A recessive ryanodine receptor 1 mutation in a CCD patient increases channel activity.

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Ryanodine receptors plays a crucial role in skeletal muscle excitation-contraction coupling by releasing calcium ions required for muscle contraction from the sarcoplasmic reticulum. At least three phenotypes associated with more than 100 RYR1 mutations have been identified; in order to elucidate possible pathophysiological mechanisms of RYR1 mutations linked to neuromuscular disorders, it is essential to define the mutation class by studying the functional properties of channels harbouring clinically relevant amino acid substitutions. In the present report we investigated the functional effects of the c.7304GRYR1 substitution (p.Arg2435Leu) found in a patient affected by central core disease. Both parents were heterozygous for the substitution while the proband was homozygous. We characterized Ca(2+) homeostasis in myoD transduced myotubes from controls, the heterozygous parents and the homozygous proband expressing the endogenous mutation. We also expressed the recombinant mutant channels in heterologous cells and characterized their [(3)H]ryanodine binding and single channel properties. Our results show that the p.Arg2435Leu substitution affects neither the resting [Ca(2+)], nor the sensitivity of the ryanodine receptor to pharmacological activators, but rather reduces the release of Ca(2+) from intracellular stores induced by pharmacological activators as well as by KCl via the voltage sensing dihydropyridine receptor.
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