https:/doi.org/10.64611/ZFPQ8598

Complex Genetic Findings in Recurrent Infantile Seizures: A Case Report of Rare Heterozygous Variants in MAGEL2, ADGRV1, and PRICKLE2

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INTRODUCTION

Infantile seizures have diverse etiologies, but when structural, metabolic, and infectious origins are excluded upon initial evaluation, genetic testing through rapid genome sequencing or comprehensive epilepsy panel has become increasingly recommended. Advances in genomic medicine have led to the identification of numerous candidate genes associated with epilepsy, although interpretation of variants—particularly those of uncertain significance—remains challenging.

We present the case of a previously healthy 4-month-old female with recurrent seizures whose epilepsy panel revealed rare heterozygous variants in *MAGEL2*, *ADGRV1*, and a novel *PRICKLE2* (p.Gly152Ser) variant. This report highlights the complexity of variant interpretation and the potential role of emerging epilepsy-associated genes.

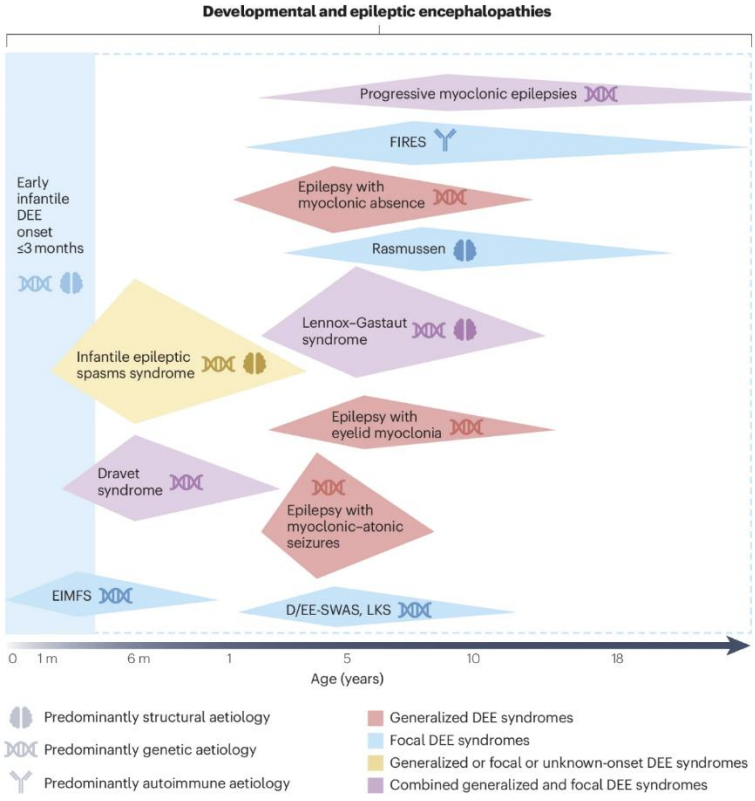

Figure 1: Etiologies of Developmental & Epileptic Encephalopathies (DEE)

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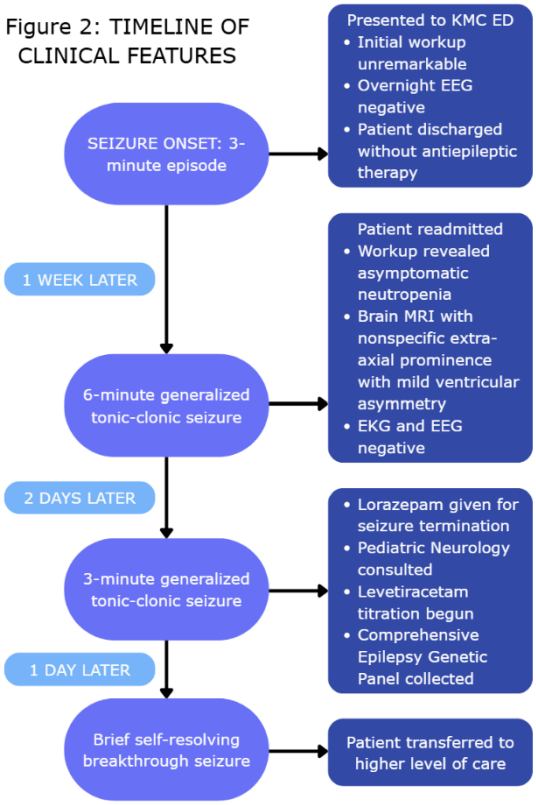
CASE DESCRIPTION

A 4-month-old female, born full-term with an unremarkable prenatal and neonatal course, presented following a 3-minute episode characterized by breath-holding, upward eye deviation, and bilateral jerking movements. Initial evaluation, including vital signs, physical examination, laboratory testing, and overnight EEG, was unremarkable. Differential diagnoses included a non-epileptic paroxysmal event, breath-holding spell, and brief resolved unexplained event (BRUE), and the patient was discharged without antiepileptic therapy.

One week later, the patient experienced a 6-minute episode consistent with a generalized tonic-clonic seizure, captured on video, prompting readmission. Repeat evaluation was again largely unremarkable except for neutropenia (ANC 0.2 × 10^3/μL) without evidence of infection. EKG and repeat EEG were normal. Brain MRI without contrast demonstrated mild lateral ventricular asymmetry, prominent subarachnoid spaces, and enlarged sulci.

Figure 2: TIMELINE OF CLINICAL FEATURES



On hospital day two, the patient experienced another 3-minute generalized tonic-clonic seizure, which responded to lorazepam. Pediatric Neurology recommended initiation of levetiracetam, titrated to a target dose of 30 mg/kg twice daily, with benzodiazepines as needed for breakthrough seizures. Despite therapy, the patient experienced one additional brief self-resolving seizure, prompting transfer to a higher level of care.

Comprehensive epilepsy panel testing identified heterozygous variants in *MAGEL2* (p.Leu1131Met), *ADGRV1* (p.Thr5240Ile), and *PRICKLE2* (p.Gly152Ser).

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DISCUSSION

The interpretation of multiple heterozygous variants identified on epilepsy panels presents a diagnostic challenge, particularly when variants are classified as of uncertain significance.

MAGEL2 is classically associated with Schaaf–Yang syndrome and is not well established as an epilepsy-associated gene. *ADGRV1* has been reported in association with epilepsy; however, current evidence suggests it may function as a susceptibility gene rather than a definitive monogenic cause due to unclear pathogenic mechanisms and inheritance patterns.

Among the identified variants, *PRICKLE2* has the strongest association with epilepsy and neurodevelopmental disorders, with most pathogenic variants arising de novo. Converging evidence from animal models demonstrates that mutations in PRICKLE orthologs produce seizure phenotypes across species, supporting a conserved role in neuronal excitability. In humans, rare heterozygous *PRICKLE2* variants have been reported in individuals with developmental delay, behavioral abnormalities, and epilepsy.

Functionally, PRICKLE2 is involved in planar cell polarity signaling and localizes to the postsynaptic density, where it interacts with synaptic scaffolding proteins and NMDA receptor-associated pathways. These roles support a biologically plausible mechanism for epileptogenesis through disruption of synaptic organization and neuronal signaling.

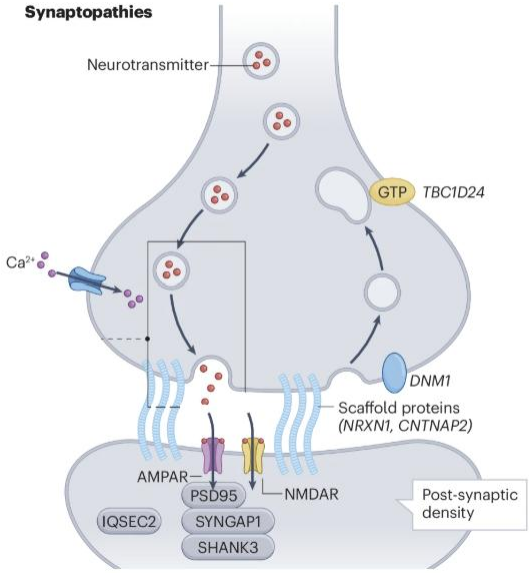

Figure 3: PRICKLE2 Effects Localized to Postsynaptic Density (NMDAR & Scaffold proteins)

Despite these associations, the pathogenicity of *PRICKLE2* variants remains incompletely defined. Some studies suggest that variants in this gene may not be sufficient alone to cause epilepsy, raising the possibility of incomplete penetrance, variable expressivity, or oligogenic inheritance. In this context, the presence of concurrent variants in *MAGEL2* and *ADGRV1* further complicate attribution of causality.

The *PRICKLE2* p.Gly152Ser variant identified in this patient has not previously been reported in the literature, representing a novel finding. Determining whether this variant occurred de novo through parental testing would significantly strengthen its potential pathogenicity. Additional supportive evidence, including in silico predictive modeling and evolutionary conservation analysis, would further aid in classification.

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At present, all identified variants are best classified as variants of uncertain significance. Careful longitudinal follow-up, including monitoring of seizure control and neurodevelopmental outcomes, is essential. Documentation of similar cases will be critical in refining genotype–phenotype correlations and improving future variant interpretation.

Unlike channelopathy-driven epilepsies where targeted therapies may be available, *PRICKLE2*-associated epilepsy lacks specific treatment guidelines. Management therefore remains symptom-directed, emphasizing the importance of individualized care and detailed reporting of treatment response.

CONCLUSION

This case highlights the importance of genetic testing in infants with recurrent seizures and unrevealing initial evaluations. The identification of a novel *PRICKLE2* (p.Gly152Ser) variant, in conjunction with *MAGEL2* and *ADGRV1* variants, underscores the complexity of interpreting genetic findings in epilepsy.

While *PRICKLE2* represents a biologically plausible candidate gene, its role in this patient's phenotype remains uncertain. Parental testing and continued clinical follow-up are essential not only to inform prognosis and guide management, but also to clarify variant pathogenicity and contribute to the growing body of literature on rare genetic epilepsies.

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