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A Novel *IRF2BPL* Gene Mutation Observed in a Case of Early Infantile Epileptic Encephalopathy Presenting as Dystonia and Neuroregression: A Case Report

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ABSTRACT

Background and Objective: The interferon regulatory factor 2-binding protein-like (IRF2BPL) gene encodes a protein expressed in multiple regions of the human body, including the central nervous system. Research indicates that this gene functions as both a transcriptional activator and ubiquitin ligase and contributes to the development and maintenance of the nervous system. Mutations in the IRF2BPL gene typically present as epileptic encephalopathy, accompanied by neurodevelopmental disorders, abnormal movements, regression, seizures, and loss of speech. We report a case of early infantile epileptic encephalopathy (EIEE) associated with a pathogenic IRF2BPL variant.

Case Report: A 9-month-old male initially presented with fever and generalized tonic-clonic seizures, which subsequently progressed to dystonia and neuroregression. Comprehensive metabolic evaluations, tandem mass spectrometry, and gas chromatography-mass spectrometry results were normal. MRI revealed mild hyperintensity in the bilateral frontal and parietal cortical and subcortical regions. Electroencephalogram results showed low-voltage complexes. Whole-exome sequencing identified a heterozygous missense variant in the single-exon IRF2BPL gene (NM_024496.4:c.1857C>A, p.Asn619Lys).

Conclusion: This novel IRF2BPL variant represents a previously unreported genetic etiology for EIEE and has not yet been documented in the literature. However, further research is necessary to establish this association.

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Introduction

Early infantile epileptic encephalopathy (EIEE) is a severe, refractory seizure disorder with onset in the first year of life, typically resulting in profound neurodevelopmental arrest or regression [1], and has a prevalence of 10 in 100,000 live births.

Single-gene disorders can also cause epileptic encephalopathy [2]. More than 70 genes have been identified as causes of epilepsy and neurodevelopmental disorders, with SCN1A and KCNQ2 being the most common [3]. Epilepsy and severe intellectual disability frequently coexist, with comorbid seizures diagnosed in more than 50% of patients with severe cognitive impairment [4]. Two distinct clinical trajectories are recognized: in classic epileptic encephalopathies (EEs), seizure onset precipitates subsequent cognitive decline or regression, whereas in developmental encephalopathies, epilepsy emerges on a background of pre-existing neurodevelopmental delay [2, 5].

The interferon regulatory factor 2-binding protein-like (IRF2BPL) gene (OMIM *618088) encodes a multifunctional protein enriched in the central nervous system that acts as a transcriptional activator and E3 ubiquitin ligase essential for neurodevelopment and long-term neuronal survival [6]. Here, we describe a patient harboring a novel heterozygous IRF2BPL mutation presenting with refractory epileptic encephalopathy, dystonia, and developmental regression.

Case Presentation

A 9-month-old male child, the second-born to a non-consanguineous couple from Bihar, India, in 2024, was delivered at full term through normal vaginal birth, weighing 2600 g. His development before the illness was typical, and his immunizations were up to date. He had a 3-year-old elder sister who was developmentally normal, and there was no significant family history.

He was brought in with a 3-day history of fever and a 4-hour episode of unresponsiveness, accompanied by frequent episodes of limb stiffening and relaxation. These symptoms were associated with eye-rolling, frothing at the mouth, and loss of bowel control. On initial examination, the child was febrile and in an active generalized tonic-clonic seizure. His oxygen saturation was 80%, which improved with free-flow oxygen. Perfusion was adequate, and the pupils were dilated but reactive to light. Fundus examination revealed no abnormalities.

Initial management included injections of lorazepam, phenytoin, and levetiracetam. Empirical treatment with intravenous fluids, broad-spectrum antibiotics, and calcium gluconate was started. The frequency of seizures gradually decreased, but the child remained drowsy. On the fifth day of admission, he developed acute dystonia characterized by an opisthotonic posture with asymmetric upper-extremity posturing (right elbow flexion and left elbow extension) that worsened with agitation. The child exhibited neuroregression, including loss of neck holding, inability to move the limbs, and difficulty swallowing. Hypotonia in all limbs, bilateral extensor plantar responses, and absent deep tendon reflexes were also noted. Initial investigations revealed a normal blood count. Serum levels of glucose, sodium, potassium, and calcium were normal. A brain CT scan was normal. Cerebrospinal fluid (CSF) analysis revealed a glucose level of 210 mg/dl, a protein level of 95.5 mg/dl, and no cells. Cultures of blood, CSF, and urine showed no bacterial growth. Viral and autoimmune encephalitis panels for CSF were normal. Tandem mass spectrometry blood and gas chromatography-mass spectrometry urine results were within normal limits. Brain MRI DWI showed mild hyperintensity in the bilateral frontal and parietal cortical and subcortical regions. Electroencephalogram (EEG) showed low-voltage complexes, likely due to sedation. Whole-exome sequencing identified a heterozygous IRF2BPL mutation in exon 1, consistent with a neurodevelopmental phenotype of developmental regression, movement disorders, speech loss, and intractable seizures. Mutation analysis of the parents was normal. The child is under follow-up and continues to have global developmental delay.

Discussion

Epileptic encephalopathy is characterized by significant epileptiform activity that disrupts

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development, leading to cognitive slowing, regression, and psychiatric and behavioral issues. This persistent epileptiform activity can precipitate neurodevelopmental regression in previously neurotypical children or accelerate deterioration in those with pre-existing developmental delay. Addressing this epileptiform activity can help improve developmental delays [2].

In our case, there was no prior developmental delay, and regression was observed following the onset of epileptic activity. Dystonia is characterized by sustained or intermittent muscle contractions that lead to abnormal, often repetitive movements, patterned postures, or both. These movements are typically patterned, twisting, and tremulous. Postures intensify with voluntary actions and stress but diminish during sleep [7]. In our case, the baby was initially treated for a seizure disorder and later developed repetitive movements involving flexion of the right elbow, extension of the left elbow, and an opisthotonus position, which were more pronounced during crying and lessened during sleep.

Mutations in IRF2BPL cause a distinct neurodevelopmental syndrome defined by developmental regression, prominent movement disorders, expressive language loss, and refractory epilepsy. Other associated symptoms include walking difficulties, ataxia, dystonia, choreoathetosis, spasticity, dysmetria, and various types of seizures. Some cases have also exhibited ocular abnormalities, such as esotropia, gaze palsies, nystagmus, and reduced saccades. In our patient, neuroregression manifested as the loss of previously achieved motor milestones, such as rolling and sitting, and the development of quadriparesis. Marcogliese et al. describe seven patients with pathogenic heterozygous mutations in the IRF2BPL gene, all of whom are experiencing neurological issues [6]. A distinct genotype–phenotype correlation has been reported in the literature: five patients harboring nonsense IRF2BPL variants manifested a severe phenotype characterized by profound neuroregression, hypotonia, progressive ataxia, coordination deficits, and refractory seizures. In contrast, two individuals with missense variants indicated a comparatively milder clinical course, presenting predominantly with global developmental delay and seizures without rapid regression [6]. In our case, a heterozygous missense variant was identified in exon 1 of IRF2BPL. Tran Mau-Them et al. described 11 unrelated patients with developmental delays and EEs, all with de novo heterozygous mutations in IRF2BPL. These patients initially achieved developmental milestones normally before undergoing profound neurodevelopmental regression and developing refractory epilepsy, accompanied by nonspecific EEG abnormalities and heterogeneous central nervous system (CNS) structural findings [8]. In our case, EEG showed low-voltage complexes, and diffusion-weighted brain MRI revealed mild hyperintensities across the bilateral frontal and parietal cortices and adjacent subcortical white matter.

Despite widespread implementation of chromosomal microarray analysis and targeted gene panel testing, the precise molecular etiology in a substantial proportion of EEs remains unresolved. In this context, next-generation approaches-particularly whole-exome and whole-genome sequencing-have proven invaluable for novel gene discovery, largely driven by the identification of *de novo* pathogenic variants [9, 10]. Whole-exome sequencing in our patient identified a heterozygous missense variant in exon 1 of the autosomal dominant IRF2BPL gene. Based on the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards, this variant was classified as a variant of uncertain significance (VUS) [11]. In our case, Sanger sequencing of the gene in the parents revealed no mutation, underscoring the novel nature of this variant. Further functional studies and the identification of additional unrelated cases are warranted to definitively establish the pathogenicity of this novel variant.

Conclusion

Our case underscores the association between the IRF2BPL gene and EIEE, characterized by seizures, dystonia, and neuroregression. Genetic testing provides valuable prognostic information to parents regarding dystonia, neuroregression, and genetic counseling for future pregnancies. However, further research on the IRF2BPL gene and epileptic encephalopathy is necessary to establish this

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association. Efforts should be made to improve accessibility and reduce the cost of genetic testing.

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Conflict of interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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