A missense mutation in canine C1C-1 causes recessive myotonia congenita in the dog.

Rhodes TH, Vite CH, Giger U, Patterson DF, Fahlke C, George AL Jr

Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN 37232, USA.

Myotonia congenita is an inherited disorder of sarcolemmal excitation leading to delayed relaxation of skeletal muscle following contractions. Mutations in a skeletal muscle voltage-dependent chloride channel, CIC-1, have been identified as the molecular genetic basis for the syndrome in humans, and in two well characterized animal models of the disease: the myotonic goat, and the arrested development of righting (adr) mouse. We now report the molecular genetic and electrophysiological characterization of a canine CIC-1 mutation that causes autosomal recessive myotonia congenita in miniature Schnauzers. The mutation results in replacement of a threonine residue in the D5 transmembrane segment with methionine. Functional characterization of the mutation introduced into a recombinant CIC-1 and heterologously expressed in a cultured mammalian cell line demonstrates a profound effect on the voltage-dependence of activation such that mutant channels have a greatly reduced open probability at voltages near the resting membrane potential of skeletal muscle. The degree of this dysfunction is greatly diminished when heterodimeric channels containing a wild-type and mutant subunit are expressed together as a covalent concatemer strongly supporting the observed recessive inheritance in affected dog pedigrees. Genetic and electrophysiological characterization of the myotonic dog provides a new and potentially valuable animal model of an inherited skeletal muscle disease that has advantages over existing models of myotonia congenita.