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

Nicolas J. Abreu1,2 | Amy E. Siemon3 | Adriane L. Baylis4,5,6,7 | Richard E. Kirschner4,5,6 | Ruthann B. Pfau5,8,9 | Mai-Lan Ho10,11 | Scott E. Hickey3,5 | Kristen V. Truxal3,5

1Center for Gene Therapy, The Abigail Wexner Research Institute of Nationwide Children’s Hospital, Columbus, Ohio, USA
2Division of Neurology, Nationwide Children’s Hospital, Columbus, Ohio, USA
3Division of Genetic & Genomic Medicine, Nationwide Children’s Hospital, Columbus, Ohio, USA
4Department of Plastic and Reconstructive Surgery, Nationwide Children’s Hospital, Columbus, Ohio, USA
5Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio, USA
6Department of Plastic and Reconstructive Surgery, The Ohio State University College of Medicine, Columbus, Ohio, USA
7Department of Speech and Hearing Science, The Ohio State University, College of Arts and Sciences, Columbus, Ohio, USA
8The Steve and Cindy Rasmussen Institute for Genomic Medicine, The Abigail Wexner Research Institute of Nationwide Children’s Hospital, Columbus, Ohio, USA
9Department of Pathology, The Ohio State University College of Medicine, Columbus, Ohio, USA
10Department of Radiology, Nationwide Children’s Hospital, Columbus, Ohio, USA
11Department of Radiology, The Ohio State University College of Medicine, Columbus, Ohio, USA

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 pillaris 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), dysgryia 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
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, another with right cerebellar hypoplasia, and a third person with cerebellar dysplasia and inferior vermis hypoplasia. Further, other disorders associated with VPD like 22q11.2 deletion syndrome have reduced cerebellar volumes. 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.

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**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

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SUPPORTING INFORMATION
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