NEUROSCIENCE

GABRB3 Point Mutations Cause a Range of Epilepsy: Genetic Cases of Lennox-Gastaut Syndrome and Childhood Absence Epilepsy

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A lack of animal models representing adequately epilepsy syndromes has hindered advancing treatment for patients. Epileptic encephalopathies are a severe subset of epilepsies associated with a high probability of impaired development and cognition. Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy characterized by a triad of features: multiple intractable seizure semiologies, slow spike wave discharge on EEG characteristic of atypical absence seizures, and encephalopathies including severe cognitive and behavioral abnormalities. A mutation resulting in the amino acid change D120N in the β3 subunit of the $GABA_A$ receptor was identified in a patient with LGS. This mutation was introduced to mice to generate the *Gabrb3*$^{+/D120N}$ knock-in mouse. We verified that this mouse exhibits all three points in the diagnostic triad of LGS thereby establishing it as a valid and useful model of LGS. Separately, a mutation identified in both families with childhood absence disorder (CAE) and autism spectrum disorder (ASD) with seizures was used to establish the *Gabrb3*$^{+/P11S}$ knock-in mouse line. CAE is not classified as an epileptic encephalopathy but rather as a genetic generalized epilepsy. The classical reporting of genetic generalized epilepsies and CAE specifically indicates that these patients have normal cognition, however the high incidence of CAE overlapping with ASD in family pedigrees and evidence that CAE is associated with significant cognitive dysfunction led

us to explore the effect of this mutation on both seizure and encephalopathic phenotypes. We verified that the *Gabrb3*$^{+/P11S}$ mouse exhibits both absence epilepsy and ASD phenotypes thereby serving as a valuable model for future research.

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