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العدد الواحد

والثلاثون

اعتلال المادة البيضاء في الدماغ مع تلاشيها في عائلة عراقية: اكتشاف استبدال

جديد في جين EIF2B3

م.م. شيماء منعم سعيد

جامعة ميسان/ قسم علوم الحياة
shayma.ms@uomisan.edu.iq

المستخلص:

يُعدّ اعتلال ببيضاء الدماغ (leukodystrophies) اضطراباً وراثياً نادراً يؤثر على المادة البيضاء في الدماغ، مما يُصعّب تشخيصه وإدارته. يُظهر أحد أنواعه، وهو اعتلال ببيضاء الدماغ المصحوب بتلاشي المادة البيضاء، مجموعة متنوعة من الأعراض العصبية بدرجات متفاوتة من الشدة. تُساعد التطورات في التشخيص، مثل تحديد الطفرات الجينية في عائلة جين EIF2B، على كشف الآليات الجينية الكامنة وراء هذه الحالة. في هذه الحالة، فُحص طفل عراقي يبلغ من العمر خمس سنوات يُعاني من أعراض ما قبل الولادة، بما في ذلك نوبات صرع، وتأخر النمو داخل الرحم، وقلة الحركة، وقلة السائل السلوي، من خلال تسلسل الإكسوم والتصوير بالرنين المغناطيسي. تم تحديد طفرة جديدة (hg38: chr1-44941633-T-C) ؛ c.327A>G ؛ p.Ile109Met في الإكسون ٤ من جين EIF2B3، تُسبب استبدال الإيزوليوسين بالميثيونين. وقد تنبأ التحليل الحاسوبي بالآثار المحتملة لهذه الطفرة. تُسلط هذه الحالة الضوء على أهمية اكتشاف طفرة جديدة، تُسهم في فهم جينات المادة البيضاء المتلاشي، وتُظهر كيف يُمكن لتقنيات التسلسل المُتقدّمة تحسين التشخيص والعلاجات المُخصّصة للاضطرابات الوراثية.

الكلمات المفتاحية: اعتلال ببيضاء الدماغ المصحوب باختفاء المادة البيضاء، جين EIF2B، طفرة، تسلسل الإكسوم.

Leukoencephalopathy with Vanishing White Matter in an Iraqi Family:

Discovery of a Novel EIF2B3 Substitution

Assis LecSHAYMAA MUNEAM SAEED



University of Misan/Department of Biology

shayma.ms@uomisan.edu.iq

Abstract:

Leukodystrophies are rare genetic disorders that affect the brain's white matter, making diagnosis and management difficult. One type, leukoencephalopathy with vanishing white matter, shows a variety of neurological symptoms with different levels of severity. Advances in diagnostics, like identifying genetic mutations in the EIF2B gene family, help uncover the genetic mechanisms behind the condition. In this case, a 5-year-old Iraqi boy with prenatal symptoms, including seizures, intrauterine growth retardation, decreased movements, and oligohydramnios, was examined through exome-sequencing and magnetic resonance imaging. A novel mutation (hg38: chr1-44941633-T-C; c.327A>G; p.Ile109Met) in exon 4 of the EIF2B3 gene was identified, causing a substitution of Isoleucine with Methionine. In silico analysis predicted the potential effects of this mutation. This case highlights the significance of finding a novel mutation, contributing to the understanding of vanishing white matter genetics and showing how advanced sequencing techniques can improve diagnostics and personalised treatments for genetic disorders.

Keywords: leukoencephalopathy with vanishing white matter, EIF2B3 gene, mutation, exome-sequencing

1.Introduction

Leukodystrophies, a subset of rare genetic disorders affecting the white matter of the brain, present a daunting challenge to both patients and medical professionals. Characterised by abnormal expansion within the brain's white matter, these conditions collectively known as leukoencephalopathies encompass a spectrum of diseases, including the enigmatic leukoencephalopathy with vanishing white matter (VWM) (Lee et al.,2021). Despite their rarity, the impact of leukodystrophies cannot be understated, often leading to progressive neurological decline and, in some cases, early mortality(Köhler & Vanderver, 2018).

Among leukodystrophies, VWM stands out as one of the more prevalent forms, with its onset and severity varying widely among affected



individuals (Hyun et al., 2019). From a mild adult-onset phenotype to the severe congenital form, VWM manifests through a myriad of symptoms including motor and intellectual impairment, chronic childhood ataxia, optic atrophy, spasticity, and a propensity for premature mortality (Kami et al., 2023) The rarity of VWM, estimated at 1 in 80,000 live births or potentially higher, underscores its significance as a clinically relevant neurogenetic disorder (Hamilton et al., 2018).

Diagnostic challenges have historically plagued efforts to identify VWM, with biochemical markers eluding researchers until recent breakthroughs. Notably, elevated glycine concentrations in cerebrospinal fluid and reduced levels of asialotransferrin have emerged as potential biomarkers, aiding in the diagnostic process alongside brain magnetic resonance imaging (MRI) scans and clinical symptom evaluation (Vanderver et al., 2005; Deginet et al., 2021).

Central to the pathogenesis of VWM are mutations within the EIF2B gene family, specifically EIF2B1 through EIF2B5, which encode vital subunits of the eukaryotic translation initiation factor 2B (EIF2B) (Labauge et al., 2009). While genetic variations within EIF2B are not uncommon, mutations resulting in a complete loss of protein are notably rare and typically occur in conjunction with missense mutations in a compound heterozygous state (Proud et al., 2012). This genetic complexity underscores the intricate interplay between EIF2B mutations and protein expression, with complete loss-of-function mutations representing a critical threshold beyond which essential cellular processes are compromised.

Moreover, numerous studies have conclusively demonstrated that stress factors can act as catalysts for significant episodes of neurological damage in patients grappling with VWM (Shimada et al., 2015). These stressors, ranging from fever and febrile seizures to head injuries, extreme fear, infections, and surgical procedures, have been identified as triggers for exacerbating neurological symptoms in affected individuals. The EIF2B protein complex emerges as a pivotal player in the intricate regulation of cellular responses to a spectrum of stressors, encompassing physical, chemical, and oxidative stress. The observed correlation underscores the



potential link between EIF2B mutations and the episodic intensification of neurological manifestations during periods of heightened tension, shedding light on the intricate interplay between genetic factors and environmental triggers in the context of VWM pathology.

Exome-sequencing has emerged as a powerful tool for identifying disease-causing mutations, particularly in consanguineous families, where the likelihood of inheriting recessive genetic disorders is significantly higher due to shared ancestry (Neissi et al., 2025). This technique focuses on sequencing the protein-coding regions of the genome, which harbor the vast majority of pathogenic mutations, making it a cost-effective and efficient method for uncovering genetic defects. By leveraging the principle of homozygosity mapping, exome-sequencing can pinpoint rare recessive mutations that might otherwise be missed in broader genome-wide analyses. Its ability to detect single-nucleotide variants (SNVs), small insertions, and deletions enables precise molecular diagnoses, aiding in understanding disease mechanisms and potential therapeutic approaches (Al-Badran et al., 2022; Neissi et al., 2024). According to this evidence, in this study, we embark on an illuminative journey through the clinical details of a 5-year-old male child from an Iraqi family, grappling with the complexities of leukoencephalopathy with VWM. This case not only unveils the challenges faced by individuals affected by VWM but also reveals a previously unreported homozygous missense mutation residing within the EIF2B3 gene, a pivotal player in the pathogenesis of this neurogenetic anomaly.

2. Methodology

Samples collection

A 5-year-old child from Iraq (Figure 1), presented with a range of neurological symptoms, including seizures, low muscle tone, delayed speech, optic atrophy, and vision loss. The patient was referred to the Noor-Gene Genetic Laboratory, a specialized center located outside Iraq, for further evaluation. The child's parents are first cousins, necessitating immediate genetic counselling. A detailed family pedigree was constructed, revealing no similar symptoms among other family members. The parents, despite their consanguinity, displayed no clinical symptoms and were



deemed healthy. The sequencing data were analyzed and interpreted in collaboration with the laboratory team using accredited bioinformatics tools and variant classification guidelines.

The patient and family members underwent a comprehensive clinical assessment. Informed consent was obtained from all participants, and a pedigree analysis was performed. The clinical manifestations of the child, in conjunction with the consanguinity of the parents, prompted genetic investigation.

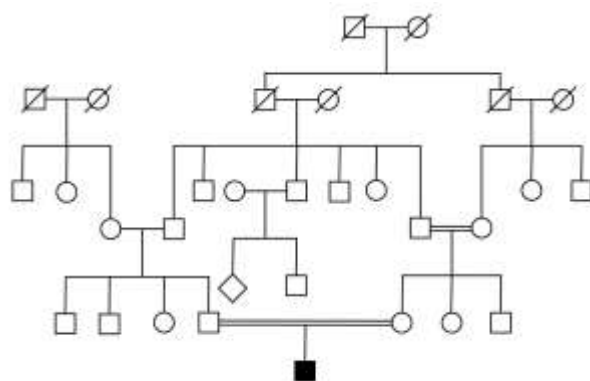


Fig.1. A family pedigree of the family with leukoencephalopathy. Parents have a family history of consanguinity. The black square represents the patient. The unfilled square represents a male, and the circle represents a female. The diagonal line on the squares and circles represents a deceased male and female and the rhombus represents a fetus with unknown gender.

DNA Extraction

Peripheral blood samples were collected from the patient and family members. DNA extraction was performed using a standard phenol-chloroform method, ensuring high-quality DNA suitable for downstream analysis.

Exome-Sequencing

Exome-sequencing was performed using the Illumina Novaseq6000 (Macrogen, Seoul, South Korea) with an average coverage depth of 100x, ensuring over 98% of the targeted regions were adequately covered. Paired-end 100 bp reads were mapped to the human reference genome (GRCh38/hg38). The analytical sensitivity was estimated at 97% for



detecting single SNVs and small insertions/deletions (indels). Variants were classified as pathogenic or likely pathogenic following the guidelines from the ClinVar database and annotated according to the recommendations of the Human Genome Variation Society (HGVS).

Bioinformatics Analysis

The variant annotation was conducted using ANNOVAR and the functional impact of the variants was predicted using several in-silico tools including Polyphen2 HDIV, SIFT, and MutationTaster. Variants were filtered based on allele frequency, inheritance mode, and pathogenicity predictions, adhering to the American College of Medical Genetics and Genomics (ACMG) guidelines. Furthermore, a protein-protein interaction (PPI) analysis was conducted using STRING (<https://string-db.org/>) to evaluate potential disruptions in molecular interactions caused by the variant, which may contribute to the observed phenotype.

PCR and Sanger Sequencing

Candidate variants were identified using polymerase chain reaction (PCR) and Sanger sequencing on an ABI 3130xl Genetic Analyzer. Custom primers were designed in collaboration with a dedicated team in the laboratory using Primer3 software based on the reference sequence of exon 4 of the EIF2B3 gene to target the specific variant in the eif2b3 gene. The primer sequences were as follows:

Forward primer: 5'– CAGAGATGTCTCAGGGACTGC –3'

Reverse primer: 5'– GCATTTTCCATTCAGGGACTGTG –3'

3. Results and discussion

Clinical Findings

The patient exhibited neurological deterioration characterised by seizures, developmental delay, and visual impairment. MRI of the patient revealed significant findings (Figure 2). There was a diffuse and symmetrical signal pattern in the cerebral white matter, consistent with cerebrospinal fluid. This unusual imaging pattern was noted across T1-weighted, T2-weighted, and FLAIR sequences, raising concerns about underlying leukoencephalopathy.

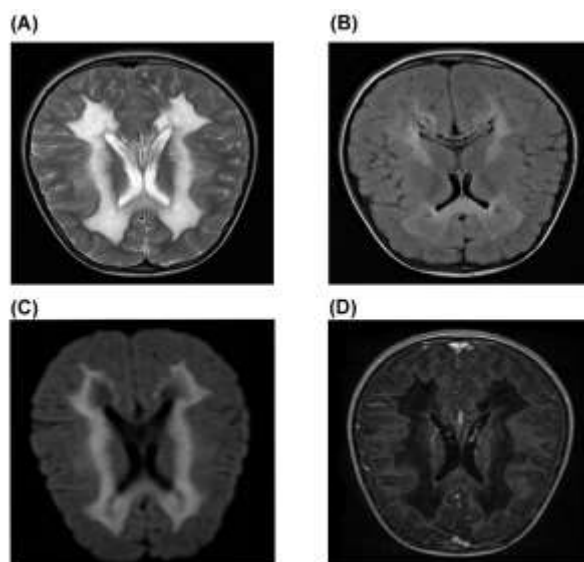


Fig.2. On T2-FLAIR and DWI images (A, B, C) symmetric and diffusely involved bilateral peri-ventricular white matter hyper signal intensity, extended to the level of subcortical arcuate fibers, are seen which appears hypo signal intensity on T1 image (D), compatible with VWM.

Genetic Findings

Exome-sequencing identified a novel homozygous missense mutation in exon 4 (NM_020365.5) of the EIF2B3 gene, c.327A>G (p.Ile109Met), located at hg38: chr1-44941633-T-C. This mutation leads to the substitution of isoleucine (Ile) with methionine (Met) at position 109 of the protein. The variant resides in a highly conserved region, suggesting its critical role in protein function. In-silico analysis using Polyphen2 HDIV, SIFT, and MutationTaster consistently predicted the mutation as pathogenic, classifying it as damaging or disease-causing (Table 1). The amino acid change alters the biochemical properties of the protein, replacing the hydrophobic isoleucine with methionine, which could disrupt the protein's structure and function. This may impair the EIF2B3 protein's involvement in protein synthesis initiation and cellular stress response mechanisms, leading to the development of disorders like leukodystrophy. PCR and Sanger sequencing confirmed the mutation in the proband, with both parents being heterozygous carriers, further supporting its pathogenic role (Figure 3).



Variant	Polyphen-2 HDIV score	SIFT score	MutationTaster
I109M	1.000 (possibly damaging)	0.001 (damaging)	Disease-causing

Table 1: Pathogenicity assessment of the variant identified by exome-sequencing

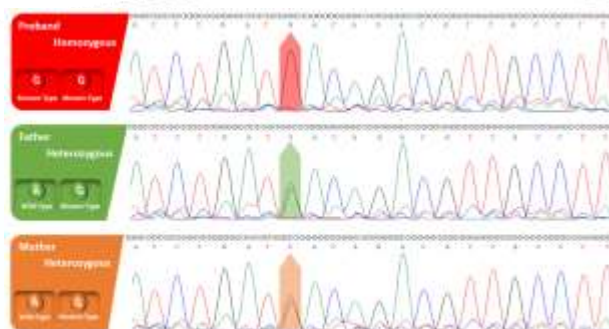


Fig.3. The result of the co-segregation analysis by Sanger sequencing. The proband was homozygous for the pathogenic variant (ATA>ATG) and his parents were heterozygous for the detected variant.

Variant Database Comparison

A comprehensive review of the EIF2B3 gene mutations was performed using the Human Gene Mutation Database (HGMD; <https://www.hgmd.cf.ac.uk/ac/index.php>), revealing that the identified variant is novel and has not been previously reported in association with leukoencephalopathy. A summary of known pathogenic variants and their associated clinical features is provided in Table

No.	Coding sequence location	Protein effect	Type of mutation	Phenotype
1	c.32G>T	p.Gly11Val	Missense	Leukoencephalopathy with vanishing white matter
2	c.41C>T	p.Ser14Phe	Missense	Vanishing white matter disease
3	c.80T>A	p.Leu27Gln	Missense	Leukoencephalopathy



				with vanishing white matter
4	c.136G>A	p.Val46Ile	Missense	Leukoencephalopathy with vanishing white matter
5	c.260C>T	p.Ala87Val	Missense	Leukoencephalopathy with vanishing white matter
6	c.272G>A	p.Arg91His	Missense	Vanishing white matter disease
7	c.407A>C	p.Gln136Pro	Missense	Leukoencephalopathy with vanishing white matter
8	c.674G>A	p.Arg225Gln	Missense	Leukoencephalopathy with vanishing white matter
9	c.687T>G	p.Ile229Met	Missense	Leukoencephalopathy with vanishing white matter
10	c.1023T>A	p.His341Gln	Missense	Leukoencephalopathy with vanishing white matter
11	c.1037T>C	p.Ile346Thr	Missense	Leukoencephalopathy with vanishing white matter
12	c.1118C>T	p.Ser373Leu	Missense	Leukoencephalopathy with vanishing white matter
13	c.1312C>T	p.Arg438Ter	Nonsense	Vanishing white matter disease

Table 2: Reported mutations in the EIF2B3 gene

Protein-Protein Interaction (PPI) Network Analysis of EIF2B3

The protein-protein interaction (PPI) network analysis of EIF2B3 revealed its strong connectivity with multiple subunits of the EIF2B complex, including EIF2B1, EIF2B2, EIF2B4, and EIF2B5, along with interactions involving EIF2S family members and RABIF (Figure 4). The identified c.327A>G (p.Ile109Met) mutation in EIF2B3, associated with



VWM, is located within this highly interconnected network, suggesting its potential impact on translational regulation and cellular stress responses. Notably, the network also demonstrated interactions with TGDS, indicating possible functional cross-talk beyond the EIF2B complex. The presence of multiple interaction edges, represented by various confidence levels, further supports the critical role of EIF2B3 within the regulatory framework of translation initiation.

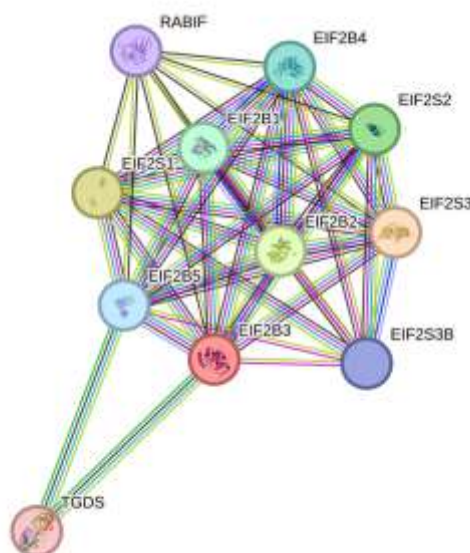


Fig.4. PPI network of EIF2B3. The network displays interactions between EIF2B3 and various associated proteins, including EIF2B complex subunits (EIF2B1, EIF2B2, EIF2B4, EIF2B5) and EIF2S family members. Different colored edges represent various types of interactions, indicating the functional connectivity of EIF2B3 within the translation initiation pathway.

Genetic Counseling and Risk Assessment

The identification of a novel EIF2B3 mutation underscores the critical need for genetic counseling in families affected by VWM disease. Given the autosomal recessive inheritance pattern, consanguineous unions substantially heighten the risk of disease transmission. Genetic counseling provides a comprehensive risk evaluation, education on inheritance mechanisms, and structured guidance for reproductive planning. This proactive approach



empowers families to make informed decisions and anticipate potential challenges associated with VWM.

Prenatal and Perinatal Management

When a pathogenic EIF2B3 variant such as c.327A>G (p.Ile109Met) is identified, targeted prenatal diagnostic measures become essential. Procedures like chorionic villus sampling (CVS) and amniocentesis enable early genetic confirmation of fetal status, allowing for timely intervention. The early detection of VWM facilitates coordinated perinatal care planning, ensuring optimal medical preparedness for potential neurological complications and disease progression.

Advanced Reproductive Options

The identification of the EIF2B3 c.327A>G (p.Ile109Met) mutation allows for the implementation of advanced reproductive technologies to mitigate recurrence risk. In vitro fertilization (IVF) combined with preimplantation genetic testing (PGT) enables precise embryo screening, ensuring the selection of unaffected embryos. This strategic intervention provides an effective means to prevent the transmission of VWM, offering families the possibility of healthier future offspring and reducing the burden of this debilitating leukodystrophy.

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Discussion

VWM disease, an autosomal recessive leukodystrophy, is instigated by mutations occurring in the subunits of EIF2B. The diagnostic process for individuals with VWM primarily involves a comprehensive assessment that integrates MRI findings with the identification of distinctive neurological symptoms. Such symptoms include spasticity, cerebellar ataxia, optic atrophy, and intellectual disability. These clinical manifestations, along with corroborating MRI results, form the basis for the accurate diagnosis of VWM (Woody et al., 2015). In the present investigation, a groundbreaking finding emerged, disclosing the identification of a previously unreported homozygous missense mutation within the EIF2B3 gene of a 5-year-old boy diagnosed with VWM. exome-sequencing technique was employed to uncover this novel genetic variant. This unique mutation, characterized as c.327A>G with the consequential amino acid alteration p.Ile109Met, is specifically situated in exon 4 (NM_020365.5) of the EIF2B3 gene. As a consequence of this mutation, there is a forecasted disturbance in the translation process of the codon, adding a layer of insight into the potential molecular mechanisms underlying the observed phenotype in this patient.



This genetic disorder can manifest both during childhood, typically between the ages of 1 and 5 years, and in adulthood, accounting for approximately 15% of cases. The EIF2B gene plays a pivotal role as the guanine exchange factor for EIF2, participating in translation initiation and the regulation of protein synthesis under various conditions, including cellular stress. Mutations within the EIF2B genes disrupt the normal cellular stress response, ultimately contributing to the progressive deterioration of clinical symptoms associated with VWM. Specifically, mutations in EIF2B3 are responsible for roughly 4% to 7% of all VWM cases, further underscoring the genetic heterogeneity within this disorder (La Piana et al., 2012). The mutants of EIF2B3 have been identified to exhibit impairments in glial cell differentiation and myelin development. Additionally, these mutations are associated with an upregulation of gene expression within the signaling pathway involved in the stress response. This dual impact on glial cells and stress response pathways underscores the intricate nature of the genetic alterations in EIF2B3 and their consequential effects on crucial aspects of cellular differentiation and stress response mechanisms (Lee et al., 2021).

In the realm of genetic exploration, a noteworthy study spearheaded by (Wongkittichote et al., 2022) unearthed a constellation of compound heterozygous variants nestled within the EIF2B3 gene, a revelation made possible through the precision of exome-sequencing. Among these variants, the research spotlighted a familiar pathogenic culprit, the c.260C>T (p.Ala87Val) mutation, alongside an entirely novel genetic aberration, the c.673C>T (p.Arg225Trp) variant. Intriguingly, the study also delved into neuroimaging assessments via brain MRI, unveiling a distinctive pattern characterized by symmetrical distribution. This pattern manifested as diffuse bilateral T2-weighted and FLAIR hyperintensity, strategically encompassing the supratentorial and cerebellar white matter, while curiously sparing the basal ganglia (Wongkittichote et al., 2022). Moreover, the diagnostic utility of MRI features in VWM disease has been indispensable over an extended period. White matter abnormalities, discerned through MRI sequences like T1-weighted, T2-weighted, and FLAIR signals, exhibit distinct sensitivities



to the structural intricacies of the brain(Ashrafi et al., 2020). Adding another layer to our understanding, our study also brought to the forefront an unprecedented variant within the EIF2B3 gene. The corresponding exploration through brain MRI illuminated diffuse and symmetrical signals in the cerebral white matter, akin to the appearance of cerebrospinal fluid in the realms of T1-weighted, T2-weighted, and FLAIR images. In our meticulous evaluation of all MRI features, a comprehensive scrutiny unveiled not only the anticipated cystic changes but also a myriad of other nuanced modifications, further enriching our comprehension of the multifaceted interplay between genetic variations and the intricate manifestations observed through neuroimaging modalities.

In a case study conducted by(Kami et al., 2023) two instances of Vanishing White Matter (VWM) disease were elucidated, involving an 8-month-old girl and a 24-month-old girl. Both cases manifested symptoms such as weakness, delays in walking and swallowing, and poor feeding. Correspondingly, akin to our study, the brain MRI of the latter case in their investigation unveiled cystic changes, characterized by the rarefaction of white matter in the peri-ventricular region of the supratentorial area. Moreover, in their study, exome-sequencing elucidated a homozygous EIF2B5 (c.461A>G) gene mutation for the first case and an EIF2B3 (c.937G>A) gene mutation for the second case. This underscored the genetic heterogeneity within VWM and reinforced the notion that the age at onset plays a pivotal role in determining the prognosis. The study by Kami A et al confirmed the expansive spectrum of phenotypes associated with VWM, emphasizing the significance of considering age as a crucial factor in prognostic assessments(Kami et al., 2023).

In a similar pediatric-onset VWM case, documented by(Khorrami et al., 2021), a homozygous missense mutation in the EIF2B3 gene (c.C590T; p.Thr197Met; NM_0203650) was identified. The case centered on a 7-year-old male child who underwent exome-sequencing due to prenatal clinical indications such as intrauterine growth retardation, oligohydramnios, and reduced fetal movements. The child presented with macrocephaly, mild intellectual disability, and white matter lesions after birth, optic atrophy, and



mild ataxia. It is noteworthy that, contrary to the reported case, our patient exhibited additional symptoms including seizures, low muscle tone, slow speech, optic atrophy, vision loss, and ataxia. The absence of seizures in the previously reported case was highlighted as a distinctive factor, possibly contributing to the chronic nature of the condition, the manifestation of mild symptoms, and the survival of the patient until the age of seven. Together, these comparative analyses deepen our understanding of VWM's clinical and genetic heterogeneity, paving the way for improved diagnostic precision and therapeutic strategies tailored to individual patients.

The recent study elucidating the association between EIF2B gene mutations and leukoencephalopathy with VWM underscores the pivotal role of EIF2B in cellular function during stress conditions and protein synthesis, revealing a spectrum of pathological characteristics including cystic degeneration and oligodendrocyte abnormalities. (Hettiaracchchi et al., 2018). In our investigation, exome-sequencing analysis of a VWM proband unveiled a novel homozygous missense mutation (c.327A>G; p.Ile109Met) in EIF2B3, expanding the genetic landscape of VWM. Additionally, our imaging analysis revealed characteristic symmetrical signal patterns in the cerebral white matter consistent with VWM features, providing clinical corroboration of the genetic findings. Together, these studies deepen our understanding of VWM pathogenesis, emphasising the significance of EIF2B mutations in driving the disorder and highlighting the importance of comprehensive genetic and imaging analyses for diagnosis and management

The PPI network analysis underscores the critical role of EIF2B3 within the EIF2B complex, which is essential for regulating translation initiation, particularly under cellular stress conditions. EIF2B3 interacts with other EIF2B subunits (EIF2B1, EIF2B2, EIF2B4, and EIF2B5) to facilitate guanine nucleotide exchange on EIF2, a process crucial for maintaining global protein synthesis (Knaap et al., 2002). The c.327A>G (p.Ile109Met) mutation in EIF2B3, associated with leukoencephalopathy with VWM, likely disrupts these interactions, impairing EIF2 recycling and leading to dysregulated stress response pathways. Since EIF2B activity is vital for oligodendrocyte function and myelin maintenance, mutations affecting



EIF2B3 can result in white matter degeneration, contributing to the progressive neurological decline observed in VWM. Furthermore, interactions with additional proteins, such as TGDS and RABIF, suggest that EIF2B3 may have broader cellular roles beyond translation regulation (Jennings et al., 2014). These findings emphasize how EIF2B3 mutations can disrupt protein-protein interactions, ultimately leading to impaired translational control, cellular stress intolerance, and the pathogenesis of leukoencephalopathy with VWM.

Finally, our analysis using exome-sequencing on an Iraqi patient diagnosed with VWM has uncovered a novel mutation in the EIF2B3 gene. In detail, this mutation involves substituting guanine with adenine at position 327 (c.327A>G), resulting in a consequential alteration in the protein product. Notably, this mutation induces a discreet amino acid change from Isoleucine to Methionine at position 109 (p.Ile109Met). Additionally, our research incorporates the use of advanced in-silico prediction tools to strengthen further the evidence supporting the probable pathogenicity of the detected mutation (c.327A>G; p.Ile109Met). These computational tools employ sophisticated algorithms and bioinformatic techniques to simulate and predict the functional consequences of genetic variations. Consistent outcomes from these analyses consistently affirm the likelihood that the specified mutation has a pathogenic impact, indicating its potential role in contributing to the VWM diagnosis in the Iraqi patient.

Conclusion

Our study reveals a novel homozygous mutation (c.327A>G; p.Ile109Met) in the EIF2B3 gene by exome-sequencing, expanding the genetic landscape associated with VWM. The observed correlation with cerebral white matter abnormalities on MRI highlights the clinical relevance of this mutation. Beyond its significance for understanding the disease, this discovery showcases the potential of advanced sequencing in streamlining genetic screening processes, holding promise for improved diagnostics and personalized interventions in the management of genetic disorders.

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None.

Author's Contributions

SHAYMAA MUNEAM SAEED: investigation; writing – original draft. The author has thoroughly reviewed and approved the final version of the manuscript.

Ethical Considerations

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or relevant ethical standards.

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