# Researchers explain mechanism behind rare muscle disorders

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Researchers have provided the first thorough mechanistic account of how a genetic defect leads to malignant hypothermia (MH) and central core disease (CCD), rare genetic skeletal muscle disorders. The study appears in the January issue of the *Journal of General Physiology*.

Mutations in the type 1 ryanodine receptor (RYR1), the calcium release channel of the sarcoplasmic reticulum (SR) activated during skeletal muscle excitation-contraction (EC) coupling, give rise to CCD. One of the most common CCD-causing mutations is Ile4895Thr. Now, Robert Dirksen (University of Rochester) and colleagues have provided a comprehensive analysis of the consequences of this mutation in muscle fibers of adult mice heterozygous for the mutation.

The team addressed several questions concerning how RYR1 function is altered by the Ile4895Thr mutation. Their findings demonstrate, for the first time, that the muscle weakness associated with MH and CCD arises from a dominant-negative effect, a reduction in the magnitude and rate of calcium release by the mutant RYR1 receptors during EC coupling. The reduction in calcium release in turn leads to reduced muscle force generation.

**More information:** Loy, R.E. 2010. J. Gen. Physiol. doi:10.1085/jgp.201010523