

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

Sage Richardson, OMS III; Manas Aavula, OMS III; Nikita Shah, OMS III; Pallavi Sripathi, OMS III; Thiagarajan Nandhagopal, MD

Kern Medical Center & Western University of Health Sciences

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.

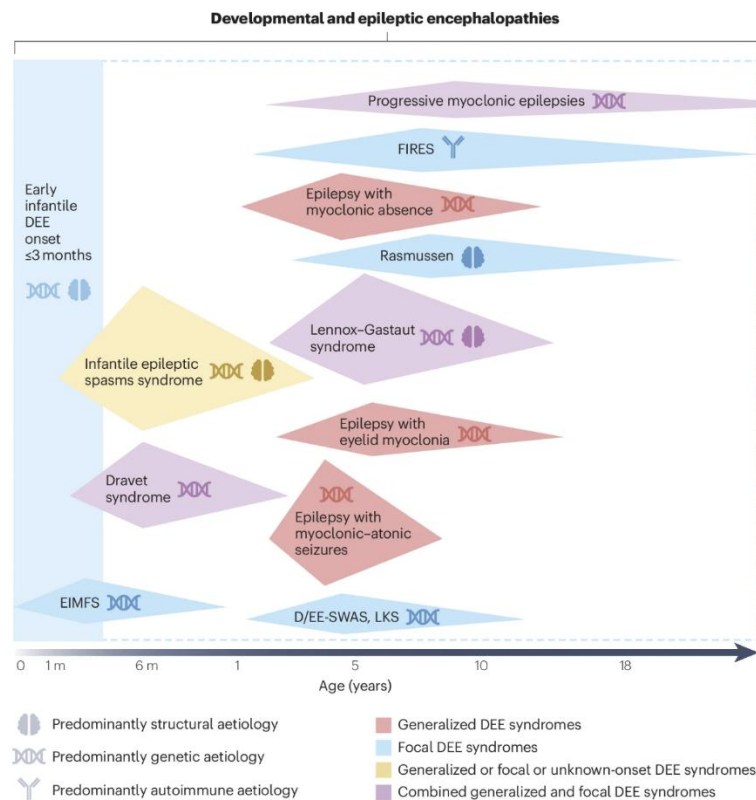


Figure 1: Etiologies of Developmental & Epileptic Encephalopathies (DEE)

CASE DESCRIPTION

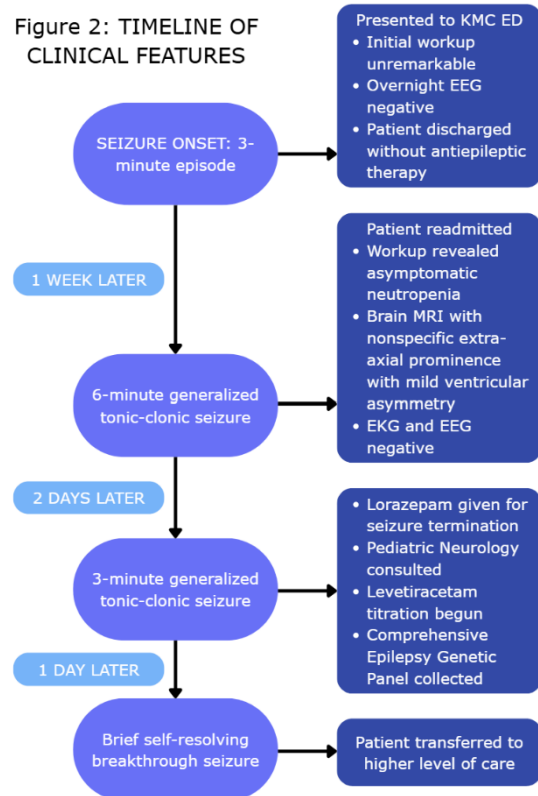
A 4-month-old female, born full-term with an unremarkable prenatal and neonatal course, presented following a 3-minute episode characterized by breath-holding, upward eye deviation, and bilateral jerking movements. Initial evaluation, including vital signs, physical examination, laboratory testing, and 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 ($ANC\ 0.2 \times 10^3/\mu L$) 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.

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).

Figure 2: TIMELINE OF CLINICAL FEATURES



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.

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.

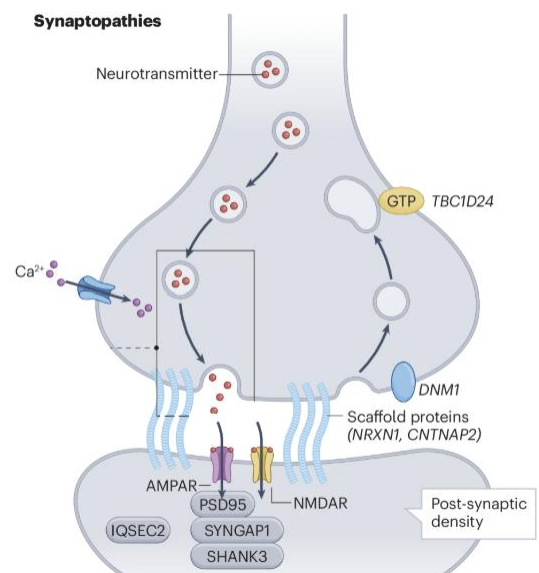


Figure 3: PRICKLE2 Effects Localized to Postsynaptic Density (NMDAR & Scaffold proteins)

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.

References:

- Bayat, Allan, et al. "PRICKLE2 revisited-further evidence implicating PRICKLE2 in neurodevelopmental disorders." *European Journal of Human Genetics*. 2021 Aug;29(8):1235-1244. doi: 10.1038/s41431-021-00912-y. Epub 2021 Jun 7. PMID: 34092786; PMCID: PMC8385026.
- D'Gama AM, et al. "Evaluation of the feasibility, diagnostic yield, and clinical utility of rapid genome sequencing in infantile epilepsy (Gene-STEPS): an international, multicentre, pilot cohort study." *Lancet Neurology*. 2023 Sep;22(9):812-825. doi: 10.1016/S1474-4422(23)00246-6. Erratum in: *Lancet Neurol*. 2023 Dec;22(12):e13. doi: 10.1016/S1474-4422(23)00411-8. PMID: 37596007; PMCID: PMC11860300.
- Fernández-Marmiesse A, et al. "Rare Variants in 48 Genes Account for 42% of Cases of Epilepsy With or Without Neurodevelopmental Delay in 246 Pediatric Patients." *Front Neurosci*. 2019 Nov 8;13:1135. doi: 10.3389/fnins.2019.01135. PMID: 31780880; PMCID: PMC6856296.
- Koh HY, Smith L, Wiltout KN, et al. "Utility of Exome Sequencing for Diagnosis in Unexplained Pediatric-Onset Epilepsy." *JAMA Network Open*. 2023;6(7):e2324380. doi:10.1001/jamanetworkopen.2023.24380
- Liu J, Tong L, Song S, Niu Y, Li J, Wu X, Zhang J, Zai CC, Luo F, Wu J, Li H, Wong AHC, Sun R, Liu F, Li B. "Novel and de novo mutations in pediatric refractory epilepsy." *Molecular Brain*. 2018 Sep 5;11(1):48. doi: 10.1186/s13041-018-0392-5. Erratum in: *Mol Brain*. 2018 Oct 16;11(1):59. doi: 10.1186/s13041-018-0399-y. PMID: 30185235; PMCID: PMC6125990.
- Sanri A, Akca U, Mutlu MB, Sezer O, Sanri E, Karakaya T, Kurtgoz S. "Targeted gene panel testing in pediatric epilepsy: Diagnostic outcomes and expanding genetic insights." *Brain Development*. 2026 Feb;48(1):104498. doi: 10.1016/j.braindev.2025.104498. Epub 2026 Jan 9. PMID: 41518736.
- Symonds JD, et al. "Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort." *Brain*. 2019 Aug 1;142(8):2303-2318. doi: 10.1093/brain/awz195. PMID: 31302675; PMCID: PMC6658850.
- Tao, Hirotaka, et al. "Mutations in prickle orthologs cause seizures in flies, mice, and humans." *American Journal of Human Genetics*. 2011 Feb 11;88(2):138-49. doi: 10.1016/j.ajhg.2010.12.012. Epub 2011 Feb 3. PMID: 21276947; PMCID: PMC3035715.
- Yang Y, Mao Y, Zhang Y, Xiong T. "Evolving Insights into Prickle2 in Neurodevelopment and Neurological Disorders." *Molecular Neurobiology*. 2025 Jul;62(7):8540-8550. doi: 10.1007/s12035-025-04795-8. Epub 2025 Feb 26. PMID: 40009262.
- Zhou Peng, et al. "ADGRV1 Variants in Febrile Seizures/Epilepsy With Antecedent Febrile Seizures and Their Associations With Audio-Visual Abnormalities." *Frontiers in Molecular Neuroscience*. 2022 Jun 23;15:864074. doi: 10.3389/fnmol.2022.864074. PMID: 35813073; PMCID: PMC9262510.

Figures:

- Perilli, L., Mastromoro, G., Murciano, M., Amedeo, I., Avenoso, F., Pizzuti, A., Guido, C. A., & Spalice, A. (2022). Myoclonic Epilepsy: Case Report of a Mild Phenotype in a Pediatric Patient Expanding Clinical Spectrum of KCNA2 Pathogenic Variants. *Frontiers in neurology*, 12, 806516. <https://doi.org/10.3389/fneur.2021.806516>
- Scheffer, I.E., Zuberi, S., Mefford, H.C. et al. Developmental and epileptic encephalopathies. *Nat Rev Dis Primers* 10, 61 (2024). <https://doi.org/10.1038/s41572-024-00546-6>