Format: Abstract

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Molecular basis of impaired extraocular muscle function in a mouse model of congenital myopathy due to compound heterozygous Ryr1 mutations.

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Abstract

Mutations in the RYR1 gene are the most common cause of human congenital myopathies and patients with recessive mutations are severely affected and often display ptosis and/or ophthalmoplegia. In order to gain insight into the mechanism leading to extraocular muscle involvement, we investigated the biochemical, structural and physiological properties of eye muscles from mouse models we created knocked-in for Ryr1 mutations. Ex vivo force production in extraocular muscles from compound heterozygous RyR1p.Q1970fsX16 + p.A4329D mutant mice was significantly reduced compared to that observed in wild type, single heterozygous mutant carriers or homozygous RyR1p.A4329D mice. The decrease in muscle force was also accompanied by approximately a 40% reduction in RyR1 protein content, a decrease in electrically evoked calcium transients, disorganization of the muscle ultrastructure and a decrease in the number of calcium release units. Unexpectedly, the superfast and ocular-muscle specific myosin heavy chain-EO isoform was almost undetectable in RyR1p.Q1970fsX16 + p.A4329D mutant mice. The results of this study show for the first time that the extraocular muscle phenotype caused by the RyR1p.Q1970fsX16 + p.A4329D compound heterozygous Ryr1 mutations is complex and due to a combination of modifications including a direct effect on the macromolecular complex involved in calcium release and indirect effects on the expression of myosin heavy chain isoforms.

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