

# Atypical Rett Syndrome and Intractable Epilepsy With Novel *GRIN2B* Mutation

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Rett syndrome is a genetic disorder most often caused by a mutation in the *MECP2* gene.<sup>1</sup> Whole-exome sequencing has implicated a growing number of other genetic causes.<sup>2</sup> We present a female with atypical Rett syndrome and intractable epilepsy caused by a previously unreported pathogenic variant in *GRIN2B*.

## Patient Description

The patient was apparently normal until 8 months of age, when her development began to stagnate. Her head circumference at birth was normal and her head growth decelerated postnatally. She walked at age 5 years but gradually lost the ability in late childhood. She never developed speech. She had midline hand stereotypies, aerophagia, bruxism, peripheral vasomotor changes, and impaired sleep. She was diagnosed with “variant” Rett syndrome based on the clinical diagnostic criteria in use at the time.<sup>3</sup> Brain magnetic resonance imaging at age 14 years was normal. Negative genetic investigations included chromosomal microarray; 15q11-q13 methylation testing for Angelman syndrome; and genetic analysis of *MECP2*, *FOXG1*, *CDKL5*, and *WDR45*. Subsequent research-based whole-exome sequencing identified a de novo variant in *GRIN2B* (NM\_000834.3, c.1928T>C, p.L643P).

Epileptic seizures began at age 9 years with both generalized tonic and tonic-clonic patterns. She has remained medically refractory despite numerous antiepileptic drug trials involving different combinations of dilantin, lacosamide, levetiracetam, valproic acid, topiramate, gabapentin, clobazam, and rufinamide. Seizure frequency at age 19 years was up to 15 tonic seizures per day, with about half progressing to a clonic phase. Electroencephalograms showed interictal generalized discharges and tonic seizures. Given the intractability of her

seizures and the finding of a *GRIN2B* variant, memantine 10 mg twice daily was added to her existing regimen of phenytoin, levetiracetam, and lacosamide. It was discontinued at 3-month follow-up after a slight worsening in seizure frequency was reported.

## Discussion

The *GRIN2B* gene encodes a subunit of the N-methyl-D-aspartate (NMDA) receptor, which is a glutamate-activated ion channel found at excitatory synapses throughout the brain. *GRIN2B* encephalopathy is a newly described disorder causing developmental disability with or without seizures. Platzer et al<sup>4</sup> described 86 individuals with de novo heterozygous *GRIN2B* mutations. While the phenotype is variable, 60% have severe intellectual disability, over half have childhood-onset epilepsy, and approximately half of those with epilepsy are medically refractory. Only 7% have a history of regression, which is a mandatory criterion for a diagnosis of Rett syndrome.<sup>1</sup> Our

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patient met clinical diagnostic criteria for atypical Rett syndrome while presenting with intractable epilepsy, which is atypical for Rett syndrome caused by *MECP2* mutations.<sup>1</sup>

The original clinical diagnosis of variant Rett syndrome was made when our patient was a preschool-aged child and was based on the existing clinical diagnostic criteria.<sup>3</sup> Although the pivotal role of pathogenic variants in the *MECP2* gene in classic and atypical Rett syndrome was already known in 2002, both Hagberg et al<sup>3</sup> and Neul et al<sup>1</sup> elected to continue to base the diagnosis of Rett syndrome exclusively on clinical grounds, a decision that resulted in some controversy.<sup>5</sup> With the gradual discovery that Rett-like features were an important part of the phenotypes seen in pathogenic variants of other genes whose products were functionally linked to *MECP2* (eg, *CDKL5*, *FOXG1*, *WDR45*), a parallel nomenclature has evolved based on gene diagnosis: *MECP2*-related disorders, *CDKL5*-related disorders, and so on. Thus, from the gene diagnosis perspective, our patient has *GRIN2B*-related disorder.

Two recent papers each report a *GRIN2B* pathogenic variant detected with whole-exome sequencing in groups of patients with Rett syndrome and Rett-like presentations. Additional clinical details were not provided to allow comparisons with our patient.<sup>6,7</sup> Another patient with a loss-of-function *GRIN2B* variant and Rett-like features was described. However, that paper was retracted because of inadvertent use of L-serine as a treatment instead of the intended D-serine. The clinical description did not specify the presence of regression but included motor delays, behavioral abnormalities, hand stereotypies, and impaired sleep.<sup>8,9</sup>

Memantine, an NMDA receptor antagonist, has been proposed as a selective treatment for gain-of-function mutations in GluN2 subunits such as *GRIN2B*.<sup>10</sup> Platzter et al<sup>4</sup> showed that memantine can reduce NMDA receptor hyperactivity in vitro; however, treatment of 4 individuals with gain-of-function variants in *GRIN2B* with memantine did not significantly reduce seizure frequency. We observed worsening of seizure activity in our patient.

This case highlights that *GRIN2B* variants can cause atypical Rett syndrome with medically refractory epilepsy and that there is a growing need for an understanding of the underlying pathophysiology based on the patient's genotype. With this information, new targeted treatments for these patients can be developed.

### Author Contributions

PK and VM contributed equally to this work.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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