Received: 18 June 2021 | Accepted: 27 December 2021

DOI: 10.1002/ccr3.5277

Clinical Case Reports Open Access WILEY

CASE REPORT

Novel truncating variant in *KMT2E* associated with cerebellar hypoplasia and velopharyngeal dysfunction

Nicolas J. Abreu[1,2] | **Amy E. Siemon**[3] | **Adriane L. Baylis**[4,5,6,7] | **Richard E. Kirschner**[4,5,6] | **Ruthann B. Pfau**[5,8,9] | **Mai-Lan Ho**[10,11] | **Scott E. Hickey**[3,5] | **Kristen V. Truxal**[3,5]

[1]Center for Gene Therapy, The Abigail Wexner Research Institute of Nationwide Children's Hospital, Columbus, Ohio, USA

[2]Division of Neurology, Nationwide Children's Hospital, Columbus, Ohio, USA

[3]Division of Genetic & Genomic Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA

[4]Department of Plastic and Reconstructive Surgery, Nationwide Children's Hospital, Columbus, Ohio, USA

[5]Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio, USA

[6]Department of Plastic and Reconstructive Surgery, The Ohio State University College of Medicine, Columbus, Ohio, USA

[7]Department of Speech and Hearing Science, The Ohio State University, College of Arts and Sciences, Columbus, Ohio, USA

[8]The Steve and Cindy Rasmussen Institute for Genomic Medicine, The Abigail Wexner Research Institute of Nationwide Children's Hospital, Columbus, Ohio, USA

[9]Department of Pathology, The Ohio State University College of Medicine, Columbus, Ohio, USA

[10]Department of Radiology, Nationwide Children's Hospital, Columbus, Ohio, USA

[11]Department of Radiology, The Ohio State University College of Medicine, Columbus, Ohio, USA

Correspondence
Kristen V. Truxal, Clinical Assistant Professor of Pediatrics, The Ohio State University, Division of Genetic and Genomic Medicine, Nationwide Children's Hospital & Research Institute, Columbus, OH, USA.
Email: Kristen.Truxal@nationwidechildrens.org

Funding information
The authors report no funding relevant to the manuscript

Abstract

KMT2E-related neurodevelopmental disorder is a recently described intellectual disability syndrome often with speech difficulties. Here, we describe an individual with a heterozygous frameshift variant in *KMT2E* (NM_182931.2:c.2334_2337delTTAC, p.[Tyr779AlafsTer41]), intellectual disability, cerebellar hypoplasia, and velopharyngeal dysfunction. This case suggests potential mechanisms of speech disturbance in the disorder, requiring further investigation.

KEYWORDS
cerebellar hypoplasia, KMT2E, neurodevelopmental disorder, velopharyngeal dysfunction

1 | INTRODUCTION

Lysine-specific methyltransferase 2E (KMT2E) belongs to a family of enzymes that regulates histone methylation critical for transcriptional control.[1] Heterozygous variants in *KMT2E* have been associated with neurodevelopmental disabilities typically characterized by intellectual disability, hypotonia, gastrointestinal concerns, and mild facial dysmorphisms.[1] Here, we further expand the phenotype of *KMT2E*-related neurodevelopmental disorder in an individual with a novel truncating variant with cerebellar hypoplasia, dysarthria, and velopharyngeal dysfunction (VPD).

2 | CASE REPORT

The proband is a 15-year-old boy born to nonconsanguineous parents after an unremarkable pregnancy and delivery. His early developmental milestones were normal. Beginning around 2 years of age, hypernasal speech, an articulation disorder, and reduced intelligibility were noted. At 6 years old, he was diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).

He received multiple sets of tympanostomy tubes for recurrent episodes of otitis media, but with no evidence of hearing loss. He was also identified to have gastroesophageal reflux, severe hyperopia, alternating exotropia, right eye amblyopia, and regular astigmatism.

Neuropsychological evaluation at 10 years 9 months was consistent with mild intellectual disability with a full-scale intelligence quotient of 47 on the Stanford-Binet Intelligence Scales, 5th edition, and an adaptive behavior composite standard score of 60 on the Vineland Adaptive Behavior Scales, 2nd Edition. There was insufficient evidence for autism spectrum disorder with a score below cutoff on the Autism Diagnostic Observation Schedule, 2nd edition, Module 3.

He was diagnosed with velopharyngeal dysfunction at 12 years of age through team evaluation with a specialist speech-language pathologist and plastic surgeon. His speech was characterized by phonological errors, primarily stopping, fronting, and glottal stop substitutions, and hypernasality. Consistent inaudible nasal emission was also observed during nasal mirror testing. Nasometry, an acoustic test to measure nasality in speech, revealed elevated scores, consistent with hypernasality. Intraoral examination confirmed normal oropharyngeal anatomy and ruled out a submucous cleft palate, thus a neurogenic cause of VPD was suspected. In addition to his articulation difficulties, his speech was characterized by reduced variability in tone, stress, pitch, and loudness suggestive of a complex motor speech disorder, with features of both dysarthria and apraxia of speech.

On examination, the individual had normal stature (Z = 0.23), weight (Z = 0.46), and a mildly enlarged head (Z = 1.37). His facial dysmorphisms included deep-set eyes, upslanting palpebral fissures, long, straight eyebrows, a broad nasal tip, mildly prominent upper helices, and a thin upper lip (Figure 1A,B). He had keratosis pilaris and bilateral fifth finger clinodactyly. Mental status was notable for dysarthric, hypernasal, and fluent speech (Video S1). End-gaze nystagmus was noted in previous examinations and there was breakdown in smooth pursuit on our evaluation. There was no evidence of dysmetria. He had mild unsteadiness of tandem gait but no ataxia. There was mild hypotonia but normal reflexes.

Previous evaluations were non-diagnostic, including a karyotype, single nucleotide polymorphism-based microarray, Fragile X analysis, and an ataxia gene panel for trinucleotide repeat disorders (*ATN1*, *FXN*, *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *ATXN8*, *ATXN8OS*, *ATXN10*, *PPP2R2B*, *TBP*, and *NOP56*). Brain MRI at 12 years 11 months demonstrated mild global cerebellar hypoplasia, patchy periventricular white matter T2 hyperintensities (Figure 1C,D), dysgyria of the sylvian fissures, small olfactory bulbs, and underrotated hippocampi.

Whole exome sequencing (WES) was performed at The Steve and Cindy Rasmussen Institute for Genomic Medicine Clinical Laboratory at Nationwide Children's Hospital. As the father was not available for testing, DNA was analyzed from peripheral blood of the proband and his mother. WES was initially unrevealing; however, reanalysis identified a heterozygous variant in *KMT2E* (NM_182931.2:c.2334_2337delTTAC, p.[Tyr779AlafsTer41]) after *KMT2E*-related neurodevelopmental disorders were reported in the medical literature.[1] This variant was absent from population databases (ACMG/AMP: PM2), and predicted to encode a premature stop in translation in a gene where loss of function is reported (ACMG/AMP: PVS1).[1,2] Taken together, this variant was classified as likely pathogenic and was not identified in his mother.

3 | DISCUSSION

The proband demonstrates many overlapping features with previously described patients, including intellectual disability, large head size, hypotonia, and gastrointestinal symptoms.[1,3,4] His frameshift variant is located outside of the two known functional domains but is expected to lead to loss of function because of nonsense-mediated decay. Our case is consistent with previous findings that truncating variants are more likely to be associated with larger head size as well as reduced likelihood of seizures compared to individuals with missense variants.[1,5]

Here, we analyzed the proband's speech difficulties, which is a common symptom of *KMT2E*-related neurodevelopmental disorder reported in at least 44% of affected individuals,[4] and found VPD and apraxia of speech. Often VPD occurs in the setting of a structural oropharyngeal anomaly like a cleft palate, however, this was not seen in our patient nor previously reported.[1,3,4] We believe this may be an important finding to help inform speech and language therapy interventions for individuals with this disorder, but this aspect of the phenotype requires further investigation across a larger cohort. A number of genetic and neurologic causes of non-cleft VPD exist,[6] and so we recommend that *KMT2E*-related neurodevelopmental

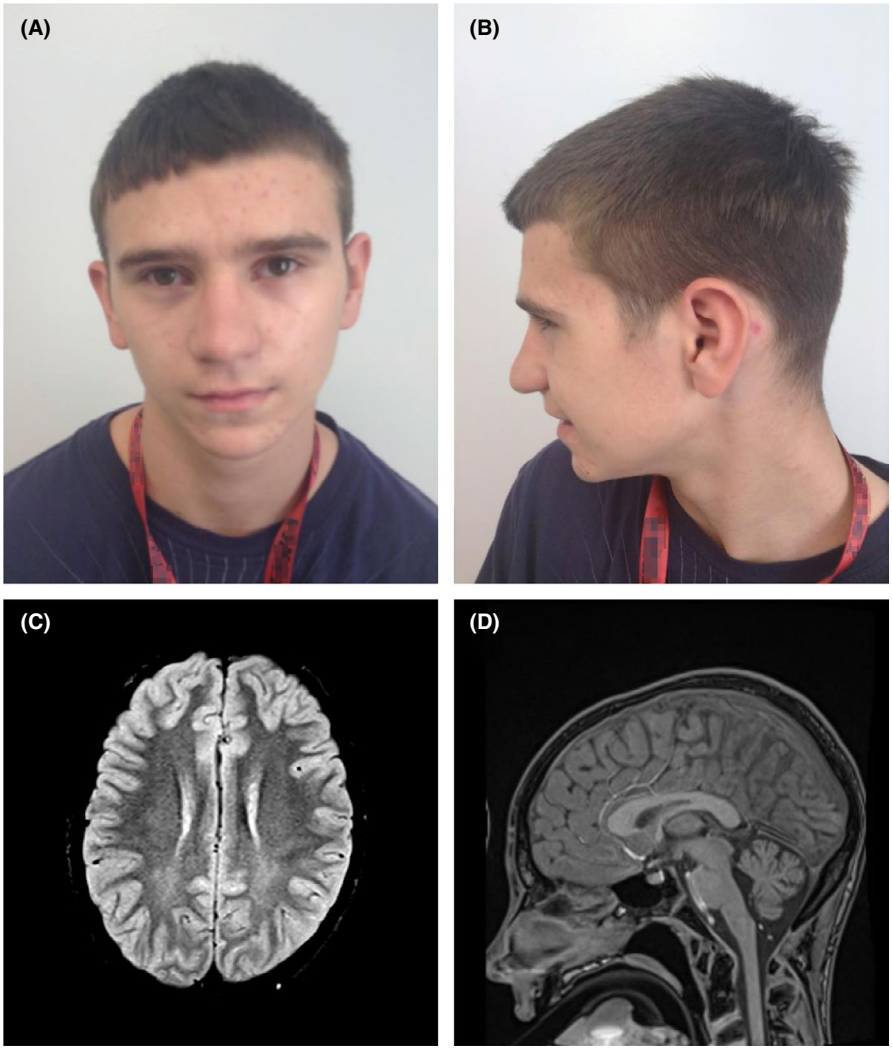

FIGURE 1 (A) Frontal and (B) profile photographs of the proband at 15 years of age demonstrating long, straight eyebrows with deep-set eyes, broad nose with prominent tip, ears with outward deviation of upper helices, mildly smooth philtrum, and thin upper lip. Brain MRI was performed under general anesthesia at 12 years of age in which (C) axial T2 FLAIR sequence shows patchy posterior-predominant white matter hyperintensities and (D) sagittal MPRAGE sequence highlights reduced cerebellar volume

disorder be considered in the list of possible etiologies, especially when there is co-existing intellectual disability.

Given the finding of reduced cerebellar volume in our case, we speculate whether at least some of the proband's phenotype may be explained through *KMT2E*-related cerebellar disruption. Evidence of cerebellar dysfunction in our case included impaired smooth pursuit and difficulty with tandem gait, as well as a history of nystagmus and alternating exotropia. Cerebellar abnormalities have been reported in three other individuals with *KMT2E*-related neurodevelopmental disorder, including one individual with diffuse cerebellar atrophy,[5] another with right cerebellar hypoplasia,[1] and a third person with cerebellar dysplasia and inferior vermis hypoplasia.[3] Further, other disorders associated with VPD like 22q11.2 deletion syndrome have reduced cerebellar volumes.[7] In this report, we extend prior work highlighting a potential neuroanatomical basis of the neurodevelopmental features of *KMT2E*-related disorders and we encourage special attention to speech and neuroimaging phenotyping to understand the disease spectrum.

ACKNOWLEDGEMENTS

We gratefully acknowledge the patient and his family for entrusting us with his care. We appreciate the correspondence of Dr. Lance Rodan of Boston Children's Hospital, who provided topical expertise.

CONFLICTS OF INTERESTS

None of the authors has a relevant conflict of interest.

AUTHOR CONTRIBUTION

Nicolas J. Abreu designed and conceptualized study; acquired and interpreted data; drafted the manuscript. Amy E. Siemon, Adriane L. Baylis, Richard E. Kirschner, and Ruthann B. Pfau acquired and interpreted the data; revised the manuscript for intellectual content. Mai-Lan Ho interpreted the data; revised the manuscript for intellectual content. Scott E. Hickey designed and conceptualized study; interpreted the data; revised the manuscript for intellectual content. Kristen V. Truxal designed and conceptualized study; acquired and interpreted the data; revised the manuscript for intellectual content.

CONSENT

The patient and his family provided written consent for the publication of the case, including use of identifying photographs and video.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

ORCID

Nicolas J. Abreu https://orcid.org/0000-0002-8288-6268

REFERENCES

1. O'Donnell-Luria AH, Pais LS, Faundes V, et al. Heterozygous variants in KMT2E cause a spectrum of neurodevelopmental disorders and epilepsy. *Am J Hum Genet*. 2019;104(6):1210-1222. doi:10.1016/j.ajhg.2019.03.021
2. Richards S, Aziz N, Bale S, 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(5):405-424. doi:10.1038/gim.2015.30
3. Conforti R, Iovine S, Santangelo G, et al. ODLURO syndrome: personal experience and review of the literature. *Radiol Med*. 2021;126(2):316-322. doi:10.1007/s11547-020-01255-2
4. Sharawat IK, Panda PK, Dawman L. Clinical characteristics and genotype-phenotype correlation in children with KMT2E gene-related neurodevelopmental disorders: report of two new cases and review of published literature. *Neuropediatrics*. 2021;52(2):98-104. doi:10.1055/s-0040-1715629
5. Li Y, Fan L, Luo R, et al. Case report: de novo variants of KMT2E cause O'Donnell-Luria-Rodan syndrome: additional cases and literature review. *Front Pediatr*. 2021;9:641841. doi:10.3389/fped.2021.641841
6. Goudy S, Ingraham C, Canady J. Noncleft velopharyngeal insufficiency: etiology and need for surgical treatment. *Int J Otolaryngol*. 2012;2012:1-3. doi:10.1155/2012/296073
7. Haenssler AE, Baylis A, Perry JL, Kollara L, Fang X, Kirschner R. Impact of cranial base abnormalities on cerebellar volume and the velopharynx in 22q11.2 Deletion syndrome. *Cleft Palate Craniofac J*. 2020;57(4):412-419. doi:10.1177/1055665619874175

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Abreu NJ, Siemon AE, Baylis AL, et al. Novel truncating variant in *KMT2E* associated with cerebellar hypoplasia and velopharyngeal dysfunction. *Clin Case Rep*. 2022;10:e05277. doi:10.1002/ccr3.5277