Compound RYR1 heterozygosity resulting in a complex phenotype of malignant hyperthermia susceptibility and a core myopathy.

Kraeva N1, Heytens L2, Jungbluth H3, Treves S4, Voermans N5, Kamsteeg E6, Ceuterick-de Groote C7, Baets J8, Riazi S9.

Author information

Abstract

Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic myopathy triggered by exposure to volatile anesthetics and/or depolarizing muscle relaxants. Susceptibility to MH is primarily associated with dominant mutations in the ryanodine receptor type 1 gene (RYR1). Recent genetic studies have shown that RYR1 variants are the most common cause of dominant and recessive congenital myopathies - central core and multi-minicore disease, congenital fiber type disproportion, and centronuclear myopathy. However, the MH status of many patients, especially with recessive RYR1-related myopathies, remains uncertain. We report the occurrence of a triplet of RYR1 variants, c.4711A>G (p.Ile1571Val), c.10097G>A (p.Arg3366His), c.11798A>G (p.Tyr3933Cys), found in cis in four unrelated families, one from Belgium, one from The Netherlands and two from Canada. Phenotype-genotype correlation analysis indicates that the presence of the triplet allele alone confers susceptibility to MH, and that the presence of this allele in a compound heterozygous state with the MH-associated RYR1 variant c.14545G>A (p.Val4849Ile) results in the MH susceptibility phenotype and a congenital myopathy with cores and rods. Our study underlines the notion that assigning pathogenicity to individual RYR1 variants or combination of variants, and counseling in RYR1-related myopathies may require integration of clinical, histopathological, in vitro contracture testing, MRI and genetic findings.

KEYWORDS: Compound RYR1 heterozygosity; Core myopathies; Malignant hyperthermia

PMID: 25958340 DOI: 10.1016/j.nmd.2015.04.007

[Indexed for MEDLINE]
Compound RYR1 heterozygosity resulting in a complex phenotype of malignant hyperthermia susceptibility and a core myopathy. - PubMed - NCBI