TECHNOLOGY

KCNMA1-D434G Transgenic Mouse Line

OVERVIEW

KCNMA1-D434G knock-in mice express a gain-of-function (GOF) autosomal dominant aspartic acid to glycine substitution at position 434 of the potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (*KCNMA*) gene. Mice exhibit increased BK channel activity and decreased seizure thresholds. These mice may be useful for studying paroxysmal nonkinesigenic dyskinesia (PNKD3) with increased seizure propensity.

KCNMA1 (potassium large conductance calcium-activated channel, subfamily M, alpha member 1) encodes the pore-forming alpha subunit of the "Big K+" (BK) voltage and calcium-sensitive potassium channel (KCa1.1). BK channels regulate membrane potential and repolarization of action potentials and are widely expressed in neurons, smooth muscle, neuroendocrine and non-excitable cells such as bone and kidney. In excitable cells, BK channels regulate action potential repolarizations and afterhyperpolarizations, neurotransmitter release, and calcium transients. Human KCNMA1 mutations are primarily associated with neurological conditions, including seizures, movement disorders, developmental delay, and intellectual disability, specifically paroxysmal non-kinesigenic dyskinesia (PKND3) with or without epileptic seizures.

KCNMA1-D434G knock-in mice express a gain-of-function (GOF) aspartic acid to glycine substitution at position 434 (D434G, rs137853333). Patients have a heterozygous D434G genotype and experience seizures and paroxysmal dyskinesia with ~50% penetrance. D434G is located within the ?A and ?B of the AC domain, which is within the regulator of conductance of potassium 1 (RCK1) domain that regulates calcium-dependent gating. The D434G mutation validates the seizure and dyskinesia phenotype exhibited by patients. KCNMA1-D434G? mice heterozygous for the mutation are viable and fertile, and homozygous mice are viable but fertility has not been conclusively evaluated.??Homozygous KCNMA1-D434G?mice have a more severe phenotype with lowered seizure thresholds, hypokinetic stress-induced paroxysmal dyskinesia (episodes of immobility), and locomotor dysfunction. Heterozygous mice have lowered seizure thresholds but do not show stress-induced paroxysmal dyskinesia. BK channel currents were increased by 73% in heterozygotes and 203% in homozygotes, and both genotypes exhibit hyperactive neuronal activity in dentate gyrus neurons.

CONTACT INFO

Office of Technology Transfer
620 W Lexington St., 4th Floor
Baltimore, MD 21201
Email: ott@umaryland.edu
Phone: (410) 706-2380

Additional Information

INSTITUTION

University of Maryland, Baltimore

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CATEGORIES

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INVESTIGATOR(S)

Andrea Meredith

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