Genetic and functional analysis of the RYR1 mutation p.Thr84Met revealed a susceptibility to malignant hyperthermia.


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Abstract

The aim of this study was to analyze the genetic and functional role of a novel RYR1 variant c.251 C > T (p.Thr84Met) identified in a patient with muscle weakness demonstrating MH susceptibility.

DNA testing of family members was conducted for assessment of pathogenicity of the genetic variant. For functional analysis, Ca²⁺ measurement using patient-derived myotubes and p.Thr84Met RYR1-transfected human embryonic kidney (HEK)-293 cells was performed to evaluate reactivity to RYR1 activators. The half-maximal effective concentration (EC₅₀) values of two RYR1 activators, caffeine and 4-chloro-m-cresol (4CmC), were calculated from the acquired dose-response curves. The EC₅₀ was compared between two groups: for myotubes, the control group and the patient, and for HEK-293 cells, WT and p.Thr84Met.

Dose-response curves for caffeine and 4CmC were shifted to the left in both myotubes and HEK-293 cells compared to controls. The 50% effective concentration values for caffeine and 4CmC were significantly lower in both myotubes and HEK-293 cells compared to controls (P < 0.001 for all comparisons).
CONCLUSIONS: Our results of functional testing indicated RYR1 hypersensitivity to caffeine and 4CmC. We conclude that the genetic variant was associated with MH susceptibility.

KEYWORDS: Calcium release; Malignant hyperthermia; Mutation; Ryanodine receptor

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