Child Neurology: *KMT2B*-Related Dystonia in a Young Child With Worsening Gait Abnormality

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Neurology® 2023;101:328-332. doi:10.1212/WNL.0000000000207300

Abstract

KMT2B gene–related dystonia (DYT-KMT2B) is a primarily childhood-onset movement disorder that usually starts with lower limb dystonia progressing into generalized dystonia. Our patient described in this study experienced difficulty gaining weight, laryngomalacia, and feeding difficulties during infancy and later developed gait difficulties, frequent falls, and toe walking. Gait assessment revealed prominent bilateral intoeing, intermittent ankle inversion, and extension of left leg. At times, the gait seemed to be spastic. Whole-exome sequencing revealed a novel de novo heterozygous likely pathogenic variant, c.7913 T > A (p.V2638E), in the *KMT2B* gene located in chromosome 19. This variant, which has not been previously published as pathogenic or benign in the literature, can be added to the repertoire of *KMT2B* variants causing inherited dystonias.

Case Summary

A 4-year-old White boy presented with 4 months of toe walking and progressively less stable gait leading to frequent falls. The patient was born at term after an uncomplicated pregnancy to nonconsanguineous parents. During infancy, the patient had feeding difficulties and failure to thrive. Silent aspiration was detected on swallow study, and he was diagnosed with oropharyngeal dysphagia and laryngomalacia eventually needing supraglottoplasty. He was noted to be a toe walker with intoeing since he started walking at approximately 13 months of age. His voice quality had always been slightly raspy and hoarse. At age 18 months, he was evaluated by a geneticist for microcephaly, dysmorphic craniofacial features (triangular facies, prominent chin, thin upper lip, and long philtrum), and failure to thrive. Chromosomal microarray demonstrated 270 kb deletion in 6p25.1 (5,137,260–5,407,464), which was of uncertain significance. Feeding and swallowing concerns largely resolved by the age of 3 years. He was fully toilet trained by the age of 4 years. Developmental milestones were otherwise within normal limits. Family history was unremarkable. Neurologic examination at 4 years of age showed slightly hoarse voice with mildly impaired articulation, increased tone, and brisk deep tendon reflexes in the lower extremities. He held a pen with tight palmar grasp resulting in slow effortful writing. Gait assessment revealed prominent bilateral intoeing, intermittent ankle inversion, and extension of the left leg. At times, the gait seemed to be spastic (scissoring with knees touching each other). Remainder of the examination including cranial nerves was unremarkable. Comprehensive metabolic panel including liver function tests, serum creatinine kinase levels, lactate, pyruvate, and plasma amino acids were normal. Noncontrast MRI brain and spine were unremarkable. He underwent next-generation sequencing panel testing that included 78 genes associated with hereditary spastic paraplegia (HSP), which identified heterozygous variants of uncertain significance in *TECPR2* (p.Thr1219Arg) and *ZFYVE26* (p.Arg1862His). These genes are associated with autosomal recessive HSP and therefore would not explain our patient's phenotype. He then underwent whole-exome sequencing that revealed a novel heterozygous de novo (absent in parents) likely pathogenic variant, c.7913 T > A (p.V2638E), in the *KMT2B* gene. Heterozygous variants in *KMT2B* are associated with early-onset progressive generalized dystonia, although this variant has not been previously published. This variant was not observed at significant frequency in large population cohorts. In silico analysis supported that this missense variant has a deleterious effect on protein structure and function. Based

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on these criteria, we propose a diagnosis of *KMT2B*-related dystonia (DYT-*KMT2B* dystonia) in our patient. It is unclear whether the dysmorphic features, laryngomalacia, and early feeding difficulty are related to DYT-*KMT2B*.

Discussion

Our patient presented with gait abnormality due to altered muscle tone. Differentiating dystonia and spasticity in young children is extremely challenging. Therefore, conditions causing spasticity and dystonia were considered in the differential diagnoses. Spasticity, meaning involuntary muscle hyperactivity triggered by rapid passive joint movements, is characterized by velocity-dependent increase in muscle tone with enhanced deep tendon reflexes due to hyperexcitability of the stretch reflex.[1] By contrast, dystonia is described as sustained or intermittent muscle contractions resulting in abnormal movements, postures, or both.[2] In dystonia, muscle tone increases with voluntary action and passive movements and decreases at rest. Whereas muscle tone would not be affected by voluntary action or rest in spasticity. Dystonia can manifest as foot inversion, overextension or overflexion of hand, lateral flexion or retroflexion of head, torsion of spine with arching and back twisting, or a fixed grimace.[3] Sensory tricks can ameliorate dystonia.

Dystonia is classified based on clinical characteristics and etiology (Table 1).[4] Clinical characteristics include age at onset, body distribution, temporal pattern, and associated features. Etiologic characteristics include the presence or absence of CNS pathology and pattern of inheritance (acquired or inherited). Acquired dystonia is usually secondary to underlying conditions such as brain injury, stroke, infections, toxins, and antibody-mediated syndromes such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, and anti-Ma2 antibody encephalitis. Cerebral palsy (CP) is probably the most common cause of acquired dystonia.[4]

CP, the most common motor disability in childhood, refers to a group of conditions involving permanent motor dysfunction that affects muscle tone, posture, and/or movement that are caused by nonprogressive insults to the developing fetal or infant brain.[5] Several movement disorders can be seen in CP including spasticity, dystonia, dyskinesia, ataxia, or a combination of these types. Spastic CP is the most common type affecting 80% of patients with CP. Dyskinetic CP is associated with uncoordinated movements of the upper and lower extremities and can include dystonia, athetosis, and chorea.[5,6] There were no known insults to our patient during fetal development or perinatal period, making this diagnosis less likely.

HSP is a group of rare inherited disorders that presents with difficulty walking due to progressive weakness and spasticity in the leg muscles.[5] It can be divided into pure HSP or complicated HSP based on the presence or absence of other neurologic deficits. Additional features characterizing complicated HSP include ataxia, severe amyotrophy, visual problems such as optic atrophy and pigmentary retinopathy, epilepsy, neurodevelopmental deficits, icthyosis, deafness, peripheral neuropathy, and extrapyramidal signs.[7,8] Our

Table 1 Classification of Dystonia

Clinical characteristics	
1. Age at onset	Infancy (birth to 2 y)
	Childhood (3–12 y)
	Adolescence (13–20 y)
	Early adulthood (21–40 y)
	Late adulthood (>40 y)
2. Body distribution	Focal
	Segmental
	Multifocal
	Generalized (with or without leg involvement)
	Hemidystonia
3. Temporal pattern	Disease course
	Static
	Progressive
	Variability
	Persistent (persists at about same extent throughout the day)
	Action-specific (occurs only with a particular task)
	Diurnal (fluctuates during the day)
	Paroxysmal (sudden-onset self-resolved episodes with returning to neurologic baseline)
4. Associated features	Isolated (dystonia is the only motor manifestation except tremor
	Combined (dystonia combined with other movement disorders)
Etiology	
1. Nervous system pathology	Evidence of degeneration
	Evidence of structural, often static, lesions
	No evidence of degeneration or structural lesions
2. Inherited or acquired	Inherited
	Autosomal dominant, autosomal recessive, x-linked recessive, mitochondrial
	Acquired
	Perinatal brain injury, infection, drug, toxic, vascular, neoplastic, brain injury, psychogenic
	Idiopathic
	Sporadic, familial

Table 2 Pediatric-Onset Inherited Dystonias

Gene	Symbol	Onset	Phenotype; associated syndrome
Autosomal dominant forms			
Dystonia as primary manifestation			
TOR1A	DYT1	Childhood to adolescence	Early-onset generalized dystonia
GCH1	DYT5a	Childhood	Dopa responsive dystonia; Segawa syndrome
THAP1	DYT6	Adolescence	Mixed type dystonia
KMT2B	DYT28	Childhood	Early-onset generalized dystonia
Dystonia as secondary or associated feature			
MR1	DYT8	Adolescence	Paroxysmal nonkinesingenic dyskinesia 1
PRRT2	DYT10	Childhood to adolescence	Episodic/paroxysmal kinesigenic dyskinesia 1
SGCE	DYT11	Childhood to adolescence	Myoclonus and dystonia
KCTD17	DYT26	Childhood to early adulthood	Myoclonus and dystonia
ATP1A3	DYT12	Childhood to adulthood	Rapid-onset dystonia—parkinsonism
SLC2A1	DYT18	Childhood	Paroxysmal exercise-induced dyskinesia
FXN	NA	Adolescence	Friedreich ataxia
HTT	NA	Adolescence	Huntington disease
ATXN3	SCA3	Childhood to adulthood	Spinocerebellar ataxia 3
Autosomal Recessive Forms			
Dystonia as primary manifestation			
TH	DYT5b	Infancy to childhood	Dopa responsive dystonia; Segawa syndrome
SPR	NA	Infancy to childhood	Dopa responsive dystonia
Dystonia as secondary or associated feature			
DDC	NA	Infancy	Aromatic L-amino acid decarboxylase deficiency
ATM	NA	Childhood	Ataxia-telengiectasia
FUCA1	NA	Infancy	Fucosidosis
GCDH	NA	Infancy	Glutaric acidemia
PLA2G6	NBIA2a	Infancy	Infantile neuroaxonal dystrophy
PKRN	PARK2	Adolescence	Juvenile parkinsonism
ATP13A2	PARK9	Childhood to adulthood	Kufor-Rakeb syndrome
MUT, MMADHC	NA	Infancy	Methylmalonic aciduria
NPC1, NPC2	NA	Infancy to adulthood	Niemann-Pick disease type C
PANK2	NBIA1	Childhood	Pantothenate kinase-associated neurodegeneration
HEXA	NA	Infancy to adulthood	Tay-Sachs disease
ATP7B	NA	Childhood to adulthood	Wilson disease
DCAF17	NA	Adolescence	Woodhouse-Sakati syndrome
X-Linked (Dystonia as secondary or associated feature)			
HPRT	NA	Childhood	Lesch-Nyhan syndrome
PLP1	NA	Infancy	Pelizaeus-Merzbacher disease
MECP2	NA	Infancy	Rett syndrome
TIMM8A	NA	Childhood to adulthood	Mohr-Tranebjaerg dystonia-deafness syndrome

NA: not available; mitochondrial disorders such as Leber optic atrophy and Leigh syndrome can have dystonia as an associated feature.

patient did not have any of these other characteristics, making this diagnosis unlikely. Pure HSP was a consideration.

Inherited dystonias are those with proven genetic etiology (Table 2).[4,9] While there are many genetic forms of dystonia, DYT-TOR1A is the most common accounting for approximately 70% of cases. DYT-TOR1A is caused by a defect in *TOR1A (DYT1)* gene that encodes the protein torsinA. DYT-TOR1A dystonia typically begins in childhood with limb onset often progressing to generalized dystonia. However, there is a wide phenotypic spectrum with variability even within families.[10] Other genes associated with early-onset inherited dystonia include THAP domain containing 1 (THAP1), *KMT2B* (lysine methyltransferase 2B), and guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1).[2,11,12] Dopa-responsive dystonia or Segawa disease is another unusual form of inherited progressive dystonia that presents within the first decade of life. Dystonia usually starts in the legs. Additional clinical features such as hyperreflexia, rigidity, and tremor can be seen. The hallmark is sustained response to levodopa. The most common form is associated with *GCH1* gene.[9]

DYT-KMT2B accounts for approximately 10 percent of early-onset generalized dystonia. Symptoms usually start with lower limb focal dystonia progressing into generalized dystonia with prominent cranial, cervical, and laryngeal involvement. The median age at symptom onset is 5 years. Patients present with both neurologic and non-neurologic symptoms. Neurologic manifestations include lower limb dystonia progressing into generalized dystonia. Patients with lower limb dystonia usually manifest toe walking, foot posturing, and abnormal gait.[11] Progression to generalized dystonia typically occurs over a median of 2 years. The prominent cervical, laryngeal, and oromandibular dystonia is often disabling for patients causing torticollis, dysphagia, dysarthria, and dysphonia. Many patients also develop spasticity. Myoclonic seizures, global developmental delay, and intellectual disability are also commonly reported. Microcephaly and subtle dysmorphic features including elongated face and bulbous nasal tip are frequently noted. Cases of DYT-KMT2B with adult-onset cerebellar ataxia and mild dystonia have been reported. Neuropsychiatric manifestations including anxiety, depression, and attention deficit hyperactivity disorder often coexist. Ophthalmologic manifestations including strabismus, oculomotor apraxia, astigmatism, retinal dystrophy, and delay in saccade initiation are seen. Dermatological manifestations including sparse to absent eyelashes, sparse hair, hypertrichosis, ichthyotic skin, and profound acne are noted. Failure to thrive from dysphagia can also be seen. Most patients with DYT-KMT2B have characteristic subtle and symmetric hypointense lateral streaks in the external globus pallidus on T_2, diffusion, and susceptibility-weighted sequences on brain MRI. However, these findings are nonspecific.[11,13,14]

DYT-KMT2B is inherited in an autosomal dominant manner. The *KMT2B* (lysine methyl transferase 2B) gene is located on chromosome 19q13.12. It encodes for a lysine methyl transferase involved in the H3K4 methylation, which is an epigenetic modifier associated with active gene transcription. The exact molecular mechanism by which *KMT2B* variants cause dystonia remains to be elucidated. The diagnosis of DYT-KMT2B is established in a patient when there is a heterozygous pathogenic or likely pathogenic variant in *KMT2B* or a heterozygous interstitial deletion of 19q13.12 that encompasses the entirety of *KMTB2* gene. Most individuals with this disorder have a de novo *KMT2B* pathogenic variant while approximately 16% inherit the *KMT2B* variant. Reported pathogenic variants include frameshift, nonsense, splice site, missense, and deletions. Chromosomal deletions and protein-truncating variants have been associated with a more severe phenotype.[11]

Management is symptomatic and supportive. Treatment with levodopa and other antidystonic agents such as trihexiphenidyl, baclofen, gabapentin, and tetrabenazine have not resulted in long-term benefit for most individuals with DYT-*KMT2B*. However, a trial of these agents can be considered. Bilateral globus pallidus interna deep brain stimulation has shown substantial clinical improvement, particularly in younger individuals, and should be considered as a therapeutic option for patients with DYT-*KMT2B*.[11,15]

In conclusion, we describe a case of childhood-onset inherited dystonia highlighting the challenges in neurologic examination and differential diagnoses. We suggest that the variant p.V2638E be added to the repertoire of *KMT2B* mutations causing inherited dystonias.

Study Funding

The authors report no targeted funding.

Disclosure

K. Schuberth; P. Ramani; and E. Beemarajan report no disclosures relevant to the manuscript; A. Veerapandiyan has received compensation for ad hoc advisory boards/consulting activity with Biogen, Novartis, AveXis, Sarepta therapeutics, PTC therapeutics, Scholar Rock, Fibrogen, AMO pharma, Pfizer, Muscular Dystrophy Association, Parent Project Muscular Dystrophy, and France Foundation. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* November 3, 2022. Accepted in final form March 2, 2023. Submitted and externally peer reviewed. The handling editor was Resident & Fellow Section Deputy Editor Ariel Lyons-Warren, MD, PhD.

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Continued

Appendix (continued)

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References

1. Biering-Sorensen F, Nielsen JB, Klinge K. Spasticity-assessment: a review. *Spinal Cord*. 2006;44(12):708-722.
2. Balint B, Mencacci NE, Valente EM, et al. *Nat Rev Dis Primers*. 2018;4(1):25.
3. Pana A, Saggu BM. *Dystonia*. StatPearls. Treasure Island. FL; 2022.
4. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord*. 2013;28(7):863-873.
5. Ikeudenta BA, Rutkofsky IH. Unmasking the enigma of cerebral palsy: a traditional review. *Cureus*. 2020;12(10):e11004.
6. Metz C, Jaster M, Walch E, Sarpong-Bengelsdorf A, Kaindl AM, Schneider J. Clinical phenotype of cerebral palsy depends on the cause: is it really cerebral palsy? A retrospective study. *J Child Neurol*. 2022;37(2):112-118.
7. Hedera P. Hereditary spastic paraplegia overview. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews((R))*; 1993.
8. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol*. 2008;7(12):1127-1138.
9. Klein C, Lohmann K, Marras C, Munchau A. Hereditary dystonia overview. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews((R))*; 1993.
10. Park J, Damrauer SM, Baras A, Reid JG, Overton JD, Gonzalez-Alegre P. Epidemiology of DYT1 dystonia: estimating prevalence via genetic ascertainment. *Neurol Genet*. 2019;5:e358.
11. Abela L, Kurian MA. KMT2B-Related dystonia. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews((R))*; 2018.
12. Bressman SB, Raymond D, Fuchs T, Heiman GA, Ozelius LJ, Saunders-Pullman R. Mutations in THAP1 (DYT6) in early-onset dystonia: a genetic screening study. *Lancet Neurol*. 2009;8(5):441-446.
13. 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(2):245-256.
14. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. *Nat Genet*. 2017;49(2):223-237.
15. Rajan R, Garg K, Saini A, et al. GPi-DBS for *KMT2B* -associated dystonia: systematic review and meta-analysis. *Mov Disord Clin Pract*. 2022;9(1):31-37.

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