TECHNOLOGY

KCNMA1-N999S Transgenic Mouse Line

OVERVIEW

KCNMA1-N999S knock-in mice express a gain-of-function (GOF) asparagine to serine substitution at position 999 of the potassium large conductance calcium-activated channel, subfamily M, alpha member 1 gene. Mice exhibit increased channel activity, decreased seizure thresholds, and become immobile following (stress) restraint. These mice may be useful as a model for 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-N999S knock-in mice express gain-of-function (GOF) asparagine to serine substitution at position 999 (N999S; rs886039469). The heterozygous N999S mutation is the most common de novo KCNMA1 variant found in patients (17%), half of which develop seizures, paroxysmal non-kinesigenic dyskinesia (PKND3), or both. N999S is located in the helix bend in the middle of the S10 domain within the regulator of conductance of potassium 2 (RCK2) domain. Mice heterozygous for the mutation are viable and fertile with no apparent abnormalities. Heterozygote x heterozygote crosses do not produce homozygous progeny. KCNMA1-N999S mice exhibit lowered seizure thresholds, locomotor dysfunction, hypokinetic stress-induced paroxysmal dyskinesia (episodes of immobility),and increased BK channel activity (increased currents [69%] and action potential firing [25-30%]). In addition, severely affected KCNMA1-N999S/WT mice become immobile (hypokinetic) for 101+/-11 seconds as compared to wildtype (63+/-6 seconds after stress restraint, a trigger for paroxysmal dyskinesia. The stress-induced paroxysmal dyskinesia exhibited by KCNMA1-N999S mice is mitigated by acute dextroamphetamine treatment, consistent with the amphetamine responsiveness of PNKD3-affected patients harboring the N999S variant.

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