Hum Mol Genet. 2019 May 20. pii: ddz105. doi: 10.1093/hmg/ddz105. [Epub ahead of print]

Mouse model of severe recessive RYR1-related myopathy.

Brennan S[1,2], Garcia-Castañeda M[3], Michelucci A[3], Sabha N[1], Malik S[3], Groom L[3], Wei-La-Pierre L[3], Dowling JJ[1,2,4], Dirksen RT[3].

Author information

Abstract

RYR1 related myopathies (RYR1 RM) are a clinically and histopathologically heterogeneous group of conditions that represent the most common subtype of childhood onset non-dystrophic muscle disorders. There are no treatments for this severe group of diseases. A major barrier to therapy development is the lack of an animal model that mirrors the clinical severity of pediatric cases of the disease. To address this, we used CRISPR/Cas9 gene editing to generate a novel recessive mouse model of RYR1 RM. This mouse (Ryr1TM/Indel) possesses a patient relevant point mutation (T4706M) engineered into one allele and a 16 base pair frameshift deletion engineer into the second allele. Ryr1TM/Indel mice exhibit an overt phenotype beginning at 14 days of age that consists of reduced body/muscle mass and myofibre hypotrophy. Ryr1TM/Indel mice become progressively inactive from that point onward and die at a median age of 42 days. Histopathological assessment shows myofibre hypotrophy, increased central nuclei, and decreased triad number, but no clear evidence of metabolic cores. Biochemical analysis reveals a marked decrease in RYR1 protein levels (20% of normal) as compared to only a 50% decrease in transcript. Functional studies at end stage show significantly reduced electrically-evoked Ca2+ release and force production. In summary, Ryr1TM/Indel mice exhibit a post-natal lethal recessive form of RYR1 RM that pheno-copies the severe congenital clinical presentation seen in a subgroup of RYR1 RM children. Thus, Ryr1TM/Indel mice represent a powerful model for both establishing the pathomechanisms of recessive RYR1 RM and pre-clinical testing of therapies for efficacy.

PMID: 31107960 DOI: 10.1093/hmg/ddz105

LinkOut - more resources