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Quantitative reduction of RyR1 protein caused by a single-allele frameshift mutation in RYR1 ex36 impairs the strength of adult skeletal muscle fibres.

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Abstract

Here we characterized a mouse model knocked-in for a frameshift mutation in RYR1 exon 36 (p.Gln1970fsX16) that is isogenic to that identified in one parent of a severely affected patient with recessively inherited multiminicore disease. This individual carrying the RYR1 frameshifting mutation complained of mild muscle weakness and fatigability. Analysis of the RyR1 protein content in a muscle biopsy from this individual showed a content of only 20% of that present in a control individual. The biochemical and physiological characteristics of skeletal muscles from RyR1Q1970fsX16 heterozygous mice recapitulates that of the heterozygous parent. RyR1 protein content in the muscles of mutant mice reached 38% and 58% of that present in total muscle homogenates of fast and slow muscles from wild-type (WT) littermates. The decrease of RyR1 protein content in total homogenates is not accompanied by a decrease of Cav1.1 content, whereby the Cav1.1/RyR1 stoichiometry ratio in skeletal muscles from RyR1Q1970fsX16 heterozygous mice is lower compared to that from WT mice. Electron microscopy (EM) revealed a 36% reduction in the number/area of calcium release units accompanied by a 2.5-fold increase of dyads (triads that have lost one junctional sarcoplasmic reticulum element); both results suggest a reduction of the RyR1 arrays. Compared to WT, muscle strength and depolarization-induced calcium transients in RyR1Q1970fsX16 heterozygous mice muscles were decreased by 20% and 15%, respectively. The RyR1Q1970fsX16 mouse model provides mechanistic insight concerning the phenotype of the parent carrying the RYR1 ex36 mutation and suggests that in skeletal muscle fibres there is a functional reserve of RyR1.

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