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CASE REPORT

Harrison et al: RYR1/BCHE variants and succinylcholine

Succinylcholine-induced rhabdomyolysis in a patient with *RYR1* and *BCHE* variants: A case report

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ABSTRACT

Masseter muscle spasm after succinylcholine can herald malignant hyperthermia (MH) in genetically susceptible individuals. We aimed to describe the perioperative course and genetic findings in a patient who developed transient masseter spasm and postoperative rhabdomyolysis after general anesthesia. This single-patient case report draws on perioperative observations, laboratory testing, and whole-genome sequencing. Immediately after induction with propofol and succinylcholine, the patient experienced transient masseter spasm; anesthesia was then maintained with total intravenous anesthesia (propofol and remifentanil). Postoperatively, laboratory studies showed severe rhabdomyolysis with mild pigment nephropathy; the patient received intravenous hydration, laboratory values normalized by postoperative day 4, and discharge occurred in good condition. Whole-genome sequencing identified heterozygous ryanodine receptor 1 (*RYR1)* c.1840C>T (p.Arg614Cys)—a known MH-susceptibility variant in the skeletal-muscle ryanodine receptor—and butyrylcholinesterase (*BCHE)* c.293A>G (p.Asp98Gly), which reduces butyrylcholinesterase activity and delays succinylcholine hydrolysis. The coexistence of these variants likely synergistically increased sarcoplasmic reticulum Ca^{2+} release and prolonged succinylcholine effect, precipitating rhabdomyolysis; to our knowledge, this appears to be the first reported case linking concurrent *RYR1* and *BCHE* variants to rhabdomyolysis following general anesthesia.

Keywords: Butyrylcholinesterase deficiency, rhabdomyolysis, ryanodine receptor variant, skeletal muscle.

INTRODUCTION

Ryanodine receptor 1 (RYR1) is a large calcium-release channel located on the sarcoplasmic reticulum membrane of striated skeletal muscle. The controlling core of muscle excitation-contraction coupling is the calcium channel protein complex, which is composed of RYR1 and the dihydropyridine receptor (DHPR), an L-type voltage-gated calcium channel located on the T-tubular sarcolemmal membrane. In response to depolarization of the muscle membrane induced by acetylcholine or succinylcholine, DHPR undergoes a conformational change that activates the RYR1, resulting in calcium release from the sarcoplasmic reticulum. Genetic variants of the RYR1 protein may result in excessive cytosolic calcium after depolarization, thereby leading to oxidative overload, myopathy, and skeletal muscle breakdown.

Variants of RYR1 are known to cause a wide spectrum of inherited muscle disorders, including malignant hyperthermia (MH) [1, 2]. MH is a pharmacogenetic life-threatening hypermetabolic reaction triggered by exposure to halogenated anesthetics and succinylcholine [3, 4]. Halogenated agents directly interact with the RYR1 channel, whereas succinylcholine acts indirectly by binding to nicotinic acetylcholine receptors, inducing membrane depolarization, which in turn triggers calcium release from the sarcoplasmic reticulum via RYR1.

In patients carrying a pathogenic *RYR1* variant, calcium efflux into the cytosol following succinylcholine administration can become excessive, leading to sustained muscle contraction, myofibrillar disruption, and rhabdomyolysis [1]. We report a patient who experienced mild masseter spasm following succinylcholine during anesthetic induction, subsequently developing severe rhabdomyolysis in the postanesthesia care unit (PACU), suggestive of an underlying *RYR1*-related disorder. Whole-genome sequencing later identified two variants that likely acted synergistically to produce this severe clinical presentation.

CASE REPORT

According to institutional policy at Mayo Clinic, IRB review is not required for a single-patient case report. A 48-year-old otherwise healthy man with hearing loss secondary to medial canal fibrosis underwent hearing aid insertion under general anesthesia.

Anesthesia was induced with intravenous propofol and succinylcholine. Mild masseter muscle spasm was observed following induction; however, after administration of additional propofol, mouth opening improved, allowing for successful tracheal intubation. The presence of masseter spasm raised concern for MH susceptibility. Consequently, anesthesia was maintained using total intravenous anesthesia with propofol and remifentanil. Throughout the procedure, core temperature, end-tidal carbon dioxide, and heart rate were closely monitored and remained within normal limits. At the conclusion of the two-hour surgery, the patient's trachea was extubated, and he was transferred to the PACU. Initial recovery was unremarkable, with discharge criteria met within 60 minutes.

Immediately before discharge, the patient reported passing "black-colored urine," raising concern for rhabdomyolysis. Laboratory tests performed 6 hours after succinylcholine administration revealed a serum potassium of 4.6 mmol/L (reference, 3.6–5.2 mmol/L), serum creatine kinase (CK) of 14,143 U/L (reference, 39–308 U/L), and urine myoglobin >5,000 μg/L (reference, ≤65 μg/L). Given the presence of rhabdomyolysis with myoglobinuria, the patient was admitted for vigorous intravenous hydration and observation. At 14 hours after succinylcholine administration, the patient's creatine kinase (CK) level had risen to 49,884 U/L, peaking at 74,320 U/L at 24 hours (Figure 1A). To assess potential kidney injury, serum creatinine and cystatin C levels were serially monitored. Serum creatinine remained stable (0.94–1.16 mg/dL), whereas serum cystatin C, a non-glycosylated protein used to estimate glomerular filtration rate (GFR), increased from 0.91 mg/L on postoperative day 1 to 1.20 mg/L on day 2 (reference range: 0.63–1.03 mg/L) (Figure 1B). This corresponded to a decline in estimated GFR from 92 to 64 mL/min/1.73 m², consistent with mild pigment nephropathy. Serum alanine aminotransferase level was 63 U/L in the PACU and transiently increased to 228 U/L at postoperative day 2 (reference, 7-55 U/L). Serum aspartate aminotransferase level was 144 U/L in the PACU and transiently increased to 818 U/L on postoperative day 2 (reference, 8-48 U/L). His preoperative platelet count was 264 × 10^9/L, which decreased to 75 × 10^9/L on postoperative day 1 and rebounded to 275×10^9/L on postoperative day 2 (reference, 135-317 × 10^9/L). His white blood cell count was 17.2×10^9/L on postoperative day 1 (reference, 3.4-9.6 × 10^9/L). Hepatitis panels (A, B,

and C) were all negative. He was discharged on postoperative day 4, with all laboratory test values in the normal range.

Genetic counseling and testing

Given the suspicion for MHS, the patient was referred for genetic evaluation. A clinical genomics consultant performed a comprehensive assessment and obtained additional details of the patient's medical history that had not been documented prior to the procedure. During directed questioning, the patient reported experiencing intermittent muscle spasms and pain following physical exertion, particularly when performed in warm environments. These episodes were most often localized to the abdominal muscles but occasionally involved more generalized muscle cramping affecting multiple muscle groups. The patient described the spasms as transient and self-limited, occurring primarily after strenuous activity, with no associated weakness, or other systemic symptoms reported. No prior formal evaluation for these symptoms had been undertaken. The patient further reported a history of two prior surgical procedures performed under general anesthesia in his hometown, but information regarding the specific anesthetic agents used was unavailable. The first procedure, an appendectomy at age 18, was reportedly uncomplicated. Following the second procedure, an ambulatory otologic surgery performed at 39 years of age, the patient reported the onset of dark urine, myalgia, and abdominal muscle cramps within 24 hours post-discharge. All manifestations resolved spontaneously within one day, and the patient therefore did not seek medical evaluation or inform the treating physician at that time. Additionally, the patient noted a family history of similar, though milder, symptoms: his father and two older brothers occasionally experience muscle cramping, particularly after physical exertion.

In view of this clinical history, rapid whole-genome sequencing was performed at the Rady Children's Institute for Genomic Medicine Clinical Laboratory (Clinical Genome Center) San Diego, California, USA, as this testing is not available at the Mayo Clinic. Whole-genome sequencing identified two heterozygous gene variants. First, we identified a c.1840C>T variant in the *RYR1* gene, resulting in a missense mutation that substitutes arginine with cysteine at position 614 (p.Arg614Cys). This substitution is consistent with *RYR1* receptor-related disorders and is strongly associated

with MHS [1, 2]. Second, we identified a 293A>G variant in the gene encoding *BCHE*, which results in an aspartic acid to glycine substitution at position 98 of *BCHE* (c.293A>G; p.Asp98Gly). This substitution causes *BCHE* deficiency which slows the hydrolysis of choline esters (eg, succinylcholine) and thereby leads to protracted succinylcholine-induced muscle cell membrane depolarization. The specific genetic constellation of these two variants most likely contributed to the phenotypic presentation in our patient. Specifically, the pathogenic effects of the *RYR1* variant on skeletal muscle breakdown were most likely potentiated by sustained cell membrane depolarization caused by delayed succinylcholine degradation due to *BCHE* deficiency. Comprehensive genetic counseling was provided, emphasizing preventive measures to reduce the risk of recurrent rhabdomyolysis and advising the patient to wear a MH susceptibility alert bracelet.

Ethical statement

Written informed consent has been obtained from the patient to publish this report. The principles outlined in Declaration of Helsinki were followed.

DISCUSSION

This case report describes the simultaneous presence of pathogenic variants in the *RYR1* and *BCHE* genes in a patient who developed mild masseter spasm after receiving succinylcholine, followed by severe rhabdomyolysis, and mild pigment nephropathy. We propose that the coexistence of *BCHE* deficiency and a pathogenic *RYR1* variant synergistically contributed to the severity of rhabdomyolysis. Specifically, impaired succinylcholine hydrolysis resulting from *BCHE* deficiency likely prolonged muscle membrane depolarization, permitting sustained calcium release from the sarcoplasmic reticulum into the cytosol. This prolonged calcium efflux may have triggered persistent muscle contraction and extensive myofibrillar breakdown. Figure 2 illustrates the proposed pathophysiologic pathway underlying the rhabdomyolysis observed in this patient, and animations of the mechanism are provided in the Electronic Supplementary Material.

Biochemical abnormalities in our patient with rhabdomyolysis

Our patient demonstrated several biochemical abnormalities, most notably a transient rise in serum transaminases. The increased transaminase levels were most likely due to muscle breakdown [5] rather than damage to the hepatic parenchyma, which was further evidenced by negative hepatitis panels. Another abnormal finding was thrombocytopenia. While this can arise from various causes, including hemodilution due to overhydration, the most plausible explanation in this case is related to rhabdomyolysis. During rhabdomyolysis, myoglobin-derived heme released from damaged muscle tissue is converted to hemin in the bloodstream [6]. Hemin has been shown to induce platelet activation and subsequent consumption, leading to a reduction in platelet count [7, 8]. The patient also had leukocytosis, a response related to inflammatory stress (release of epinephrine, norepinephrine, and/or inflammatory cytokines such as IL-6 and TNF-alpha) associated with muscle tissue content release into the bloodstream [9], however other etiologies such as volume depletion with hemoconcentration may also be contributory.

Prevalence of *RYR1* and *BCHE* genetic variants in the general population

The prevalence of pathogenic *RYR1* variants in the general population is estimated at 1 in approximately 300 individuals [10]. The *RYR1 c.*1840C>T (p.Arg614Cys) variant, specifically associated with MHS, has an allele frequency of about 1 in 5,000 [11]. Because many RYR1 variants show incomplete penetrance, and clinical manifestations generally require exposures to triggering agent (e.g., volatile anesthetics or succinylcholine), the reported incidence of MH is substantially lower, ranging from ~1 in 10,000 to 1 in 30,000 anesthetics in children [12] and ~1 in 50,000 to ~1 in 100,000 in adults [13, 14]. Heterozygous *BCHE* deficiency occurs in approximately 1 in 25 to 1 in 50 individuals [15]. Because these two gene variants represent independent pathophysiologic processes, the probability of both occurring in the same individual can be estimated by multiplying their respective frequencies. Based on published allele frequency data, the estimated prevalence of coexisting *RYR1* c.1840C>T (p.Arg614Cys) and heterozygous *BCHE* c.293A>G (p.Asp98Gly) variants in a single individual ranges from approximately 1 in 125,000 to 1 in 250,000. To the best of our knowledge, this is

the first reported case of a patient harboring both variants and presenting with rhabdomyolysis following exposure to a triggering anesthetic agent.

The pathogenic *RYR1* variant in our patient has been reported in patients with MH and other *RYR1*-related myopathies [16-19]. Although many single-nucleotide variants in genes related to skeletal muscle calcium release have been described [16, 20, 21], the only variants positively associated with MHS are located in the *RYR1* (19q13.2), *CACNA1S* (1q32.1), and *STAC3* (12q13.3) genes.

Genotype–phenotype correlations in individuals with *RYR1* variants

The severity of clinical presentation of an *RYR1*-related myopathy depends on the genetic variant (variant site and homozygous vs heterozygous trait) [22, 23]. Because of the close association between genotype and phenotype [21, 24, 25], patients with heterozygous *RYR1* variants have a less severe clinical picture than those with homozygous variants [26]. This association between genotype and phenotype was reported in an analysis of a German family affected by MHS [16]. A patient (son) had an MH crisis during anesthesia, and a homozygous variant in *RYR1* associated with MH was identified [16]. The patient's sister also had a homozygous variant, and the parents (mother and father) each had heterozygous variants. Consequently, MHS was diagnosed with the in vitro caffeine-halothane contracture test (ie, the standard for MH and MHS diagnoses) for the parents [16]. The son and sister with homozygous variants had greater contracture responses to both halothane and caffeine than did their heterozygous parents, suggesting that genotype (homozygous vs heterozygous) is an important contributor to the MH phenotype. However, the interpretation of genetic tests may be complex, and most patients with MH have a heterozygous *RYR1* variant [16, 23]. Homozygosity has been reported for only two patients with the Cys35Arg substitution and for one patient with the Arg614Cys substitution [16, 24, 27]. Therefore, individuals carrying MH-associated *RYR1* variants, even in the heterozygous state, should be considered at risk for malignant hyperthermia.

Anesthetic agents implicated in triggering MH

Halogenated anesthetics are the principal (direct) triggers of the biochemical disturbances associated with MH in patients carrying *RYR1* variants, with succinylcholine acting as an independent (indirect) contributory factor [28]. Notably, succinylcholine alone has been

reported to trigger MH in approximately 15.5% of susceptible individuals [28]. This may be attributed to its indirect effect on *RYR1*, as succinylcholine induces sustained muscle action potentials, whereas volatile anesthetic agents exert continuous stimulation throughout the duration of anesthesia.

Masseter muscle rigidity as a sign of MHS

Masseter muscle spasm following succinylcholine administration is a concerning clinical sign that may indicate MHS or an underlying myopathy [4]. A patient with marked rigidity of the jaw muscles should be observed overnight, and should be observed for at least 12 hours [12]. Because the probability for MH development after isolated use of succinylcholine appears to be low, continuing anesthesia with intravenous agents is perhaps preferred to the more conservative approach compared to abandoning the surgical procedure [4].

CONCLUSION

We report a patient harboring two genetic variants that contributed to succinylcholine-induced masseter spasm and severe rhabdomyolysis. One variant is associated with *RYR1*-related myopathy, while the other prolongs recovery after succinylcholine due to *BCHE* deficiency. Although these variants have distinct clinical effects, their coexistence may produce a synergistic interaction. Specifically, the *RYR1*-related susceptibility was likely exacerbated by prolonged skeletal muscle membrane depolarization resulting from delayed succinylcholine hydrolysis.

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FIGURES WITH LEGENDS

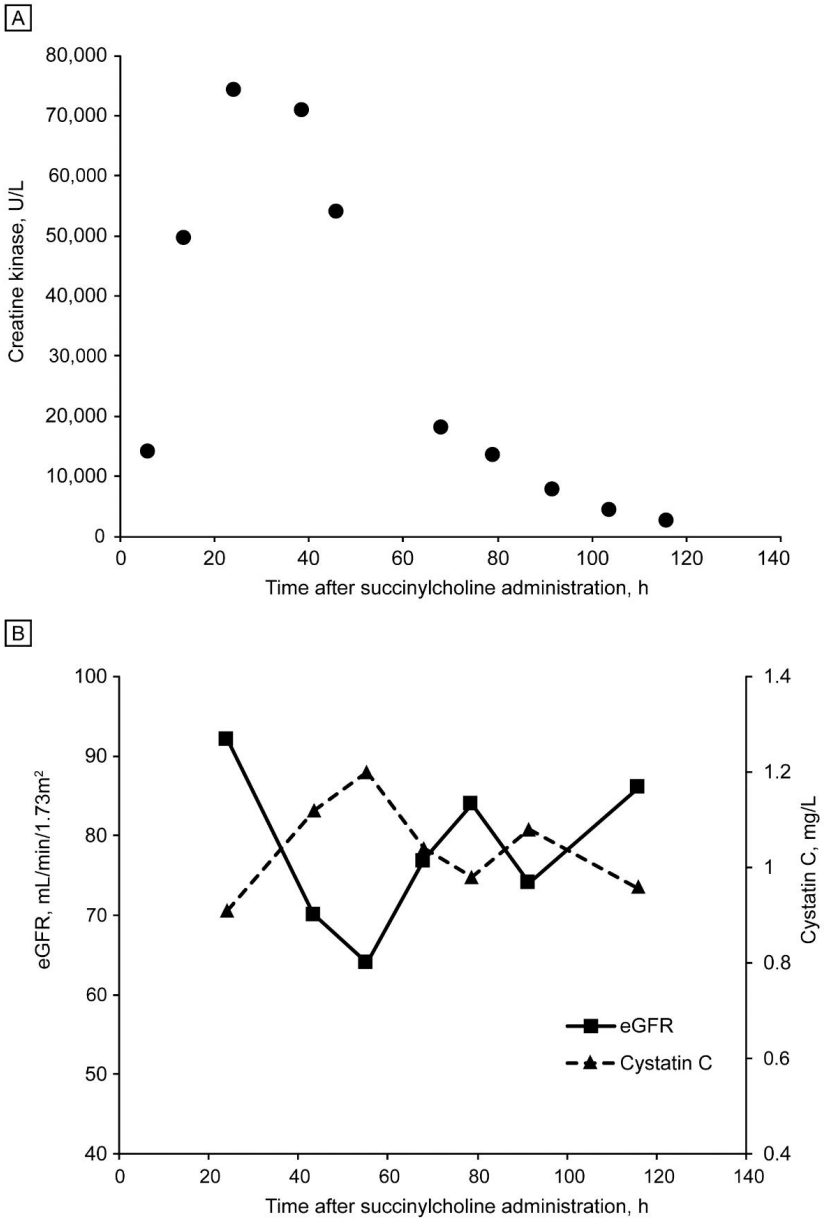


Figure 1. Biomarkers of rhabdomyolysis following succinylcholine administration in a patient with *BCHE* and *RYR1* variants. (A) Serum creatine kinase levels. (B) Serum cystatin C levels and cystatin C–estimated glomerular filtration rate (eGFR).

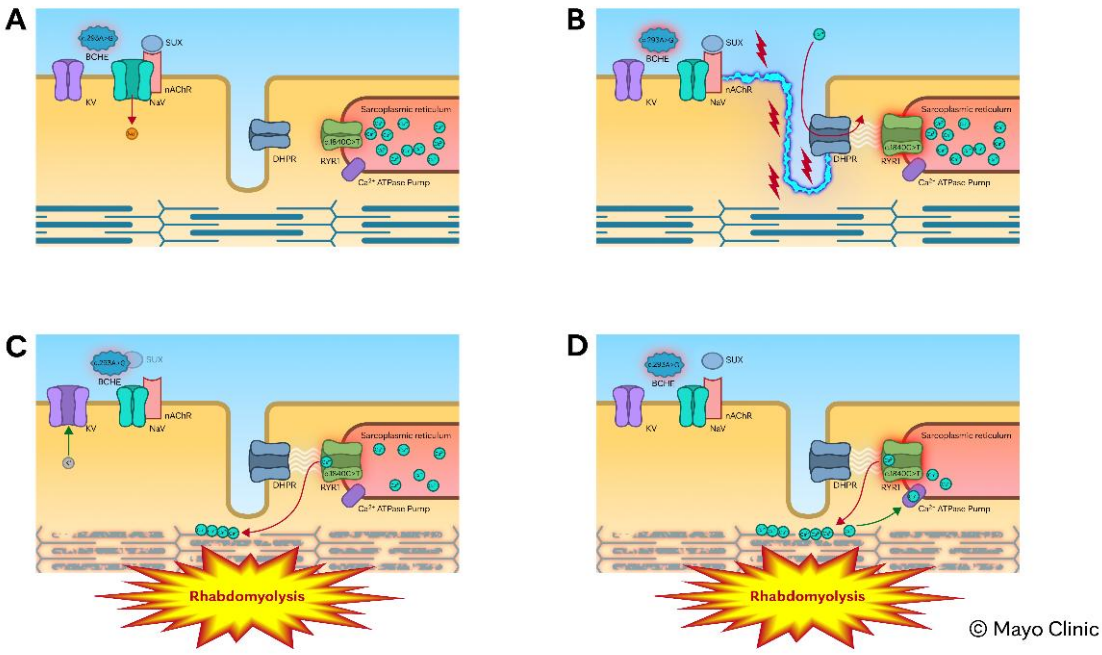
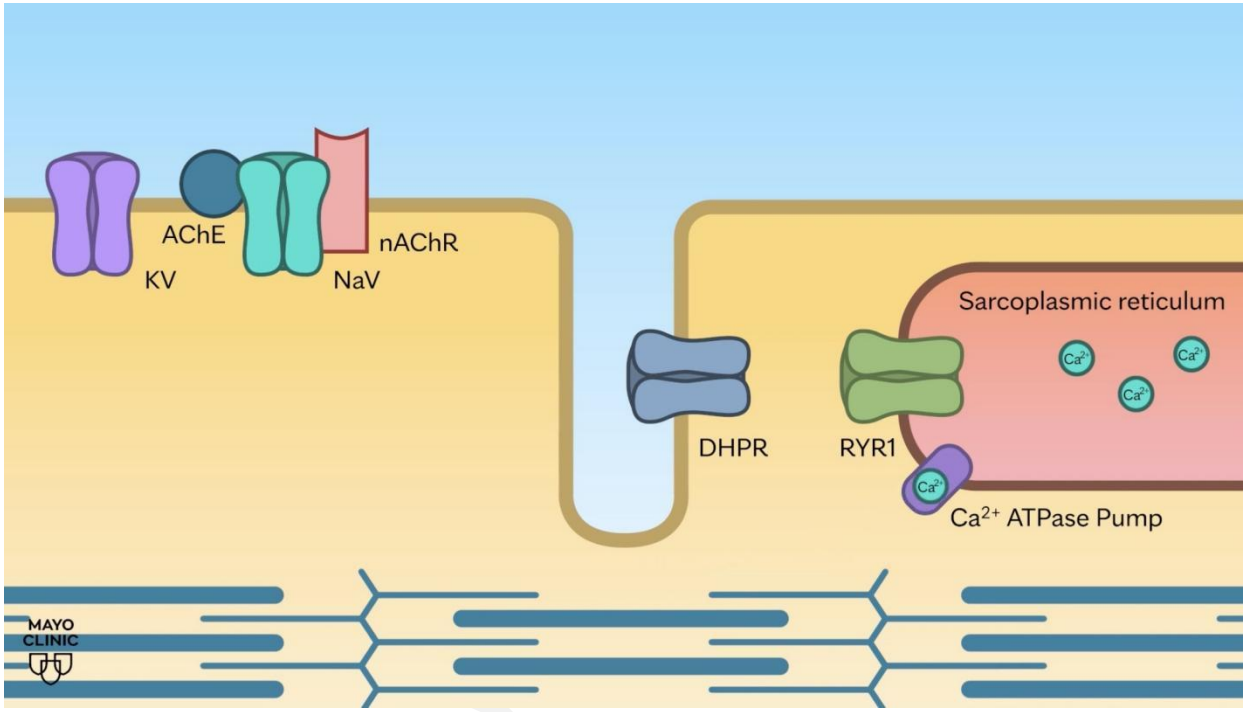


Figure 2. Proposed mechanism of severe rhabdomyolysis in a patient with *BCHE* deficiency and an *RYR1* pathogenic variant. (A) Key components involved in skeletal muscle contraction are illustrated. (B) Succinylcholine (SUX) binds to nicotinic acetylcholine receptors (nAChRs), triggering the opening of voltage-gated sodium channels (NaV) and initiating skeletal muscle membrane depolarization (blue serrated line). This depolarization activates the dihydropyridine receptor (DHPR), which subsequently opens the ryanodine receptor 1 (*RYR1*) calcium channel on the sarcoplasmic reticulum membrane. In normal muscle, *RYR1* opens briefly to release calcium into the cytosol, then closes to allow relaxation. However, in the presence of an *RYR1* pathogenic variant [c.1840C>T (p.Arg614Cys)], the channel remains abnormally open, leading to excessive and prolonged calcium release, sustained muscle contraction, and eventual rhabdomyolysis. (C, D) In a patient with butyrylcholinesterase (*BCHE)* deficiency [c.293A>G (p.Asp98Gly)], the metabolism of SUX is impaired, leading to delayed breakdown. This prolongs depolarization of the muscle membrane, which in turn causes sustained activation of the RYR1. This further enhances calcium leakage into the cytosol, perpetuating sustained myofibrillar contraction and contributing to severe muscle damage with rhabdomyolysis.

SUPPLEMENTAL DATA

We provide simplified animations that illustrate the sequence of cellular mechanisms involved in physiologic muscle contraction and pathogenic muscle contraction observed in a patient with pathogenic variants in *RYR1* and *BCHE*.



Animation File 1. Scenario 1: Development of a normal action potential and the sequence of cellular events associated with muscle contraction and relaxation (YouTube: https://www.youtube.com/watch?v=55HEWeyNBck).

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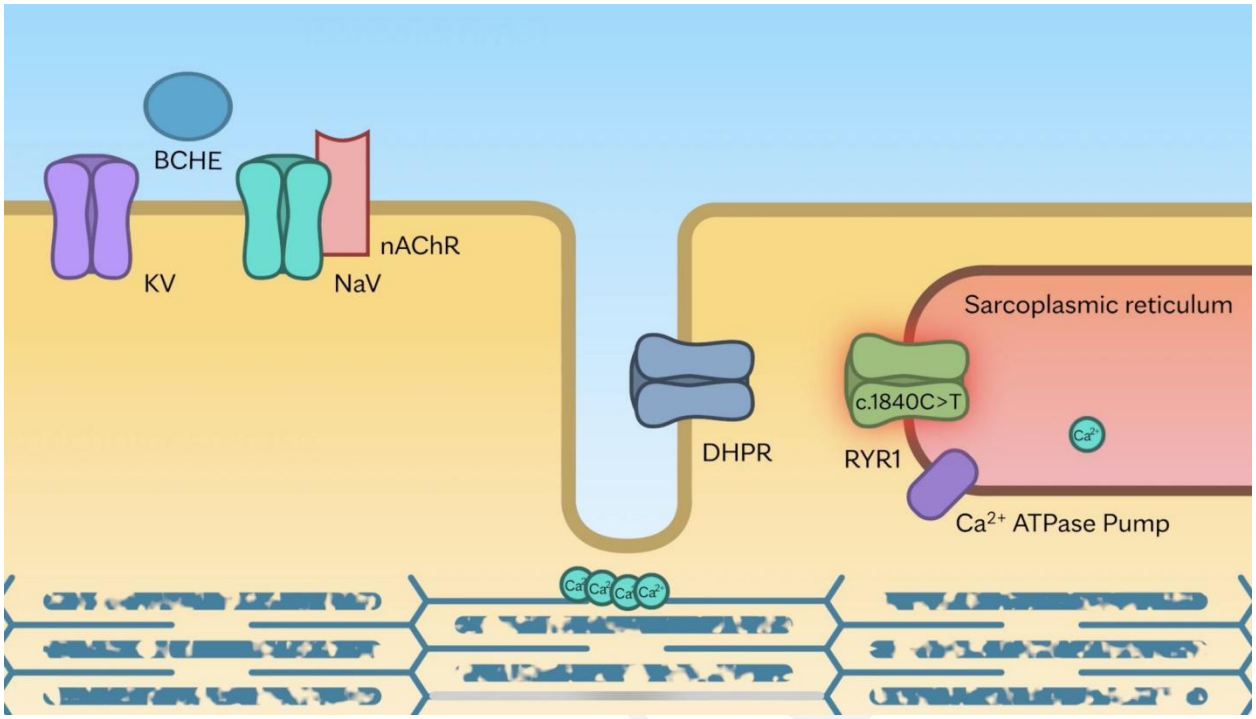

Animation File 2. Scenario 2: Use of succinylcholine in patient with a pathogenic *RYR1* variant triggers prolonged myofilament stimulation resulting in myofibrillar disruption (YouTube: https://www.youtube.com/watch?v=worhWZhCsY4).

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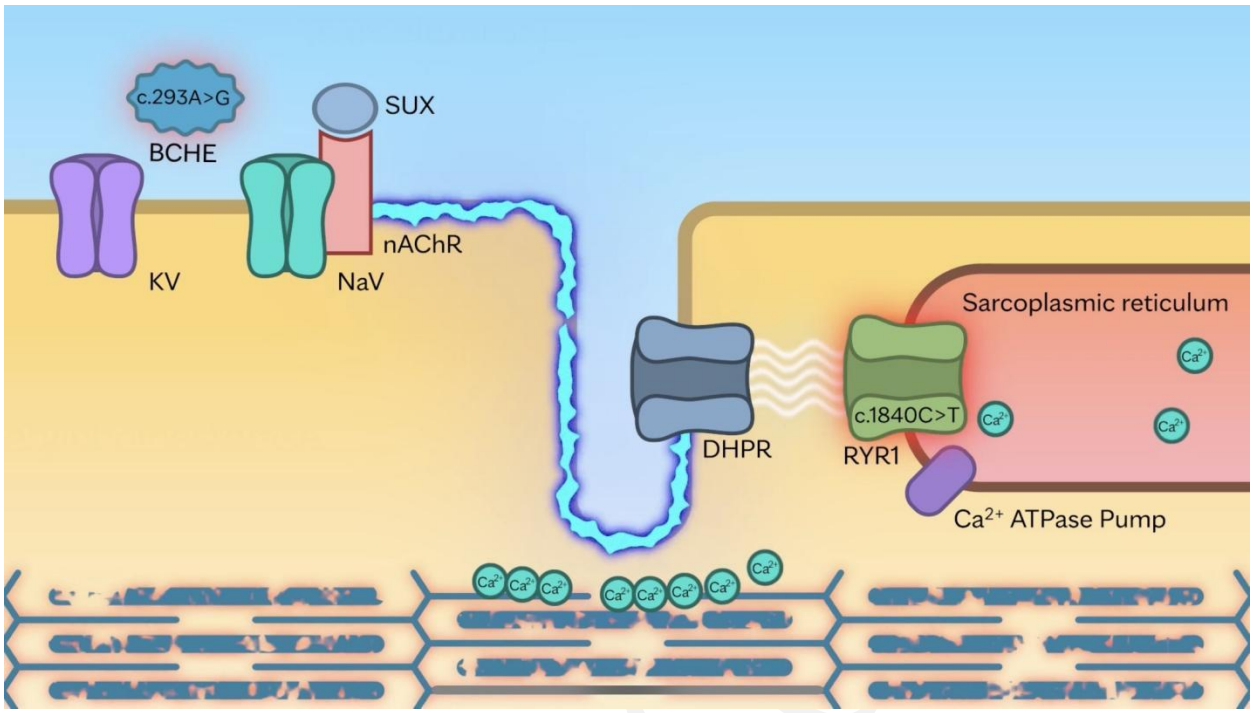

Animation File 3. Scenario 3: Use of succinylcholine in a patient with butyrylcholinesterase deficiency and the pathogenic *RYR1* variant induces sustained depolarization, further extending myofilament stimulation and resulting in severe myofibrillar disruption with rhabdomyolysis (YouTube: https://www.youtube.com/watch?v=k-bY2cIRal0).

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