylation array. A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with DYT-*KMT2B* [Levy et al 2021, Lee et al 2022, Mirza-Schreiber et al 2022]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive findings of DYT-*KMT2B* but in whom no pathogenic variant in *KMT2B* has been identified via sequence analysis or CMA; or (2) suggestive findings of DYT-*KMT2B* and a *KMT2B* variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

Table 1. Molecular Genetic Testing Used in *KMT2B*-Related Dystonia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KMT2B	Sequence analysis [3]	26/36 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown (no data available)
	CMA [7]	10/36 [4, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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.
4. Meyer et al [2017]
5. Zech et al [2016], Lange et al [2017], Zech et al [2017a] (this paper includes two variants of uncertain significance), Zech et al [2017b]
6. 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.
7. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays identifies deletion of 19q13.12.
8. Dale et al [2012]

Clinical Characteristics

Note: Except where indicated, information in this section is based on Zech et al [2016], Lange et al [2017], Meyer et al [2017], Zech et al [2017a], Zech et al [2017b], and Gorman et al [2018].

Clinical Description

KMT2B-related dystonia (DYT-*KMT2B*) is a complex childhood-onset movement disorder. It typically presents with a progressive disease course evolving commonly from lower-limb focal dystonia into generalized dystonia with prominent cervical, cranial, and laryngeal involvement. Additional neurologic, psychiatric, and systemic

features are commonly reported. Many affected individuals follow a similar disease course, though milder and atypical cases have been described.

DYT-*KMT2B* has been recently described in 36 probands. Of these, one proband had an affected mother and another had a similarly affected father and grandfather (total 39 individuals reported).

Disease onset typically occurs between ages one and 10 years (33/39 individuals); however, onset in the second decade was reported in five individuals for whom data were available. Mean age of onset was 7.05 years in 38 individuals for whom data were available.

Presenting manifestations (documented for 37/39 individuals) include the following:

- Lower-limb dystonia characterized by foot posturing, toe walking, and gait disturbance (in 28 individuals)
- Upper-limb dystonia leading to abnormal hand/arm posturing, dystonic tremor, and difficulties in handwriting and hand dexterity (6)
- Cervical dystonia (1)
- Truncal/axial dystonia (1)
- Dystonic tremor and (action) myoclonus (1)

Over time, the majority of individuals developed progressive cranial, cervical, and laryngeal dystonia with features of retrocollis, torticollis, dysarthria/anarthria, dysphonia, and difficulties in swallowing and chewing.

Affected individuals often have communication difficulties, secondary to articulation difficulties and low speech volume.

Bulbar dysfunction leads to impaired swallowing, which can cause substantial morbidity because of the risk of aspiration pneumonia. A few individuals with DYT-*KMT2B* have required gastrostomy insertion for feeding difficulties.

Generalized dystonia becomes evident in most individuals (34/39) within two to 11 years of initial presentation. The level of gross motor disability comprises a broad spectrum ranging from minor gait disturbance to wheelchair dependence (GMFCS II-V).

Developmental delay, described in 16 of 39 affected individuals, usually precedes the onset of dystonia and is thought to be non-progressive. Eight presented with neurodevelopmental delay, seven had isolated speech delay, and one had only delay in attainment of fine motor skills.

Mild cognitive impairment was reported in 21 of 39 affected individuals, most of whom developed variable degrees of functional independence in adolescence and adulthood.

Life expectancy is not known, but individuals in the seventh decade of life with DYT-*KMT2B* have been reported [Zech et al 2016].

Additional clinical features of DYT-*KMT2B* included the following (note that 9 individuals had >1 additional clinical feature):

- Eye movement abnormalities including strabismus, astigmatism, delay in saccade initiation, hypometric vertical saccades, oculomotor apraxia (in 8 individuals)
- Dermatologic features of ectodermal dysplasia including cutis aplasia, sparse hair, sparse to absent eyelashes or brows, hypertrichosis, and ichthyotic skin with criss-cross pattern under the feet and at the knees (5). Although broad postsurgical scarring and "phimosis" have been reported, it is not currently known if these features are incidental or truly disease related. Future identification of further individuals with molecularly confirmed DYT-*KMT2B* may better clarify these associations.

- Psychiatric comorbidities including attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and obsessive-compulsive disorder (3)
- Myoclonus (3)
- Microcephaly (3)
- Seizures (2), including one with absence seizures
- Spasticity (1)
- Sensorineural hearing loss (1)
- Subtle dysmorphic features that may include an elongated face and bulbous nasal tip [Zech et al 2016, Meyer et al 2017, Zech et al 2017a, Zech et al 2017b]

The following atypical DYT-*KMT2B* disease manifestations [Meyer et al 2017] are rarely reported:

- Paroxysmal cervical dystonia, reported in one individual. Notably, the mother of this proband, who was found to harbor this *KMT2B* variant, had onset of symptoms in early adulthood. She developed gait abnormalities, a progressive inability to run, and periodic paroxysmal upper-limb and neck dystonia.
- Solely oromandibular features without clinical evidence of limb dystonia

Genotype-Phenotype Correlations

Meyer and colleagues [2017] reported statistically significant earlier disease onset in individuals with DYT-*KMT2B* with loss-of-function variants (e.g., interstitial deletions; frameshift, splice site, and stop-gain variants) compared to those with missense variants. However, genotype does not appear to influence the rate of disease progression, disease severity, or clinical response to deep brain stimulation.

Early neurodevelopmental delay was reported in 5/10 individuals with a heterozygous 19q13.12 contiguous gene deletion, compared to 11/29 with intragenic *KMT2B* pathogenic variant. Likewise, the majority of individuals (8/10) with a heterozygous 19q13.12 contiguous gene deletion had mild cognitive impairment, compared to 13/29 with an intragenic *KMT2B* pathogenic variant. Identification of additional individuals with DYT-*KMT2B* will determine if this is a true genotype-phenotype correlation.

Penetrance

DYT-*KMT2B* is postulated to show reduced penetrance as asymptomatic heterozygotes have been identified. Although parental status is not always known, to date two (6%) of 32 reported pathogenic variants have been inherited from a seemingly unaffected parent [Meyer et al 2017].

Male-female differences in penetrance have not been observed to date.

Prevalence

Disease prevalence is not yet established. To date, 39 individuals (from 36 families) with DYT-*KMT2B* have been described.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *KMT2B*.

Differential Diagnosis

Table 2. Disorders Associated with Complex Early-Onset Generalized Dystonia to Consider in the Differential Diagnosis of *KMT2B*-Related Dystonia

Disorder	Gene(s)	MOI	Additional Overlapping Clinical Features	Distinguishing Features of Differential Diagnosis Disorder		
				Clinical	MRI	Laboratory Findings
Inherited forms of dystonia [1]						
DYT-TOR1A (DYT1)	*TOR1A*	AD		Isolated dystonia w/less prominent cervical/ cranial/bulbar features early in disease course		
DYT-THAP1 (DYT6)	*THAP1*	AD	Early craniofacial involvement & laryngeal dystonia	Isolated dystonia w/ older average age of onset		
DYT-PRKRA (DYT16)	*PRKRA*	AR		Mild parkinsonism		
Early-onset NBIA disorders [2]						
PKAN	*PANK2*	AR		• Parkinsonism • Spasticity • Eye movement abnormalities • Optic atrophy • Axonal neuropathy • Seizures	Characteristic T_2-weighted hypointensity in globus pallidus & substantia nigra	
PLAN	*PLA2G6*	AR				
MPAN	*C19orf12*	AR				
BPAN	*WDR45*	XL				
FAHN	*FA2H*	AR				
Kufor-Rakeb syndrome	*ATP13A2*	AR				
CoPAN	*COASY*	AR				
Disorders of heavy metal metabolism						
Wilson disease	*ATP7B*	AR	Psychiatric comorbidities	• Tremor • Liver disease • Kayser-Fleischer corneal ring	Face-of-the-giant-panda sign	• ↓ serum ceruloplasmin • ↑ serum non-ceruloplasmin-bound copper
SLC39A14 deficiency	*SLC39A14*	AR		• Parkinsonism • Spasticity • Dysarthria • Bulbar dysfunction	T_1-weighted hyperintensities & T_2-weighted hypointensities in basal ganglia & anterior pituitary gland, cerebellum, dorsal pons, spinal cord	Hypermanganesemia
Dystonia/ parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease	*SLC30A10*	AR		• Parkinsonism • Liver disease	T_1-weighted hyperintensities in basal ganglia	• Hypermanganesemia • Polycythemia

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Additional Overlapping Clinical Features	Distinguishing Features of Differential Diagnosis Disorder		
				Clinical	MRI	Laboratory Findings
Neurotransmitter disorders						
Sepiapterin reductase deficiency	*SPR*	AR	Hypotonia	• Progressive parkinsonism-dystonia • Eye movement disorder • Delayed motor milestones	Reduced tracer uptake on DaTSCAN images (DTDS)	CSF neurotransmitter abnormalities
GTPCH1 deficiency (OMIM 233910)	*GCH1*	AR				
Tyrosine hydroxylase deficiency	*TH*	AR				
Aromatic L-amino acid decarboxylase deficiency	*DDC*	AR				
Brain serotonin-dopamine deficiency [Rilstone et al 2013]	*SLC18A2*	AR				
SLC6A3-related dopamine transporter deficiency syndrome	*SLC6A3*	AR				
Mitochondrial disorders						
Mitochondrial cytopathies	See footnote 3.	AD AR Mat		Multisystemic involvement	• Commonly shows "Leigh" radiologic appearance of T_2-weighted hyperintensities in basal ganglia / brain stem / medulla • Leukodystrophy	• ↑ lactate, pyruvate • Metabolic acidosis
POLG-related disorders	*POLG*	AR				
Other inherited metabolic disorders						
Alpha-fucosidosis (OMIM 230000)	*FUCA1*	AR		• ID • Dementia • Delayed motor skills • Dysostosis multiplex • Seizures • Spasticity • Angiokeratomas • Distinct facial features		
Glutaric acidemia type 1	*GCDH*	AR		• Encephalopathic crisis assoc w/ infections/fever (age 6-18 mos) • Macrocephaly	• Frontotemporal atrophy • Widening of sylvian fissures • T_2-weighted hyperintensities in basal ganglia	• ↑ urinary 3-OH-glutaric acid • Glutaryl carnitine

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Additional Overlapping Clinical Features	Distinguishing Features of Differential Diagnosis Disorder		
				Clinical	MRI	Laboratory Findings
Methylmalonic acidemia, late-onset (See Isolated Methylmalonic Acidemia.)	*MCEE* *MMAA* *MMAB* *MMADHC* *MUT*	AR	Hypotonia; psychiatric symptoms	• Failure to thrive • Renal syndromes • ID • Metabolic stroke-like events		• ↑ plasma & urine MMA w/normal B_{12}, tHcy, & methionine levels • ↑ propionylcarnitine (C3) • Hyperammonemia • Lactic acidosis
Propionic acidemia, late-onset	*PCCA* *PCCB*	AR		• Failure to thrive • DD • ID • Gastrointestinal symptoms		• ↑ propionylcarnitine (C3) in plasma, ↑ 3-hydroxypropionate in urine, hyperammonemia, lactic acidosis
Niemann-Pick disease type C	*NPC1* *NPC2*	AR		• Spasticity • Hepatomegaly/ splenomegaly • Supranuclear gaze palsy • Cataplexy • Seizures • Psychiatric comorbidities		↑ oxysterol levels
GM1 gangliosidosis, type III (See *GLB1*-Related Disorders.)	*GLB1*	AR		• Extrapyramidal signs • Skeletal abnormalities • Cardiomyopathy		
Lesch-Nyhan syndrome	*HPRT1*	XL		• Pyramidal signs • Self-mutilation		Hyperuricemia
Other monogenic disorders with prominent dystonia phenotype						
ADCY5 dyskinesia	*ADCY5*	AD	Hypotonia	• Chorea • Orolingual dyskinesia • Myoclonus • Spasticity • Episodic exacerbations of movement disorder		

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Additional Overlapping Clinical Features	Distinguishing Features of Differential Diagnosis Disorder		
				Clinical	MRI	Laboratory Findings
Rapid-onset dystonia-parkinsonism (See *ATP1A3*-Related Neurologic Disorders.)	*ATP1A*	AD		• Parkinsonism • DD • Neuropsychiatric features • Seizures	↓ tracer uptake on DaTSCAN images	
Juvenile-onset Parkinson disease (See Parkinson Disease Overview.)	*DNAJC6* *FBX07* *PARK7 (DJ1)* *PINK1* *PRKN (PARK2)*	AR				
Young-onset dystonia-parkinsonism (DYT16) [Camargos et al 2008]	*PRKRA*	AR				
TUBB4A-related leukodystrophy (H-ABC)	*TUBB4A*	AD		• ID • Motor delay • Spasticity	• Hypomyelinating leukodystrophy • Cerebellar & basal ganglia atrophy	
Deafness-dystonia-optic neuronopathy syndrome	*TIMM8A*	XL				
Pyruvate carboxylase deficiency	*PC*	AR				

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; Mat = maternal inheritance; MOI = mode of inheritance; XL = X-linked

1. See Hereditary Dystonia Overview.

2. See Neurodegeneration with Brain Iron Accumulation Disorders Overview.

3. Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with DYT-*KMT2B*, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Complete detailed neurologic examination to delineate movement disorder phenotype (dystonia, myoclonus, spasticity)
- Consider early assessment for possible effectiveness of deep brain stimulation
- Physiotherapy, occupational therapy, and speech and language therapy assessment
- Evaluation of swallowing safety (videofluoroscopy may be needed)

- Nutritional evaluation to ensure adequate calorie intake
- Developmental assessment / IQ testing
- Orthopedic examination for secondary complications including fixed contractures, joint dislocation, and/or kyphoscoliosis
- Ophthalmologic examination including assessment of vision and eye movements
- Assessment of hearing
- Formal neuropsychiatric testing
- Dermatologic examination
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Dystonia. Although pharmacologic treatment with levodopa and other commonly used anti-dystonic agents (e.g., trihexiphenidyl, baclofen, gabapentin, tetrabenazine, benzodiazepines) has not proven to result in long-term benefit for the majority of individuals with DYT-*KMT2B* [Zech et al 2016, Meyer et al 2017, Zech et al 2017a], a trial of these anti-dystonia agents would be considered reasonable. Lange and colleagues [2017] observed a significant improvement of motor manifestations on treatment with an antimuscarinic (anticholinergic) agent.

Bilateral globus pallidus interna deep brain stimulation (DBS) results in substantial clinical improvement, particularly in younger individuals, and should be considered as a possible therapeutic route for patients with DYT-*KMT2B* based on the following results [Zech et al 2016, Meyer et al 2017, Zech et al 2017a, Zech et al 2017b]:

- Three patients regained independent ambulation.
- Five patients demonstrated sustained clinical effect at eight years following implantation.

Early initiation of physiotherapy and a tailored exercise program is essential to maintain function and prevent secondary orthopedic complications such as joint contractures, hip dislocation, and/or kyphoscoliosis.

Adaptive aids (e.g., ankle-foot orthoses, walkers) should be supplied to support and maintain ambulation.

Speech and language therapy is crucial to assist in feeding skills and communication. Some affected individuals may need communication devices.

Nutrition specialists / dieticians are of utmost importance to assess calorie needs and reduce the risk of malnutrition.

Videofluoroscopy can be used to evaluate the risk of aspiration and assess the need for alternative means of feeding.

For individuals with respiratory compromise from chest deformities related to scoliosis, prophylactic antibiotics during the winter months, regular physiotherapy, and influenza immunizations should be considered because of the increased risk of pulmonary infections.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; 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.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, 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 as a result of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions such as 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 (e.g., medication used to treat ADHD) when necessary.

Surveillance

Surveillance includes regular monitoring of the following:

- Weight and height using age-appropriate and sex-matched growth charts in children
- Nutritional status to evaluate dietary requirements
- Swallowing to evaluate risk for aspiration
- Speech and language regarding needs for augmentative communication
- Adaptive functioning (ability to perform activities of daily living)
- Potential orthopedic complications (e.g., hip dislocation and kyphoscoliosis with hip and spine x-rays every 6 to 12 months)
- Hearing
- Strabismus and refractive errors
- Skin examination for changes requiring appropriate management
- Psychiatric status

Evaluation of Relatives at Risk

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

Pregnancy Management

Before conception, counseling on the potential effects of antidystonic medications on the pregnancy and developing fetus should be discussed and an appropriate plan on managing medications during pregnancy should be established. Pregnant women with DYT-*KMT2B* should also be advised about the induction of dystonic side effects of antiemetics [Nageshwaran et al 2011].

Data on the use of antidystonic agents in pregnancy are scarce. Although single case reports of medical treatment with trixhexyphenidyl, levodopa/carbidopa, and clonazepam during pregnancy have not observed adverse effects on the affected mother or the fetus [Watanabe et al 2009, Mendhekar & Andrade 2011, Nageshwaran et al 2011, Robottom & Reich 2011, Serikawa et al 2011, Watanabe & Matsubara 2012, Dostal et al 2013], oral medications may be preferably tapered to the lowest effective dose.

Treatment with DBS has been reported in a series of cases with implantation prior to conception [Scelzo et al 2015, Ziman et al 2016, Park et al 2017]. No adverse effects on the affected mother and the fetus have been reported to date.

See MotherToBaby for further information on medication use during pregnancy.

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

Mode of Inheritance

KMT2B-related dystonia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- When parental DNA was available (32/39), ~84% of individuals diagnosed with DYT-*KMT2B* had the disorder as the result of a *de novo KMT2B* pathogenic variant [Zech et al 2016, Lange et al 2017, Meyer et al 2017, Zech et al 2017a, Zech et al 2017b].
- Approximately 16% of individuals diagnosed with DYT-*KMT2B* inherited a *KMT2B* variant: 10% from an affected parent and 6% from a clinically asymptomatic parent (see Penetrance) [Zech et al 2016, Meyer et al 2017]. Clinical variability within families is reported.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *KMT2B* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with DYT-*KMT2B* may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the *KMT2B* pathogenic variant first occurred, the parent may have somatic (and germline) mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected and/or is known to be heterozygous for the *KMT2B* pathogenic variant, the risk to sibs of inheriting the pathogenic variant is 50%, intrafamilial clinical variability and reduced penetrance have been observed in DYT-*KMT2B*.
- If the *KMT2B* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the estimated recurrence risk to sibs is 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If both parents are clinically unaffected but have not been tested for the *KMT2B* pathogenic variant, the sibs of a proband are still at increased risk for DYT-*KMT2B* because of the possibility of reduced penetrance in a heterozygous parent or germline mosaicism in a parent.

Offspring of a proband. Each child of an individual with DYT-*KMT2B* has a 50% chance of inheriting the *KMT2B* pathogenic variant; reduced penetrance and intrafamilial clinical variability have been reported [Meyer et al 2017, Zech et al 2016].

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *KMT2B* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence

of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *KMT2B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Dystonia Coalition**
  dc.rarediseasesnetwork.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **Dystonia UK**
  United Kingdom
  Email: info@dystonia.org.uk
  dystonia.org.uk
- **German Dystonia Registry**
  Germany
  Email: odorfer_t@ukw.de
  DysTract
- **MedlinePlus**
  Dystonia
- **Dystonia Europe**
  Connecting People for Dystonia
  Belgium
  Phone: 46 739 98 49 61
  Email: sec@dystonia-europe.org
  dystonia-europe.org

- **Global Dystonia Registry**
  Dystonia Medical Research Foundation
  Email: Coordinator@globaldystoniaregistry.org
  globaldystoniaregistry.org

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. KMT2B-Related Dystonia: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
KMT2B	19q13.12	Histone-lysine N-methyltransferase 2B	KMT2B	KMT2B

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 KMT2B-Related Dystonia (View All in OMIM)

606834	LYSINE-SPECIFIC METHYLTRANSFERASE 2B; KMT2B
617284	DYSTONIA 28, CHILDHOOD-ONSET; DYT28

Molecular Pathogenesis

KMT2B encodes a ubiquitously expressed lysine-specific histone methyl-transferase. Histone methylation represents a post-translational epigenetic mechanism to either repress or activate gene transcription in a residue-specific manner [Shi & Whetstine 2007, Shilatifard 2008]. KMT2B is a member of the SET/MLL protein family that is specifically involved in histone 3 lysine 4 (H3K4) methylation. H3K4 is enriched at promoter, enhancer, and other regulatory sequences and associated with active transcription [Barski et al 2007, Zhou et al 2011]. Besides gene activation, H3K4 is also thought to be essential for transcriptional stability and enhanced transcriptional consistency [Muramoto et al 2010, Benayoun et al 2014].

The exact pathogenic mechanisms in DYT-*KMT2B* still remain to be fully elucidated. Given that dysregulated H3K4 methylation has an effect on the transcriptional activation and stability of a variety of genes, it is likely that additional genes or other genetic mechanisms contribute to DYT-*KMT2B*.

Several patients harbor small deletions on chromosome 19q.13.12, a region that encompasses *KMT2B.* It is possible that other genes within these genomic deletions could additionally contribute to the affected individual's phenotype.

Gene structure. The protein coding transcript NM_014727.2 encompasses 37 exons.

Pathogenic variants. *KMT2B* variants have been identified in 39 individuals with early-onset complex dystonia [Zech et al 2016, Meyer et al 2017]. In addition to frameshift, nonsense, splice site, and missense variants, small overlapping interstitial deletions of chromosome 19q13.12 have also been detected. For the ten individuals with reported small deletions, the smallest region of overlap spanned from 36,191,000 bp to 36,229,548 bp, encompassing two genes, *ZBTB32* and *KMT2B* (*MLL4*). Given that a number of loss-of-function pathogenic variants are reported in DYT-*KMT2B*, it is likely that pathogenic variants result in *KMT2B* haploinsufficiency.

Novel missense variants have been reported recently in another four unrelated individuals [Zech et al 2017a, Zech et al 2017b]:

- Two variants are of uncertain significance because of unknown parental inheritance.
- Two variants showed strong conservation and were predicted to be likely protein damaging [Zech et al 2017a]:
  - p.Ala1541Val was transmitted to two unaffected adult offspring.
  - p.Arg1779Gln was present in an individual in the ExAC population database.

Lange et al [2017] identified a proband with early-onset dystonia with a novel three-bp in-frame deletion that affects a highly conserved amino acid located within the PHD-like domain that is important for DNA-protein and protein-protein interaction. Protein modeling revealed altered loop formation and impaired coordination of a zinc ion.

Table 3. Pathogenic *KMT2B* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.4622C>T	p.Ala1541Val	NM_014727.2 NP_055542.1
c.5336G>A	p.Arg1779Gln	

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.

Normal gene product. *KMT2B* has a single protein-coding transcript of 8,469 bp. The protein encompasses 2,715 amino acids and consists of multiple functional domains including a CXXC zinc finger, three PHD/PHD-like zinc fingers domains, two FY-rich domains, and a C-terminal SET (*s*uppressor of variegation, *e*nhancer of zeste, and *t*rithorax) domain (RefSeq, Jul 2008). The KMT2B protein belongs to the MLL (mixed-lineage leukemia) protein family, which is characterized by a conserved C-terminal catalytic SET domain. KMT2B is ubiquitously expressed in the brain with highest expression in the cerebellum [Meyer et al 2017].

Abnormal gene product. Loss-of-function *KMT2B* pathogenic variants are predicted to alter gene dosage, leading to *KMT2B* haploinsufficiency. The effect of missense variants remains to be fully elucidated, but they may affect normal protein stability and function. Abnormal KMT2B protein function may lead to dysregulated gene expression.

The role of *KMT2B* has been investigated using a mouse model [Kerimoglu et al 2013]. A conditional knockdown of *KMT2B* in forebrain excitatory neurons resulted in downregulation of a specific subset of genes. The mouse model had evidence of impaired memory formation but no dystonia.

Chapter Notes

Author Notes

Dr Lucia Abela

Developmental Neurosciences

UCL-Great Ormond Street Institute of Child Health, London

Dr Abela is a senior resident in pediatric neurology and currently a research fellow in Dr Kurian's research group with a special interest in childhood movement disorders.

Dr Manju Kurian

Developmental Neurosciences

UCL-Great Ormond Street Institute of Child Health, London

Dr Kurian is a pediatric neurologist and clinician-scientist with a clinical and research interest in childhood movement disorders.

Dr Kurian's web page

Acknowledgments

Dr Kurian is funded by an NIHR Research Professorship and the Wellcome Trust. Dr Abela is funded by a Swiss National Foundation Advanced Postdoc Mobility fellowship.

Revision History

- 29 September 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis, Option 2)
- 26 April 2018 (bp) Review posted live
- 19 October 2017 (la/mak) Original submission

References

Literature Cited

Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, Wei G, Chepelev I, Zhao K. High-resolution profiling of histone methylations in the human genome. Cell. 2007;129:823-37. PubMed PMID: 17512414.

Benayoun BA, Pollina EA, Ucar D, Mahmoudi S, Karra K, Wong ED, Devarajan K, Daugherty AC, Kundaje AB, Mancini E, Hitz BC, Gupta R, Rando TA, Baker JC, Snyder MP, Cherry JM, Brunet A. H3K4me3 breadth is linked to cell identity and transcriptional consistency. Cell. 2014;158:673-88. PubMed PMID: 25083876.

Camargos S, Scholz S, Simón-Sánchez J, Paisán-Ruiz C, Lewis P, Hernandez D, Ding J, Gibbs JR, Cookson MR, Bras J, Guerreiro R, Oliveira CR, Lees A, Hardy J, Cardoso F, Singleton AB. DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. Lancet Neurol. 2008;7:207-15. PubMed PMID: 18243799.

Dale RC, Grattan-Smith P, Nicholson M, Peters GB. Microdeletions detected using chromosome microarray in children with suspected genetic movement disorders: a single-centre study. Dev Med Child Neurol. 2012;54:618-23 PubMed PMID: 22515636.

Dostal M, Weber-Schoendorfer C, Sobesky J, Schaefer C. Pregnancy outcome following use of levodopa, pramipexole, ropinirole, and rotigotine for restless legs syndrome during pregnancy: a case series. Eur J Neurol. 2013;20:1241-6. PubMed PMID: 23083216.

Gorman KM, Meyer E, Kurian MA. Review of the phenotype of early-onset generalised progressive dystonia due to mutations in KMT2B. Eur J Paediatr Neurol. 2018;22:245-56 PubMed PMID: 29289525.

Kerimoglu C, Agis-Balboa RC, Kranz A, Stilling R, Bahari-Javan S, Benito-Garagorri E, Halder R, Burkhardt S, Stewart AF, Fischer A. Histone-methyltransferase MLL2 (KMT2B) is required for memory formation in mice. J Neurosci. 2013;33:3452-64. PubMed PMID: 23426673.

Lange LM, Tunc S, Tennstedt S, Münchau A, Klein C, Assmann B, Lohmann K. A novel, in-frame KMT2B deletion in a patient with apparently isolated, generalized dystonia. Mov Disord. 2017;32:1495-7. PubMed PMID: 28921672.

Lee S, Ochoa E, Barwick K, Cif L, Rodger F, Docquier F, Pérez-Dueñas B, Clark G, Martin E, Banka S, Kurian MA, Maher ER. Comparison of methylation episignatures in KMT2B- and KMT2D-related human disorders. Epigenomics. 2022;14:537-47. PubMed PMID: 35506254.

Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of Mendelian disorders. HGG Adv. 2021;3:100075. PubMed PMID: 35047860.

Mendhekar DN, Andrade C. Uneventful use of haloperidol and trihehexyphenidyl during three consecutive pregnancies. Arch Womens Ment Health. 2011;14:83-4. PubMed PMID: 21116668.

Meyer E, Carss KJ, Rankin J, Nichols JME, Grozeva D, Joseph AP, Mencacci NE, Papandreou A, Ng J, Barral S, Ngoh A, Ben-Pazi H, Willemsen MA, Arkadir D, Barnicoat A, Bergman H, Bhate S, Boys A, Darin N, Foulds N, Gutowski N, Hills A, Houlden H, Hurst JA, Israel Z, Kaminska M, Limousin P, Lumsden D, McKee S, Misra S, Mohammed SS, Nakou V, Nicolai J, Nilsson M, Pall H, Peall KJ, Peters GB, Prabhakar P, Reuter MS, Rump P, Segel R, Sinnema M, Smith M, Turnpenny P, White SM, Wieczorek D, Wiethoff S, Wilson BT, Winter G, Wragg C, Pope S, Heales SJH, Morrogh D, UK10K Consortium, Deciphering Developmental Disorders Study, NIHR BioResource Rare Diseases Consortium, Pittman A, Carr LJ, Perez-Dueñas B, Lin JP, Reis A, Gahl WA, Toro C, Bhatia KP, Wood NW, Kamsteeg EJ, Chong WK, Gissen P, Topf M, Dale RC, Chubb JR, Raymond FL, Kurian MA. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49:223-37. PubMed PMID: 27992417.

Mirza-Schreiber N, Zech M, Wilson R, Brunet T, Wagner M, Jech R, Boesch S, Škorvánek M, Necpál J, Weise D, Weber S, Mollenhauer B, Trenkwalder C, Maier EM, Borggraefe I, Vill K, Hackenberg A, Pilshofer V, Kotzaeridou U, Schwaibold EMC, Hoefele J, Waldenberger M, Gieger C, Peters A, Meitinger T, Schormair B, Winkelmann J, Oexle K. Blood DNA methylation provides an accurate biomarker of KMT2B-related dystonia and predicts onset. Brain. 2022;145:644-54. PubMed PMID: 34590685.

Muramoto T, Müller I, Thomas G, Melvin A, Chubb JR. Methylation of H3K4 is required for inheritance of active transcriptional states. Curr Biol. 2010;20:397-406. PubMed PMID: 20188556.

Nageshwaran S, Nageshwaran S, Edwards MJ, Morcos M. Management of DYT1 dystonia throughout pregnancy. BMJ Case Rep. 2011;2011.

Park HR, Lee JM, Park H, Shin CW, Kim HJ, Park HP, Kim DG, Jeon BS, Paek SH. Pregnancy and delivery in a generalized dystonia patient treated with internal globus pallidal deep brain stimulation: a case report. J Korean Med Sci. 2017;32:155-9. PubMed PMID: 27914146.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rilstone JJ, Alkhater RA, Minassian BA. Brain dopamine-serotonin vesicular transport disease and its treatment. N Engl J Med. 2013;368:543-50. PubMed PMID: 23363473.

Robottom BJ, Reich SG. Exposure to high dosage trihexyphenidyl during pregnancy for treatment of generalized dystonia: case report and literature review. Neurologist. 2011;17:340-1. PubMed PMID: 22045287.

Scelzo E, Mehrkens JH, Bötzel K, Krack P, Mendes A, Chabardès S, Polosan M, Seigneuret E, Moro E, Fraix V. Deep brain stimulation during pregnancy and delivery: experience from a series of "DBS Babies". Front Neurol. 2015;6:191 PubMed PMID: 26388833.

Serikawa T, Shimohata T, Akashi M, Yokoseki A, Tsuchiya M, Hasegawa A, Haino K, Koike R, Takakuwa K, Tanaka K, Tanaka K, Nishizawa M. Successful twin pregnancy in a patient with parkin-associated autosomal recessive juvenile parkinsonism. BMC Neurol. 2011;11:72. PubMed PMID: 21682904.

Shi Y, Whetstine JR. Dynamic regulation of histone lysine methylation by demethylases. Mol Cell. 2007;25:1-14. PubMed PMID: 17218267.

Shilatifard A. Molecular implementation and physiological roles for histone H3 lysine 4 (H3K4) methylation. Curr Opin Cell Biol. 2008;20:341-8. PubMed PMID: 18508253.

Watanabe T, Matsubara S. Good obstetric outcome in a patient with Segawa disease. Arq Neuropsiquiatr. 2012;70:559-60. PubMed PMID: 22836471.

Watanabe T, Matsubara S, Baba Y, Tanaka H, Suzuki T, Suzuki M. Successful management of pregnancy in a patient with Segawa disease: case report and literature review. J Obstet Gynaecol Res. 2009;35:562-4. PubMed PMID: 19527400.

Zech M, Boesch S, Maier EM, Borggraefe I, Vill K, Laccone F, Pilshofer V, Ceballos-Baumann A, Alhaddad B, Berutti R, Poewe W, Haack TB, Haslinger B, Strom TM, Winkelmann J. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. Am J Hum Genet 2016;99:1377-87. PubMed PMID: 27839873.

Zech M, Jech R, Havránková P, Fečíková A, Berutti R, Urgošík D, Kemlink D, Strom TM, Roth J, Růžička E, Winkelmann J. KMT2B rare missense variants in generalized dystonia. Mov Disord. 2017a; 32:1087-91. PubMed PMID: 28520167.

Zech M, Jech R, Wagner M, Mantel T, Boesch S, Nocker M, Jochim A, Berutti R, Havránková P, Fečíková A, Kemlink D, Roth J, Strom TM, Poewe W, Růžička E, Haslinger B, Winkelmann J. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. Neurogenetics. 2017b; 18:195-205. PubMed PMID: 28849312.

Zhou VW, Goren A, Bernstein BE. Charting histone modifications and the functional organization of mammalian genomes. Nat Rev Genet. 2011;12:7-18. PubMed PMID: 21116306.

Ziman N, Coleman RR, Starr PA, Volz M, Marks WJ Jr, Walker HC, Guthrie SL, Ostrem JL. Pregnancy in a series of dystonia patients treated with deep brain stimulation: outcomes and management recommendations. Stereotact Funct Neurosurg. 2016;94:60-5 PubMed PMID: 26977859.

License

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

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.