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Am J Physiol Cell Physiol. 2019 Jun 5. doi: 10.1152/ajpcell.00052.2019. [Epub ahead of print]

A central core disease mutation in the Ca^{2+} binding site of skeletal muscle ryanodine receptor impairs single channel regulation.

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Abstract

Cryo-electron microscopy and mutational analyses have shown that type-1 ryanodine receptor (RyR1) amino acid residues RyR1-E3893, -E3967 and -T5001 are critical for Ca^{2+}-mediated activation of skeletal muscle Ca^{2+} release channel. *De novo* missense mutation RyR1-Q3970K in the secondary binding sphere of Ca^{2+} was reported in association with central core disease (CCD) in a two-year-old boy. Here, we characterized recombinant RyR1-Q3970K mutant by cellular Ca^{2+} release measurements, single channel recordings, and computational methods. Caffeine-induced Ca^{2+} release studies indicated that RyR1-Q3970K formed caffeine-sensitive, Ca^{2+} conducting channel in HEK293 cells. However, in single channel recordings, RyR1-Q3970K displayed low Ca^{2+}-dependent channel activity and greatly reduced activation by caffeine or ATP. A RyR1-Q3970E mutant corresponds to missense mutation RyR2-Q3925E associated with arrhythmogenic syndrome in cardiac muscle. RyR1-Q3970E also formed caffeine-induced Ca^{2+} release in HEK293 cells and exhibited low activity in the presence of the activating ligand Ca^{2+}, but in contrast to RyR1-Q3970K, was activated by ATP and caffeine in single channel recordings. Computational analyses suggested distinct structural rearrangements in the secondary binding sphere of Ca^{2+} of the two mutants, whereas the interaction of Ca^{2+} with directly interacting RyR1 amino acid residues Glu3893, Glu3967 and Thr5001 was only minimally affected. We conclude that RyR1-Q3970 has a critical role in Ca^{2+}-dependent activation of RyR1, and a missense RyR1-Q3970K mutant may give rise to myopathy in skeletal muscle.

KEYWORDS: central core disease; homology modeling; ryanodine receptor; sarcoplasmic reticulum; single channel recording

PMID: 31166712 DOI: 10.1152/ajpcell.00052.2019

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