EFHC1

Mutations in the Myoclonin1/EFHC1 gene are an important cause of juvenile myoclonic epilepsy (JME) in Mexican patients [1].

EFHC1 variants are the most common mutations in inherited myoclonic and grand mal clonic-tonic-clonic (CTC) convulsions of juvenile myoclonic epilepsy (JME).

Bailey et al reanalyzed 54 EFHC1 variants associated with epilepsy from 17 cohorts based on National Human Genome Research Institute (NHGRI) and American College of Medical Genetics and Genomics (ACMG) guidelines for interpretation of sequence variants.

They calculated Bayesian LOD scores for variants in coinheritance, unconditional exact tests and odds ratios (OR) in case-control associations, allele frequencies in genome databases, and predictions for conservation/pathogenicity. We reviewed whether variants damage EFHC1 functions, whether efhc1-/- KO mice recapitulate CTC convulsions and “microdysgenesis” neuropathology, and whether supernumerary synaptic and dendritic phenotypes can be rescued in the fly model when EFHC1 is overexpressed. We rated strengths of evidence and applied ACMG combinatorial criteria for classifying variants.

Nine variants were classified as “pathogenic,” 14 as “likely pathogenic,” 9 as “benign,” and 2 as “likely benign.” Twenty variants of unknown significance had an insufficient number of ancestry-matched controls, but ORs exceeded 5 when compared with racial/ethnic-matched Exome Aggregation Consortium (ExAC) controls.

NHGRI gene-level evidence and variant-level evidence establish EFHC1 as the first non-ion channel microtubule-associated protein whose mutations disturb R-type VDCC and TRPM2 calcium currents in overgrown synapses and dendrites within abnormally migrated dislocated neurons, thus explaining CTC convulsions and “microdysgenesis” neuropathology of JME [2].

1)
Jara-Prado A, Martínez-Juárez IE, Ochoa A, González VM, Fernández-González-Aragón Mdel C, López-Ruiz M, Medina MT, Bailey JN, Delgado-Escueta AV, Alonso ME. Novel Myoclonin1/EFHC1 mutations in Mexican patients with juvenile myoclonic epilepsy. Seizure. 2012 Sep;21(7):550-4. doi: 10.1016/j.seizure.2012.05.016. Epub 2012 Jun 22. PubMed PMID: 22727576.

2)
Bailey JN, Patterson C, de Nijs L, Durón RM, Nguyen VH, Tanaka M, Medina MT, Jara-Prado A, Martínez-Juárez IE, Ochoa A, Molina Y, Suzuki T, Alonso ME, Wight JE, Lin YC, Guilhoto L, Targas Yacubian EM, Machado-Salas J, Daga A, Yamakawa K, Grisar TM, Lakaye B, Delgado-Escueta AV. EFHC1 variants in juvenile myoclonic epilepsy: reanalysis according to NHGRI and ACMG guidelines for assigning disease causality. Genet Med. 2016 Jul 28. doi: 10.1038/gim.2016.86. [Epub ahead of print] PubMed PMID: 27467453.