

CASE REPORT

Open Access



Failure to thrive - an overlooked manifestation of *KMT2B*-related dystonia: a case presentation

Andrew Ng^{1,2}, Serena Galosi³, Lisa Salz⁴, Terence Wong⁴, Caitlin Schwager⁵, Shivarajan Amudhavalli⁵, Rose Gelineau-Morel⁵, Shimul Chowdhury⁴, on behalf of Rady Children's Institute for Genomic Medicine Investigators and Jennifer Friedman^{1,2,4*}

Abstract

Background: *KMT2B*-related dystonia is a recently described form of childhood onset dystonia that may improve with deep brain stimulation. Prior reports have focused on neurologic features including prominent bulbar involvement without detailing general health consequences that may result from orolingual dysfunction. We describe a family with novel *KMT2B* mutation with several members with failure to thrive to highlight this non-neurologic, but consequential impact of mutation in this gene.

Case presentation: We present a case of a 15-year old female who was admitted and evaluated for failure to thrive. On exam, she had severe speech dysfluency, limited ability to protrude the tongue, and generalized dystonia involving the oromandibular region, right upper and left lower extremity with left foot inversion contracture. The proband and her parents underwent whole genome sequencing. A previously undescribed variant, c.4960 T > C (p.Cys1654Arg), was identified in the *KMT2B* gene in the proband and mother, and this variant was subsequently confirmed in two maternal cousins, one with failure to thrive. Literature review identified frequent reports of prominent bulbar involvement but failure to thrive is rarely mentioned.

Conclusion: Failure to thrive is a common pediatric clinical condition that has consequences for growth and development. In the presence of an abnormal neurologic exam, a search for a specific underlying genetic etiology should be pursued. With this case series, we highlight an unusual potentially treatable cause of failure to thrive, reinforce the importance of precise molecular diagnosis for patients with failure to thrive and an abnormal neurologic exam, and underscore the importance of cascade screening of family members.

Keywords: *KMT2B*, Dystonia, Failure to thrive, Whole genome sequencing

Background

Failure to thrive (FTT), a common clinical condition warrants hospitalization to ensure adequate nutrition and thorough investigation of etiology. FTT is defined as weight less than 0.4-5th percentile, weight less than 80%

normal weight for age, or weight decline across more than 2 major percentiles [1]. The causes include poor nutrition, inadequate absorption, and increased energy expenditure. Careful attention to history and comprehensive physical exam can yield clues to etiology.

Dystonia is a movement disorder characterized by involuntary hyperkinetic movements involving sustained or intermittent contractions of agonist and antagonist muscles that frequently lead to abnormal posturing or

* Correspondence: jfriedman@health.ucsd.edu

¹University of California San Diego, San Diego, CA, USA

²Rady Children's Hospital, San Diego, CA, USA

Full list of author information is available at the end of the article



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

movements [2]. Dystonia is classified based on clinical characteristics (age of onset, regional distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations) and etiology (genetic, acquired, or idiopathic) [3]. Orolingual dystonia can cause eating dysfunction leading to weight loss [4].

Lysine Methyltransferase-2B (*KMT2B*) dystonia is a recently described autosomal dominant disorder [5, 6]. The *KMT2B* gene encodes a lysine methyltransferase involved in H3K4 methylation, an epigenetic modifier active in development [7]. This condition is characterized by childhood lower-limb onset dystonia that progressively generalizes with prominent cranial, cervical, and laryngeal involvement [5, 6]. Though dysphagia has been described, reports have focused on neurologic rather than gastrointestinal symptomatology and presentation. We report the first case series where failure to thrive was the presenting feature prompting diagnosis. Our report identifies a novel *KMT2B* pathogenic variant, c.4960 T > C (p.Cys1654Arg), and expands both the spectrum of phenotypic presentation for *KMT2B* mutation and genetic causes for FTT.

Case presentation

A 15-year-old girl (III-1) was admitted to the hospital for FTT: 36 kg (0.18%ile), 151 cm (4%ile). She had not seen a physician for 2 years due to socioeconomic issues. History revealed mild cognitive impairment, gait abnormality (left foot inversion) onset age 3, speech dysfluency onset age 9, and slowness with eating onset age 13 with dysphagia to solids and liquids onset age 14. Previous evaluation for gait abnormality resulted in unsuccessful trials of muscle relaxants and orthotics. Family history was initially negative for neurologic conditions. On exam, there was severe speech dysfluency, limited ability to protrude the tongue, and generalized dystonia involving the oromandibular region, the right upper and the left lower extremity with left foot inversion contracture (Additional files 1, 2, 3).

Initially, neglect was considered a possible etiology given the delay in seeking medical evaluation. However, abnormal neurologic exam prompted further testing. Labs were normal except for mild thrombocytopenia likely due to malnutrition (Table 1). Brain magnetic resonance imaging (MRI) showed bilateral hypointensity in globi pallidi on susceptibility-weighted imaging supporting an organic etiology (Fig. 1). Radiofilm revealed left foot 5th metatarsal fracture. Muscle biopsy showed myopathic fiber size variation and mild vasculopathic changes. Video-swallow fluoroscopy showed dysphagia to liquids and solids. Gastrostomy tube was placed with significant weight gain but persistence of weight below the second percentile despite appropriate caloric intake. Levodopa/carbidopa and trihexyphenidyl

Table 1 Laboratory Values during hospital admission

LABORATORY TEST	VALUE	REFERENCE RANGE
Hemoglobin (g/dL)	14.5	12.5–15
Hematocrit (% of g/dL)	42.2	35–45
Platelets (K/uL)	135	140–440
Sodium (mmol/L)	141	133–143
Potassium (mmol/L)	4.1	3.4–4.7
Chloride (mmol/L)	105	98–106
BUN (mg/dL)	9	8–21
Creatinine (mg/dL)	0.65	0.6–1.2
Calcium (mg/dL)	9.5	8.5–10.4
AST (U/L)	26	15–30
ALT (U/L)	20	5–30
Alkaline phosphatase (U/L)	99	70–280
Glucose (mg/dL)	93	70–106
Albumin (g/dL)	4.7	3.5–5.1
Vitamin D 25 OH (ng/mL)	17	> 30
TSH (uIU/mL)	0.37	0.35–5
Free T4 (ng/dL)	0.75	0.71–1.85
CK (U/L)	44	20–128
Folate (ng/mL)	11.7	> 8
Vitamin B12 (pg/mL)	480	260–935
Copper (mcg/dL)	87	75–187
Ceruloplasmin (mg/dL)	21	21–46

AST aspartate transaminase, ALT alanine aminotransferase; Vitamin D 25 OH calcifediol, TSH thyroid stimulating hormone, CK creatinine kinase

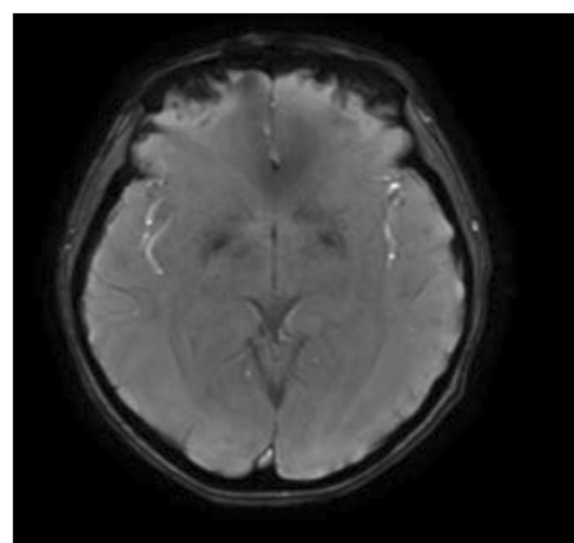


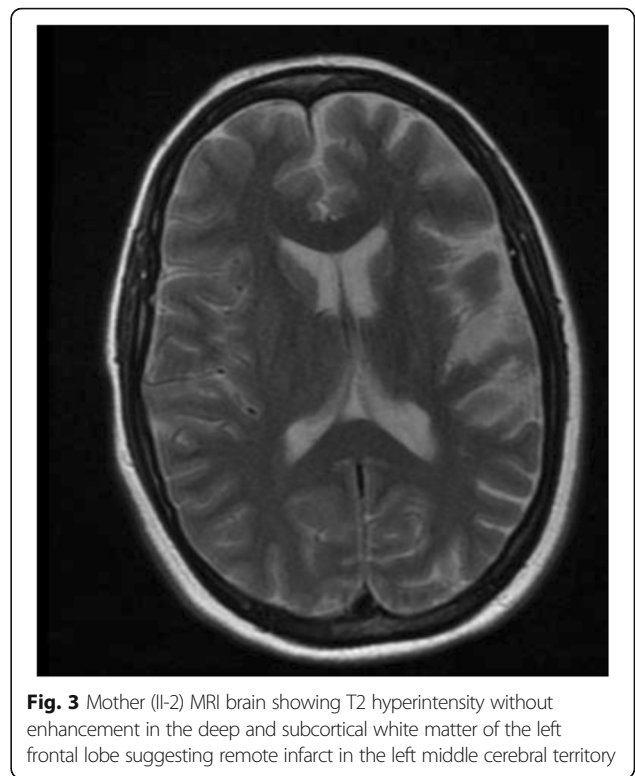
Fig. 1 Proband (III-1) MRI brain susceptibility weighted imaging demonstrates moderate symmetric hypointensity in the bilateral globi pallidi

were not beneficial. Trio whole genome sequencing (WGS) revealed a novel likely pathogenic heterozygous c.4960 T > C (p.Cys1654Arg) variant in the proband and mother in the *KMT2B* gene (Transcript ID: NM_014727.2). This variant is not present in the gnomAD database. The c.4960 T > C (p.Cys1654Arg) variant was predicted by multiple in silico tools to have a deleterious effect on protein function. No other diagnostic variants were identified.

After identification of the *KMT2B* variant in the proband and mother, additional history was obtained. A three-generation pedigree was constructed (Fig. 2). Cascade testing of maternal cousins (III-6 and III-7) revealed that they carried the same *KMT2B* c.4960 T > C (p.Cys1654Arg) variant. The father (II-4) of maternal cousins (III-6 and III-7) is an obligate carrier.

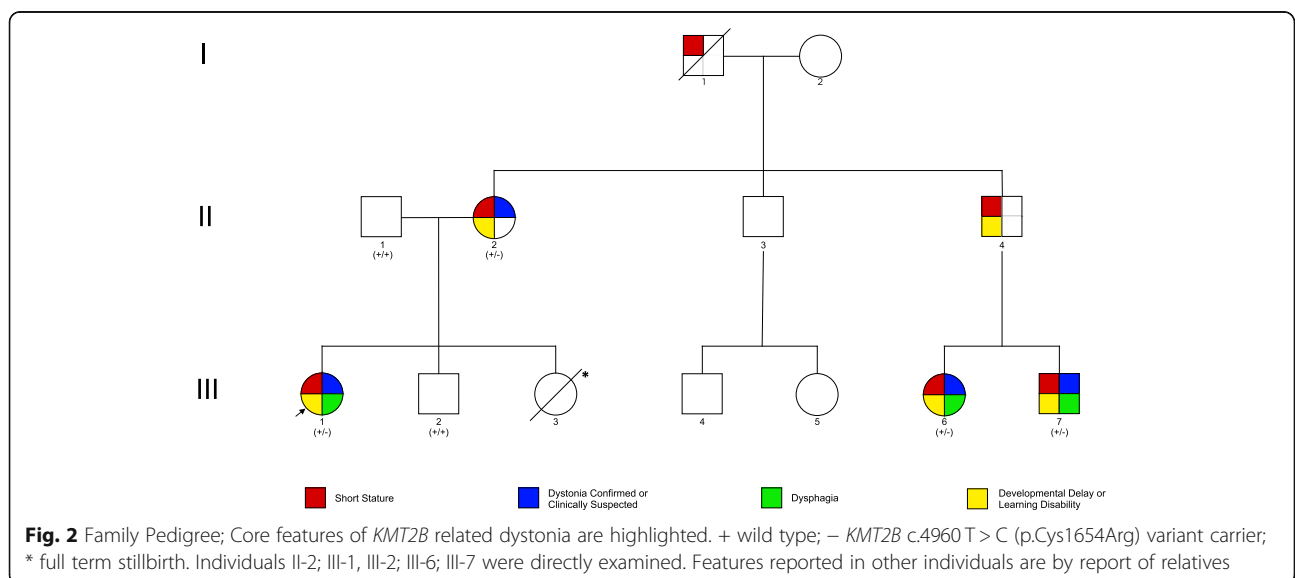
Mother, age 34(II-2), relayed history of painful right arm posturing, worsening handwriting, intermittent numbness, and gait disturbance onset age 29. She denied speech changes or dysphagia. She recalled history of encephalitis at age three. She was in special education classes and was unable to complete high school. She had anxiety onset age 19. Examination revealed normal speech, right > left hand dystonia, right foot eversion while ambulating, 4/5 weakness in finger extensors and finger intrinsic muscles on the right, and 2 beats of clonus in the right ankle (Additional files 4, 5, 6). MRI brain showed T2 hyperintensity without enhancement in the deep and subcortical white matter of the left frontal lobe suggesting remote infarct in the left middle cerebral territory (Fig. 3).

Maternal male cousin, age 4(III-7), had delayed milestones, attention deficit hyperactivity disorder, anxiety, and behavioral concerns. There was history of frequent choking; however, video-fluoroscopy was normal. Height



was consistently less than the 10th percentile and weight less than the 3rd percentile. Examination revealed hypernasal speech and preferential toe walking, although he was able to walk heel toe when prompted.

Maternal female cousin, age 6(III-6), initially presented for evaluation of hypernasal speech. A submucous cleft palate was identified and she underwent a Furlow palatoplasty without improvement. She had difficulties swallowing as an infant, requiring feed thickener.



Dysphagia resolved over time. Growth was consistently below the 10th percentile for height and weight. Early toe walking improved with therapy. She has learning delays and receives therapies and support in school. Vision abnormalities include left-sided strabismic amblyopia, hyperopia, accommodative esotropia, and astigmatism. Neurological evaluation revealed hypernasal, but fluent speech, normal resting tone with normal deep tendon reflexes, and gait with external rotation of the left leg with weight distribution on the lateral aspect of the foot, suggesting mild dystonia.

Signs and symptoms in maternal grandfather and maternal uncles are reported by other relatives; none have been examined by a neurologist. Maternal grandfather I-1 had mild short stature and was aesthenic. Maternal uncle, age 41(II-3), recently lost use of his left arm; he has not had testing for the familial variant. Maternal uncle, age 40(II-4), an obligate carrier of the variant, is intellectually impaired and has short stature. He reported tingling and numbness in the neck that progressed to painful paresthesias in all four limbs onset age 20.

Methods

Sequencing

WGS was performed as previously described [8, 9]. Variants were prioritized by allele frequency, conservation, and predicted effect on protein function and confirmed by Sanger sequencing. Phenotypic terms included the following: dysarthria, gait disturbance, failure to thrive, and dysphagia. Given MRI findings, the sequence was re-queried to specifically exclude other variants in genes associated with brain iron accumulation. Subsequent family studies were performed by targeted Sanger sequencing.

Literature review

We reviewed 80 cases obtained by PubMed Search using term *KMT2B* as well as cases in the reference list for these manuscripts or otherwise known to the author, that were not identified by PubMed search. (Additional Table).

Discussion and conclusions

Our report describes the phenotype in a family with a previously undescribed *KMT2B* variant and highlights failure to thrive, an overlooked manifestation. Thus far, 80 additional patients have been described (Additional Table) [5, 6, 10–28]. A recent report identified *KMT2B* mutations in 21.5% of patients with previously undiagnosed childhood-onset dystonia suggesting *KMT2B* mutations may be a relatively common cause of dystonia in children [26]. The natural course of *KMT2B* dystonia involves focal onset lower limb dystonia with

progression to generalization. Of reported cases, 23 noted dysphagia, 6 required gastrostomy tube but failure to thrive was rarely mentioned (Additional Table) [5, 6, 10–28]. In our series, the proband and two cousins had dysphagia. Poor weight gain despite normal swallowing study in one cousin and refractory weight gain after gastrostomy tube placement in the proband, suggest factors other than mechanical impairments to swallowing may underlie FTT in this condition.

Progressive dystonia with prominent oromandibular involvement, mild cognitive dysfunction and imaging findings in the proband are consistent with features previously described in *KMT2B* mutation carriers [6]. Other previously described neurologic features noted in the proband include dysfluency, bulbar dysfunction, dysphagia, intellectual disability, and developmental delay [5, 6]. Additional reported features not present include eye movement abnormalities, skin changes, psychiatric co-morbidities (anxiety, depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder), myoclonus, seizures, spasticity, sensorineural hearing loss, microcephaly, and parkinsonism [5, 6, 10–28].

Interestingly, the proband's mother did not manifest poor weight gain and reported no motor symptoms until age 29. Similarly, maternal uncles report only adult-onset neurologic symptoms. Reduced penetrance, variable expressivity, and adult onset up to 43 years of age have been reported [14, 26]. As neither maternal grandfather, nor either maternal uncle was examined, we cannot confirm whether dystonia is present. Similarly, it is unclear if mother's signs and symptoms are due to genetic dystonia, unrecognized cerebrovascular accident, or a combination of both given imaging evidence for remote infarct. Vascular insults have not been reported in *KMT2B* mutation carriers though most reported cases are children without long-term follow-up. Further study will be necessary to determine whether *KMT2B* mutation is a risk factor for stroke.

Since molecular diagnosis, the proband has trialed levodopa/carbidopa and trihexyphenidyl without benefit. Deep brain stimulation of globus pallidus (DBS) is reported to improve dystonia in select patients, suggesting another possible avenue for efficacious treatment for affected members of this family [5, 6, 26].

Our case series underscores the importance of careful history and thorough examination when determining etiologies for failure to thrive. In the presence of an abnormal neurologic exam or history of developmental delays, clinicians should strongly consider genetic testing. Unbiased genetic testing in this setting, including whole exome and genome sequencing, has enabled identification of rare disorders, especially those presenting with non-typical phenotypes. This case series highlights the non-neurologic aspects of *KMT2B* mutation

and demonstrates the advantages of molecular genetic testing for defining the precise and potentially treatable etiologies of FTT. It also reinforces the importance of cascade screening of family members to bring clarity of unrecognized diagnoses more broadly beyond the presenting family member.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12883-020-01798-x>.

Additional file 1. Patient (III-1) demonstrates orolingual dysphonia and dystonia. In the last segment, she is asked to protrude her tongue but cannot.

Additional file 2. Patient (III-1) demonstrates upper extremity dystonia of right arm and lower extremity of left leg while sitting.

Additional file 3. Patient (III-1) demonstrates left lower limb dystonia while ambulating.

Additional file 4. Patient's mother (II-2) has normal speech without dysarthria.

Additional file 5. Patient's mother (II-2) displays right >> left hand dystonia.

Additional file 6. Patient's mother (II-2) displays mild bilateral arm dystonia and right foot eversion while ambulating.

Additional file 7: Phenotype and Genotype of Previously Reported *KMT2B* Mutation Carriers and Patients Described in This Report. F-Female; M-Male.

Abbreviations

KMT2B: Lysine Methyltransferase-2B; FTT: Failure to thrive; MRI: Magnetic resonance imaging; WGS: Whole genome sequencing

Acknowledgements

We thank the following for support of this project: Rady Children's Institute for Genomic Medicine, San Diego, CA. Shareef Nahas, PhD
David Dimmock, MD
Stephen Kingsmore, MD

Authors' contributions

Study Concept and Design: JF, AN; Acquisition and Analysis of Data: AN, SG, LS, TW, CS, SA, RG, SC, JF (AN, SG, LS, CS, SA, RG provided clinical information and video); TW, SC analyzed genomic data); AN, SG and JF drafted and edited the initial manuscript. All authors reviewed, and critiqued manuscript drafts and approved the final manuscript.

Funding

No funding was received for this study. Dr. Friedman's spouse is Founder and Principal of Friedman Bioventure, which holds a variety of publicly traded and private biotechnology interests. In addition, he is chief operating officer of DTX Pharma which is a company developing RNA therapeutics. Other authors declare no financial disclosures.

Availability of data and materials

KMT2B variant data has been deposited in ClinVar with accession codes (<https://www.ncbi.nlm.nih.gov/clinvar/variation/692033/> Variation ID:692033). Additional data generated or analyzed during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted in compliance with all relevant ethical regulations. Informed consent was obtained from all participants. Approval for human subjects research was obtained from University of California San Diego Institutional Review Board and Rady Children's Hospital Compliance.

Consent for publication

Consent for publication of this report and accompanying videotapes was obtained from all participants and/or their legal guardians.

Competing interests

The authors declare that they have no competing interests.

Author details

¹University of California San Diego, San Diego, CA, USA. ²Rady Children's Hospital, San Diego, CA, USA. ³Sapienza University, Rome, Italy. ⁴Rady Children's Institute for Genomic Medicine, San Diego, CA, USA. ⁵Children's Mercy Hospital, Kansas City, MO, USA.

Received: 12 February 2020 Accepted: 19 May 2020

Published online: 16 June 2020

References

- Scholler I, Nittur S. Understanding failure to thrive. *Paediatr Child Health*. 2012;22(10):438–42.
- Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. *Mov Disord*. 2010;25(11):1538–49.
- Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord*. 2013;28(7):863–73.
- Papapetropoulos S, Singer C. Eating dysfunction associated with oromandibular dystonia: clinical characteristics and treatment considerations. *Head Face Med*. 2006;2(47):1–4.
- Zech M, Boesch S, Maier EM, et al. Haploinsufficiency of *KMT2B*, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. *Am J Hum Genet*. 2016;99(6):1377–87.
- Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene *KMT2B* cause complex early-onset dystonia. *Nature Genet*. 2017;49(2):223–37.
- Ansari KI, Mandal SS. Mixed lineage leukemia: roles in gene expression, hormone signaling and mRNA processing. *FEBS J*. 2010;277(8):1790–804.
- Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med*. 2018;3(10):1–8.
- Briggs B, James KN, Chowdhury S. Novel factor XII variant identified through whole-genome sequencing in a child with intracranial hemorrhage. *Cold Spring Harb Mol Case Stud*. 2018;4(6):1–5.
- Gana S, Veggiotti P, Sciacca G, et al. 19q13.11 cryptic deletion: description of two new cases and indication for a role of WTIP haploinsufficiency in hypospadias. *Eur. J Hum Genet*. 2012;20:852–6.
- Dale RC, Grattan-Smith P, Nicholson M, et al. Microdeletions detected using chromosome microarray in children with suspected genetic movement disorders: a single-Centre study. *Dev Med Child Neurol*. 2012;54:618–23.
- Melo JB, Estevinho A, Saraiva J, et al. Cutis Aplasia as a clinical hallmark for the syndrome associated with 19q13.11 deletion: the possible role for *UBA2* gene. *Mol Cytogenet*. 2015;8:21.
- Reuter M, Tawamie H, Buchert R, et al. Diagnostic yield and novel candidate genes by exome Sequencing in 152 consanguineous families with neurodevelopmental disorders. *JAMA Psychiatry*. 2017;74(3):293–9.
- Zech M, Jech R, Havránková P. *KMT2B* rare missense variants in generalized dystonia. *Mov Disord*. 2017;32(7):1087–91.
- Zech M, Jeck R, Wagner M. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. *Neurogenetics*. 2017; 18(4):195–208.
- Baizabal-Carvalho JF, Alonso-Juarez M. Generalized dystonia associated with mutation in the histone methyltransferase gene *KMT2B* (*DYT28*) and white matter abnormalities. *Parkinsonism Relat Disord*. 2018;49:116–7.
- Hackenberg A, Wagner M, Pahnke J, et al. Low voice, spasmodic dysphonia, and hand dystonia as clinical clues for *KMT2B*-associated early-onset dystonia. *Neuropediatrics*. 2018;49(5):356.
- Faundes V, Newman WG, Bernardini L. Histone lysine Methylases and Demethylases in the landscape of human developmental disorders. *Am J Hum Genet*. 2018;102(1):175–87.
- Dai L, Ding C, Fang F. An inherited *KMT2B* duplication variant in a Chinese family with dystonia and/or development delay. *Parkinsonism Relat Disord*. 2019;63:227–8.
- Zhou XY, Wu JJ, Sun YM. An atypical case of early-onset dystonia with a novel missense variant in *KMT2B*. *Parkinsonism Relat Disord*. 2019;63:224–26.

21. Kawai T, Miyamoto R, Nakagawa E, et al. Phenotype variability and allelic heterogeneity in KMT2B-associated disease. *Parkinsonism Relat Disord.* 2018; 52:55–61.
22. Klein C, Baumann H, Olschewski L. De-novo KMT2B mutation in a consanguineous family: 15-Year Follow-Up of an Afghan Dystonia Patient. *Parkinsonism Relat Disord.* 2019;64:337-39.
23. Dafsari HS, Sprute R, Wunderlich G, et al. Novel mutations in KMT2B offer pathophysiological insights into childhood-onset progressive dystonia. *J Hum Genet.* 2019;64:803-13.
24. Lange LM, Tunc S, Tennstedt S. A novel, in-frame KMT2B deletion in a patient with apparently isolated, Generalized Dystonia. *Mov Disord.* 2017; 32(10):1495–7.
25. Brás A, Ribeiro JA, Sobral F. Early-onset oromandibular-laryngeal dystonia and Charlot gait: new phenotype of DYT-KMT2B. *Neurology.* 2019;92(19): 919.
26. Carecchio M, Invernizzi F, González-Latapi P, et al. Frequency and phenotypic spectrum of KMT2B dystonia in childhood: A single-center cohort study. *Mov Disord.* 2019;34:1516-27.
27. Ma J, Wang L, Yang Y, et al. Identification of novel KMT2B variants in Chinese dystonia patients via whole-exome sequencing. *Front Neurol.* 2019; 10:1–6.
28. Kumar KR, Davis RL, Tchan MC. Whole genome sequencing for the genetic diagnosis of heterogeneous dystonia phenotypes. *Parkinsonism Related Disord.* 2019;69:111–8.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

