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A Recurrent *De Novo* Variant in *EIF2AK2* Causes a Hypomyelinating Leukodystrophy

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Abstract

De novo pathogenic variants in *EIF2AK2* have recently been reported as a novel genetic cause of leukoencephalopathy. Here, we describe a male individual who presented in the first year of life with clinical features resembling Pelizaeus-Merzbacher disease (PMD), including nystagmus, hypotonia, and global developmental delay, and which later progressed to include ataxia and spasticity. Brain MRI at the age of two revealed diffuse hypomyelination. This report adds to the limited number of individuals published and further reinforces *de novo* variants in *EIF2AK2* as a molecular cause of a leukodystrophy that clinically and radiologically resembles PMD.

Keywords

leukodystrophy, hypomyelination, *EIF2AK2*, exome sequencing

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Introduction

EIF2AK2 (OMIM *176871) encodes a ubiquitously expressed serine/threonine protein kinase tasked with inhibiting protein synthesis as part of the integrated stress response.[1] While canonically, this protein functions in response to infection by double-stranded RNA (dsRNA) viruses, cell stressors such as endoplasmic reticulum (ER) stress and amino acid deprivation can likewise activate this pathway via a dsRNA-independent mediated mechanism.[2] *De novo* pathogenic variants in *EIF2AK2* have newly been described in ten individuals as the underlying genetic cause of a white matter abnormality, also referred to as LEUDEN syndrome (OMIM #618877) for leukoencephalopathy, developmental delay, and episodic neurological regression syndrome. Here, we report the case of a patient who presented with clinical features reminiscent of Pelizaeus-Merzbacher Disease (PMD), including nystagmus in infancy, hypotonia that evolved into severe appendicular spasticity, and cognitive delay. Brain magnetic resonance imaging (MRI) at two years of age showed severe hypomyelination. Trio exome sequencing pursued at the age of five identified the variant in *EIF2AK2* (NM_001135651.3 c.325G>T, NP_001129123.1 p.Ala109Ser). The variant was detected *de novo* in the heterozygous state (parentage confirmed by SNPs) and confirmed via Sanger sequencing. The case reported here adds to the prevalence of individuals harboring a pathogenic variant in *EIF2AK2* and which show a presentation similar to PMD.

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Case

The patient, a male, was born healthy and at term to non-consanguineous parents and had an uneventful perinatal period. Family history is unremarkable, and he has a healthy younger sister. At 3 months, he was noted to have stridor and underwent laryngeal surgery. At 1 year of age, he demonstrated failure to thrive, with feeding difficulties, low body weight (6.3 kg, −4.1 SD) and a small head circumference (41 cm, −4.2 SD). Abnormal eye movements were also noted from infancy and included horizontal nystagmus, convergent squint, and jerky eye movements, the former of which subsided by 4 years of age. He would experience generalized muscle stiffness and apnea upon crying. A severe motor delay was evident, and he had difficulties reaching developmental milestones. Generalized hypotonia was noted starting in infancy and later evolved into severe appendicular spasticity. Additional features include dystonia, involuntary movements, and dysphagia. Now, at six years of age, he is cognitively delayed and shows little interest in surrounding environments. Of note, he has not experienced febrile illness-induced neurological regression, as has previously been seen in reported cases of *EIF2AK2*-related disorder.[3,4]

Various clinical testing was pursued. An EEG revealed no epileptic activity. Fundoscopy examination showed normal-appearing retina and optic discs, while both visual evoked potentials and electroretinography were severely abnormal. An initial

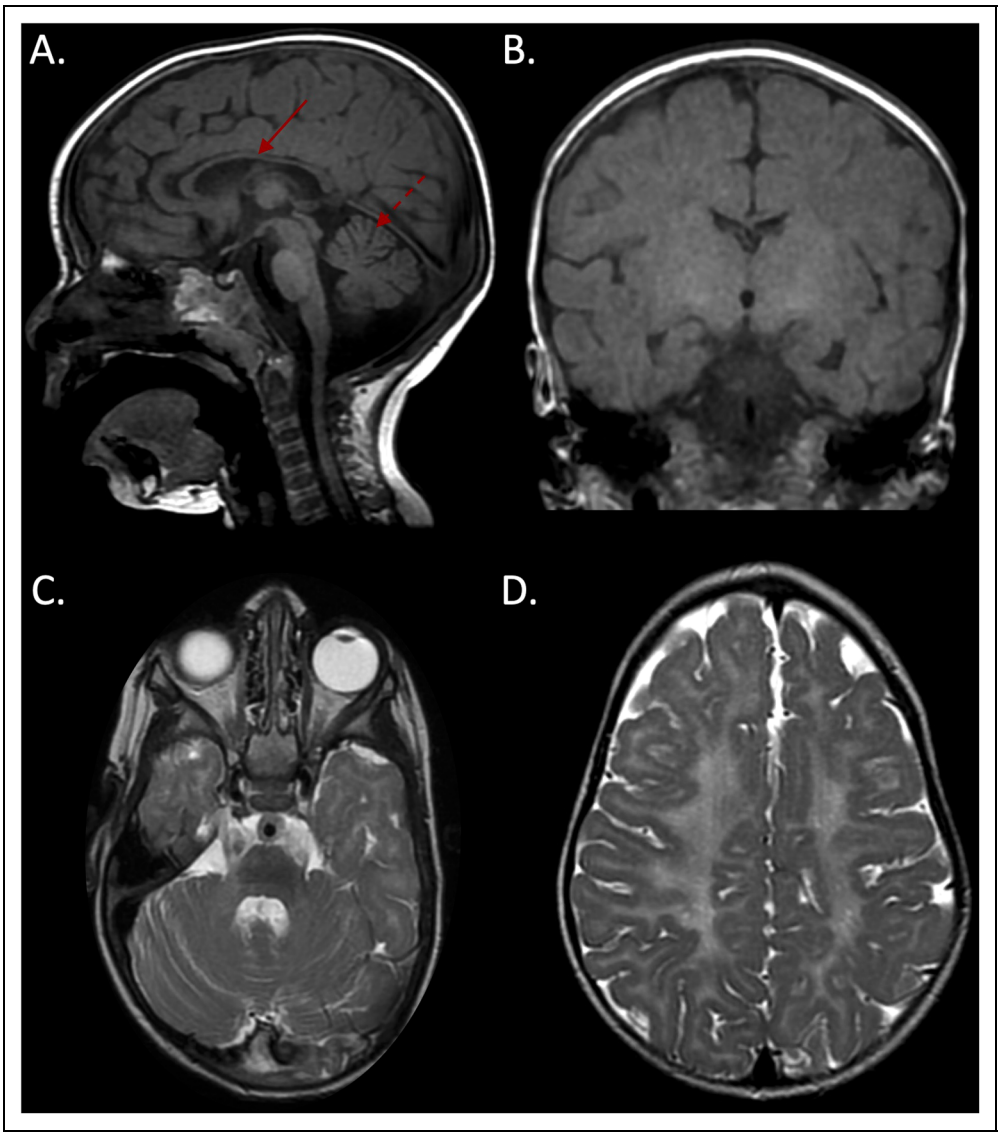

Figure 1. Brain MRI features at 2 years of age. Neuroimaging findings demonstrating diffuse hypomyelination. **A.** Sagittal T1-weighted MRI showing a thin corpus callosum (red arrow) and mild superior cerebellar vermis atrophy (red dashed arrow). **B**, **C**, **D**. Diffuse hypomyelination, with isointense signal of the cerebral white matter relative to grey matter on T1-weighted image (**B**, coronal T1) and hyperintensity of cerebral white matter on T2-weighted images (**C**, **D**, axial T2 at the levels of the pons and centrum semiovale, respectively), relative to grey matter structures.

MRI done at 7 months revealed no myelin deposition outside of the basal ganglia, thalamus, cerebellum or brainstem. Diffuse hypomyelination, with hyperintensity of the white matter on T2-weighted images and isointense white matter signal on T1-weighted images relative to grey matter structures, was likewise seen on repeat MRI at 2 years of age (Figure 1A-D). Additional neuroradiological findings included a thin corpus callosum and mild cerebellar vermis atrophy (Figure 1A).

Routine chromosome testing was normal. At 1 year of age, the patient underwent sequencing analysis for a leukodystrophy and leukoencephalopathy gene panel which did not reveal any known disease-causing mutations, including no identification of a single nucleotide variant in the gene encoding proteolipid 1 (*PLP1*), the causative gene in PMD. Comparative genomic hybridization (CGH) array was performed to test for a *PLP1* duplication, which was unremarkable. Clinical exome sequencing (ES) was later pursued and likewise, did not identify any pathogenic variants. Trio ES was pursued on a research basis at the age of five and analyzed using the Emedgene software and interpretation system (Emedgene technologies; Tel Aviv, Israel). This research ES revealed a *de novo* heterozygous variant in *EIF2AK2* at position NM_001135651.3 c.325G>T (NP_001129123.1 p.Ala109Ser), a variant that has recently been reported as disease-causing by Mao and colleagues.[3] No other variants associated with hypomyelinating leukodystrophies were identified. Parentage was confirmed by Emedgene and Sanger sequencing was performed to confirm the variant (Figure 2A,B). Of note, written informed consent from legal guardians of the patient was obtained and the study was approved by the Montreal Children's Hospital and the McGill University Health Center (11-105-PED, 2019-4972).

Discussion

Here, we describe an individual with characteristic features of hypomyelinating leukodystrophy and a complex neurological disorder in which the genetic etiology is believed to be a pathogenic variant in *EIF2AK2*. *De novo* variants in *EIF2AK2* were recently reported as a genetic cause of leukodystrophy and thus far, only ten individuals have been described in the literature. In the cohort of eight individuals initially described, the neuroradiological patterns and clinical findings were variable.[3] Following this, Calame *et al*. reported two unrelated individuals with a phenotype that closely resembles PMD including diffuse, symmetric hypomyelination. Beyond neuroradiological findings, clinical features of these two patients also overlapped with cardinal features of PMD. These common neurological findings include nystagmus, often one of the first identifying features of PMD, as well as cerebellar (e.g., ataxia) and pyramidal (e.g., spasticity) signs, and developmental delay.[5] All of these clinical and neuroradiological features are likewise present in the individual reported here (Table 1).

EIF2AK2 variants are most commonly present in one of the two dsRNA binding sites or in the kinase domain of the EIF2AK2 protein.[3] Interestingly, of the only ten previously described individuals with *EIF2AK2*-related disorder, three unrelated individuals from two independent studies have had missense mutations at the Ala109 protein position (p.Ala109Ser, p.Ala109Val), suggesting that this is a mutation hotspot.[3,4] Functional studies performed revealed that these variants (p.Ala109Ser/Val) lead to reduced EIF2AK2 protein levels, further supporting their pathogenicity.[3] Variants in *EIF2AK2* have likewise been identified in the molecular pathology of early-onset generalized dystonia (OMIM #619687), with either autosomal recessive or autosomal dominant inheritance, or occurring *de novo*.[6-9] In these cases, dystonia is seen isolated from other neurological features and the variants are found at distinct residues, although at least one variant has been reported as common between the two disorders.[3,6] We suggest that EIF2AK2-related disorders have a disease spectrum and that this spectrum might expand as more individuals with pathogenic variants in this gene are uncovered.

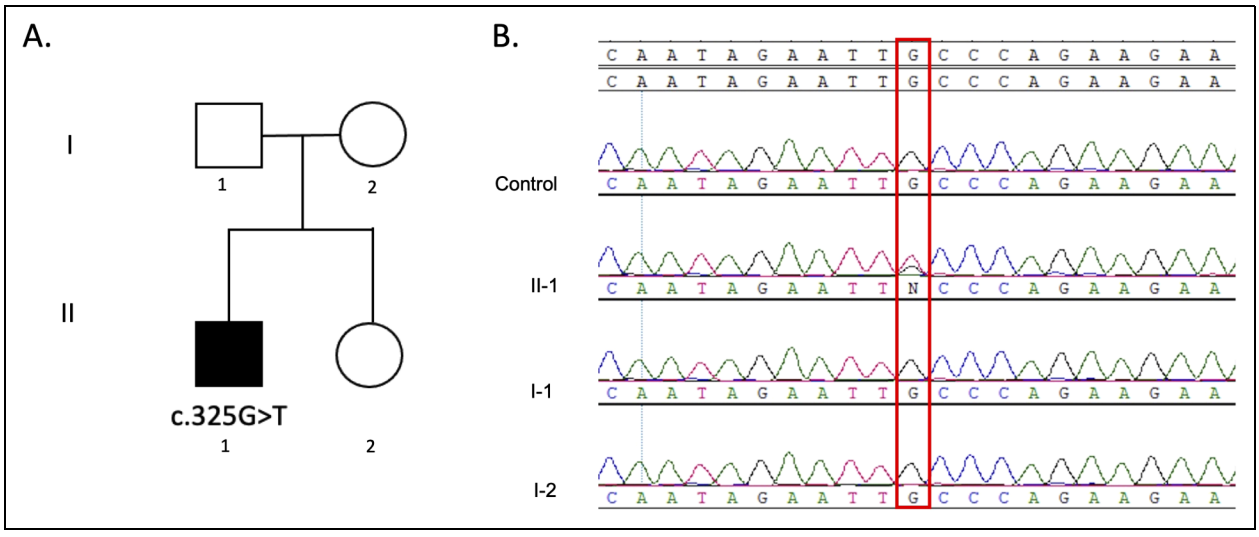

Figure 2. Genetic analysis of the *EIF2AK2* variant. A. Pedigree of family and **B**. Chromatograms of affected individual and healthy parents, confirming the variant in *EIF2AK2* is absent from the healthy parents. Of note, written informed consent from legal guardians of the patient was obtained and the study was approved by the Montreal Children's Hospital and the McGill University Health Center (11-105-PED, 2019-4972).

Table 1. Molecular, Clinical, and Neuroradiological Features of Individuals with EIF2AK2-Related Leukodystrophy. Abbreviations: +, Present; -, Absent; n.a, not available.

	Mao *et al* 2020[3]								Calame *et al* 2021[4]		
	Proband 2	Proband 3	Proband 4	Proband 5	Proband 6	Proband 7	Proband 8	Proband 9	Proband 1	Proband 2	Current case
Variant Information	c.31A > C p.Met11Leu	c.398A > T p.Tyr133Phe	c.973G > A p.Gly325Ser	c.1382C > G p.Ser461Cys	c.326C > T p.Ala109Val	c.325G > T p.Ala109Ser	c.95A > G p.Asn32Ser	c.290C > T p.Ser97Phe	c.290C > T p.Ser97Phe	c.326C > T p.Ala109Val	c.325G > T p.Ala109Ser
Inheritance	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*
Gender	Male	Male	Female	Male	Male	Male	Male	Male	Male	Male	Male
OFC at latest assessment (cm)	53.2 (Z = −0.05)	52.8 (Z = −0.66)	44.5 (Z = −1.18)	43 (Z = −3)	44.5 (Z = −2.42)	48.8 (Z = −1.4)	49 (Z = −1)	49 (Z = −1.61)	44.5 (Z = −1.17)	41 (Z = −2.67)	43.5 (Z = −6)
Failure to thrive	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	+	+	+
Ambulatory	+	+	+	−	−	+	+	−	−	−	−
Nonverbal or Dysarthria	Dysarthria	Dysarthria	Dysarthria	Nonverbal	Nonverbal	Dysarthria	Dysarthria	Nonverbal	Nonverbal	n.a.	Nonverbal
Nystagmus	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	+	+	+
Hypotonia	+	+	+	+	+	+	−	+	+	+	+
Spasticity	−	+	+	+	−	+	+	+	+	+	+
Ataxia	+	+	+	n.a.	n.a.	+	−	−	+	+	+
Dystonia	+	+	−	+	+	−	−	+	−	−	+
Epilepsy	+	−	−	+	+	−	−	+	+	−	−
Developmental delay	+	+	+	+	+	+	+	+	+	+	+
Episodic neurological regression	+	+	+	+	+	+	+	+	+	+	−
Hypomyelination/abnormal myelination	+	+	+	n.a.	n.a.	+	+	+	+	+	+
Thin corpus callosum	+	+	+	+	+	+	+	+	+	+	+
Cerebellar atrophy	+	+	−	−	+	+	−	+	+	−	+

In summary, this report further reinforces *EIF2AK2* as a molecular cause of hypomyelinating leukodystrophy, adding it to the growing list of genes associated with hypomyelinating leukodystrophy which do not contribute directly to myelination,[10] and advises for its future inclusion in leukodystrophy and leukoencephalopathy gene panels. Additionally, we aim to add to the discussion of *EIF2AK2*-related leukoencephalopathy as a disorder with a presentation that mimics PMD, the most common hypomyelinating leukodystrophy, and suggest its consideration in the differential diagnosis of PMD.

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Declaration of Conflict of Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Bernard is/was a consultant for Passage Bio Inc (2020-2022) and Ionis (2019). She is/was a site investigator for the Alexander's disease trial of Ionis (2021-present), Metachromatic leukodystrophy of Shire/Takeda (2020-2021), Krabbe and GM1 gene therapy trials of Passage Bio (2021-present), Passage Bio GM1 natural history study (2021-present) and Adrenoleukodystrophy/Hematopoietic stem cell transplantation natural history study of Bluebird Bio (2019), a site subinvestigator for the MPS II gene therapy trial of Regenxbio (2021-present) and the MPS II clinical trial of Denali (2022-present). She has received unrestricted educational grants from Takeda (2021-2022). She serves on the scientific advisory board of the Pelizaeus-Merzbacher Foundation, the Yaya Foundation Scientific and Clinical Advisory Council and is the Chair of the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation. She is a member of the Vanishing White Matter Consortium, the MLC Consortium, the H-ABC Clinical Advisory Board and the Chair of the POLR3-related (4H) Leukodystrophy Consortium. She is on the editorial boards of Neurology Genetics, Frontiers in Neurology—Neurogenetics, and Journal of Medical Genetics.

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