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TITLE: THE PHENOTYPIC AND GENETIC SPECTRUM OF *DNM1* ENCEPHALOPATHY

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ABSTRACT BODY:

Rationale: *De novo* mutations in *DNM1* encoding the presynaptic protein Dynamin 1 are an emerging cause of severe epileptic encephalopathies. We aim to define the phenotypic spectrum of *DNM1* encephalopathy by reviewing the clinical features of patients carrying *de novo* mutations in the *DNM1* gene.

Methods: We reviewed phenotypic data of patients with *DNM1* mutations including previously published and newly identified patients. We compared available mutation data to known functional data on the fitful mouse, an epilepsy mouse model with a spontaneous heterozygous mutation in the mouse *Dnm1* gene and undertook biomolecular modeling studies to assess the effect of the *DNM1* mutations on protein function.

Results: In total, we identified 12 patients with *de novo* mutations in *DNM1* including 4 new patients and 8 previously reported patients. In addition, we include one patient with a mutation of unknown inheritance. Of the 12 patients with *de novo* mutations, 4 patients carried a recurrent mutation (p.R237W). The phenotype of patients with *DNM1* encephalopathy included global developmental delay and infantile spasms starting between 2 and 6 months transitioning to Lennox-Gastaut-Syndrome with very frequent seizures and characteristic EEG features. All patients with *de novo DNM1* mutations had severe intellectual disability and hypotonia. The epilepsy was intractable to a broad range of antiepileptic medications in all patients. Comparison to existing functional mouse data suggested that many recurrent and non-recurrent mutations have a dominant negative effect on Dynamin function and cluster within the GTPase or middle domain of the protein.

Conclusions: *DNM1* alterations may result in a unique epileptic encephalopathy characterized by infantile spasms with progression to Lennox-Gastaut-Syndrome with frequent, intractable seizures and persisting high amplitude slow spike wave discharges. Up to 30% of patients with *DNM1* encephalopathy carry a recurrent p.R237W mutation and computational modeling data suggest a dominant negative effect on Dynamin function.

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