TECHNOLOGY

KCNMA1-H444Q

OVERVIEW

KCNMA1-H444Q knock-in mice express a loss-of-function (LOF) histidine to glutamine substitution at position 444 of the potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (*KCNMA*) gene. Mice exhibit locomotor dysfunction and hyperactive dyskinesia. These mice may be useful for studying paroxysmal nonkinesigenic dyskinesia (PNKD3).

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-H444Q knock-in mice express a loss-of-function (LOF) histidine to glutamic acid substitution at position 444 (H444Q). In heterologous cells, the H444Q mutation produces a loss-of-function (LOF) by slowing BK channel activation, speeding deactivation, and shifting the voltage-dependence of activation to more depolarized potentials. H444Q is located within the ?B and ?B of the AC domain, which is within the regulator of conductance of potassium 1 (RCK1) domain that regulates calcium-dependent gating. Mice homozygous for the mutation are viable and fertile with no apparent abnormalities such as locomotor dysfunction, hyperkinetic dyskinesia and impaired grip strength. KCNMA1-H444Q heterozygous mice exhibit alterations in BK channel closing, slowing activation and speeding deactivation. Seizure latency is not altered in the H444Q/WT mice as compared to wildtype. Homozygous H444Q mice exhibit reduced immobility following stress (in contrast to GOF (gain of function) mutations and reduced latencies to fall in the hanging wire test.

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AM-2019-105