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Case Report

Mosaic PPP3CA Variant in a Child with Neurodevelopmental Delay Without Epilepsy

Lynn Srour[1] and Chadi AL Alam[2]*

[1]Internal Medicine, PGY 1; LAU Medical Center-Rizk Hospital, Beirut, Lebanon

[2]Pediatrics and Pediatric Neurology, American Center for Psychiatry and Neurology - ACPN, Abu Dhabi and Al Ain, United Arab Emirates and Haykel Hospital, El koura, Lebanon

***Corresponding Author:** Chadi AL Alam, Pediatrics and Pediatric Neurology, American Center for Psychiatry and Neurology - ACPN, Abu Dhabi and Al Ain, United Arab Emirates and Haykel Hospital, El koura, Lebanon.

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Abstract

We report a 5-year-10-month-old girl with global developmental delay, speech and behavioral difficulties, and no history of epilepsy. Genetic testing revealed a heterozygous mosaic PPP3CA variant (c.843C>G; p.His281Gln) within the catalytic domain, previously associated with Developmental and Epileptic Encephalopathy Type 91 (DEE91). Brain MRI and EEG were normal. The mosaic nature of the variant likely explains the milder, non-epileptic phenotype. This case expands the clinical spectrum of PPP3CA-related disorders and highlights the modulatory effect of mosaicism on disease severity.

Keywords: Occupational Therapy (OT); PPP3CA

Introduction

PPP3CA encodes the alpha isoform of a subunit of calcineurin which encodes a calcium- and calmodulin-dependent serine/threonine protein phosphatase that has an important role in many biological processes, including being a key regulator of synaptic vesicle recycling at nerve terminals [1]. Pathogenic variants in PPP3CA are linked to developmental and epileptic encephalopathy type 91. This disorder is characterized by early-onset seizures, significant intellectual impairment, and widespread developmental delay.

The mode of inheritance of this condition is an autosomal dominant inheritance pattern, often due to a novo missense mutations [3]. Since its first description by Myers., *et al*. in 2017 [1], very few cases were reported worldwide making this disease extremely rare. Most of the patients exhibit early-onset, drug-resistant epilepsy and severe neurodevelopmental delay. However, a small subset presents with developmental delay without epilepsy.

We report a patient with a de novo mosaic PPP3CA variant (c.843C>G; p.His281Gln), exhibiting global developmental delay, behavioral dysregulation, and absence of epilepsy, adding further insight into the expanding clinical spectrum of PPP3CA-related disorders.

Case Presentation

A 5-year-10-month-old girl presented with global neurodevelopmental delay. She was born full term via normal vaginal delivery following an uneventful pregnancy and delivery. The parents are non-consanguineous. There is no known family history of neurodevelopmental or psychiatric disorders.

Developmental history

Global developmental delay was noted early in life. Gross motor milestones were mildly delayed, and fine motor coordination remains below age expectations. Speech and language development are significantly delayed, she uses a few single words but does not form sentences. She exhibits hyperactivity, poor attention span, easy distractibility, and frequent irritability. Social interaction is limited, and she is easily agitated. Sleep is regular, and appetite is good. There is no history of clinical seizures.

Therapies and interventions

She attends a specialized center where she receives occupational therapy (OT) and speech therapy (ST) regularly.

Medication history

Atomoxetine was trialed with minimal clinical benefit.

Risperidone was introduced but led to increased agitation and irritability, prompting discontinuation.

Aripiprazole was started at 2.5 mg daily and titrated to 5 mg. Shortly after dose escalation, she developed transient dystonic movements involving the eyes, neck, and shoulders. These symptoms resolved spontaneously without dose reduction or discontinuation of the medication.

Investigations

- **Brain MRI:** Normal.
- **EEG:** Normal background activity, no epileptiform discharges.
- **Genetic Testing:** Identified a heterozygous likely pathogenic variant in the PPP3CA gene: c.843C>G; p.His281Gln.

This variant is associated with Developmental and Epileptic Encephalopathy Type 91 (DEE91) and follows an autosomal dominant mode of inheritance.

Current status

The patient continues on aripiprazole 5 mg daily with stable behavior and no recurrence of dystonia. She remains enrolled in ongoing speech and occupational therapy programs, showing gradual improvement in social responsiveness and attention regulation.

Discussion

The protein phosphatase 3 catalytic subunit alpha (PPP3CA) gene encodes for the alpha isoform of the calcineurin catalytic subunit, which controls the phosphorylation status of many targets, leading to regulation of neuronal differentiation and synaptic plasticity [4].

Disruption of the calcineurin signaling by the pathogenic variants leads to neuronal excitability and development. DEE91 is characterized by delayed psychomotor development which will appear in infancy and results in severely to profoundly impaired intellectual development with poor or absent speech [2].

Frequently the seizures are multifocal and refractory. Other associated clinical features include cortical visual impairment, microcephaly, movement disorders, and autistic traits.

However, recent reports describe milder presentations with developmental delay and behavioral abnormalities without epilepsy [4,7].

The specific variant c.843C>G (p.His281Gln) lies within the catalytic domain, a region where pathogenicity is well established for DEE91 [8].

Myers., *et al*. [1] first described six unrelated patients with PPP3CA mutations, all showing psychomotor delay, seizures between 6 weeks and 4 years, and profound intellectual disability. Five of these six patients had refractory epilepsy, and all had severe developmental delay, establishing that PPP3CA is a cause of early-onset neurodevelopmental disease with epilepsy.

Subsequent reports expanded the spectrum to include missense and truncating variants causing variable severity. Truncating variants, particularly those clustered in the regulatory domain, are associated with earlier onset and more severe, drug resistant epilepsy, while missense variants in the catalytic domain may present with a broader range of neurodevelopmental outcomes, including autism spectrum disorder and, in some cases, milder phenotypes without epilepsy [4].

The mosaic nature of the variant in our patient (VAF ≈ 19%) likely contributed to the absence of seizures and milder clinical presentation.

By reducing the proportion of cells that express the mutant protein, mosaicism can mitigate the overall functional deficit and preserve any remaining enzymatic activity. This genotype–phenotype attenuation due to mosaicism is a recognized phenomenon in neurodevelopmental genetics and has been observed in other epilepsy-associated genes, such as SCN2A and KCNT1, where mosaic variants are associated with less severe clinical presentations compared to germline mutations.

Conclusion

This report describes a mosaic PPP3CA c.843C>G (p.His281Gln) variant associated with global developmental delay and behavioral symptoms in the absence of epilepsy. The finding emphasizes that PPP3CA-related disorders may occur on a phenotypic continuum, where mosaicism contributes to milder, non-epileptic presentations. Early recognition and genetic testing are essential for accurate diagnosis, counseling, and multidisciplinary management.

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