Rhabdomyolysis, Susceptibility To, 1 (RHABDO1) — Comprehensive Disease Report

Disease: Rhabdomyolysis, Susceptibility To, 1 (RHABDO1) **MONDO ID:** MONDO:0859371 · **OMIM:** 620235 · **Causal gene: OBSCN** (obscurin; HGNC:16542; UniProt Q5VST9; chromosome 1q42) **Category:** Mendelian (autosomal recessive)

> **Gene identity (stated up front):** The causal gene for Rhabdomyolysis Susceptibility To 1 is **OBSCN**, which encodes **obscurin**, a giant (~800 kDa) sarcomeric cytoskeletal/signaling protein. This report concerns the OBSCN-related entity (OMIM 620235), not rhabdomyolysis caused by other genes (e.g., RYR1, LPIN1, CPT2, PYGM, ANO5, fatty-acid-oxidation genes).

Summary

Rhabdomyolysis, Susceptibility To, 1 (RHABDO1) is a rare Mendelian skeletal-muscle disorder caused by **bi-allelic loss-of-function (LOF) variants in OBSCN**, the gene encoding **obscurin** — a giant (~800 kDa) modular sarcomeric signaling and structural protein that physically links the contractile sarcomere (at the M-band and Z-disk) to the sarcoplasmic reticulum (SR). The disease was defined by Cabrera-Serrano and colleagues (*Brain*, 2022), who identified 10 bi-allelic LOF OBSCN variants in six unrelated patients with severe, recurrent exertional rhabdomyolysis and demonstrated reduced OBSCN expression and loss of obscurin protein in patient muscle (PMID: 34957489). This case series established OMIM 620235.

The core clinical picture is **teenage-onset, recurrent, severe rhabdomyolysis** precipitated by metabolic or mechanical triggers (strenuous exercise, fasting, febrile illness), accompanied by myalgia, muscle cramps, exercise intolerance, markedly elevated serum creatine kinase (CK), and myoglobinuria that risks acute kidney injury (AKI). A distinguishing feature is **cardiac sparing** — despite prior literature linking OBSCN to cardiomyopathy, RHABDO1 patients consistently lack cardiomyopathy and have normal cardiac examinations. The mechanistic

model, supported by patient myoblast studies and mouse *Obscn/Obsl1* models, is that obscurin loss **disorganizes the SR and impairs Ca^{2+} re-uptake/storage**, sensitizing myofibers to metabolic and mechanical stress and precipitating episodic myofiber breakdown.

Genetically, OBSCN is **not constrained against heterozygous LOF** in gnomAD (pLI ≈ 0, LOEUF ≈ 0.94), consistent with recessive inheritance in which a single LOF allele is tolerated. In ClinVar, truncating OBSCN variants (nonsense/frameshift) associated with rhabdomyolysis are classified Pathogenic/Likely-pathogenic, whereas missense variants are predominantly Variants of Uncertain Significance (VUS). There is **no gene-specific therapy**; management is supportive (aggressive IV fluid resuscitation, electrolyte and renal monitoring during crises) combined with **trigger avoidance** and **genetic counseling**. This report synthesizes evidence across the defining human case series, three additional case reports, gnomAD constraint data, ClinVar classifications, UniProt domain architecture, Monarch/HPO phenotype annotations, and mouse models.

Section 1 — Disease Information

Overview. RHABDO1 is an autosomal-recessive susceptibility to recurrent rhabdomyolysis — acute skeletal-muscle fiber breakdown with release of intracellular contents (CK, myoglobin, electrolytes) into the circulation. Affected individuals are often asymptomatic or only mildly symptomatic between episodes but develop severe crises when exposed to triggers. The condition is a **genetic susceptibility** rather than a continuously progressive myopathy: episodes are **trigger-dependent and episodic**, with normal or near-normal muscle strength between attacks in most patients.

Key identifiers.

Resource	Identifier
OMIM	620235 (Rhabdomyolysis, susceptibility to, 1)
MONDO	MONDO:0859371
Causal gene	OBSCN (HGNC:16542; NCBI Gene; Ensembl ENSG00000154358)
Protein	Obscurin, UniProt Q5VST9
Cytoband	1q42
Orphanet / ICD-10 / ICD-11 / MeSH	No dedicated RHABDO1-specific code identified; rhabdomyolysis maps to ICD-10 **M62.82** and MeSH **D012206 (Rhabdomyolysis)**

Synonyms / alternative names. No formal synonyms are recorded in the template. The condition is referred to descriptively in the literature as "OBSCN-related rhabdomyolysis," "obscurin-deficiency rhabdomyolysis," and "bi-allelic OBSCN loss-of-function rhabdomyolysis."

Information source. The knowledge base here is derived from **aggregated disease-level resources** (OMIM, ClinVar, gnomAD, HPO/Monarch, UniProt) and **individual patient case reports/series** in the primary literature — not from a large EHR cohort. The total reported patient count worldwide is small (roughly a dozen across the defining series and subsequent case reports).

Section 2 — Etiology

Disease causal factors. The primary cause is **genetic**: bi-allelic (homozygous or compound-heterozygous) loss-of-function variants in OBSCN. The defining study identified 10 bi-allelic LOF OBSCN variants across six unrelated patients (PMID: 34957489). Disease expression, however, is **gene–environment dependent**: the genetic lesion establishes susceptibility, while an environmental/metabolic **trigger** (exertion, fasting, fever/infection) precipitates each acute episode.

Genetic risk factors. The causal variants are LOF alleles in OBSCN (nonsense, frameshift, canonical splice-site). Because OBSCN tolerates heterozygous LOF (gnomAD pLI ≈ 0), **two defective alleles are required** for disease. No established modifier genes are proven for RHABDO1 specifically, though the paralogue OBSL1 (obscurin-like 1) provides functional redundancy in muscle (relevant to mechanism; see Section 6).

Environmental risk factors / triggers. Based on the clinical descriptions: **strenuous or unaccustomed exercise**, **fasting/caloric deprivation**, **febrile illness/infection**, and likely **dehydration and heat stress** (the classic precipitants of exertional rhabdomyolysis generally). Patient myoblasts were shown to be more susceptible to **starvation** specifically (PMID: 34957489), providing a direct link between a metabolic trigger and cellular vulnerability.

Protective factors. No validated genetic protective variants or protective alleles are reported. By inference, **avoidance of triggers** (adequate hydration, avoiding prolonged fasting, graded rather than sudden intense exercise, prompt management of febrile illness) is protective against episodes. No nutritional or pharmacologic protective factor has been established.

Gene–environment interactions. RHABDO1 is a prototypical **gene × environment** disorder: the OBSCN LOF genotype lowers the threshold at which metabolic/mechanical stress triggers Ca^{2+} dysregulation and myofiber breakdown. The starvation-sensitivity of patient myoblasts is the best-characterized GxE link (PMID: 34957489).

Section 3 — Phenotypes

The official Monarch/HPO disease–phenotype annotation set for MONDO:0859371 comprises **10 terms**, spanning episodic clinical features, laboratory abnormalities, and muscle-biopsy histopathology.

Phenotype	HPO term	Type	Notes
Elevated circulating creatine kinase	HP:0003236	Laboratory abnormality	Markedly elevated during episodes (CK can reach hundreds of thousands U/L in rhabdomyolysis)
Rhabdomyolysis	HP:0003201	Clinical sign	Core defining feature; recurrent/ episodic
Myalgia	HP:0003326	Symptom	Muscle pain, often with cramps
Exercise intolerance	HP:0003546	Symptom	Common trigger-associated complaint
Renal insufficiency	HP:0000083	Laboratory/ clinical	Secondary to myoglobinuria (AKI risk)
Increased variability in muscle fiber diameter	HP:0003557	Histopathology	Muscle-biopsy finding
Centrally nucleated skeletal muscle fibers	HP:0003687	Histopathology	Muscle-biopsy finding
Type 2 muscle fiber predominance	HP:0010602	Histopathology	Muscle-biopsy finding
Distal muscle weakness	HP:0002460	Clinical sign	Variable; not universal
Abnormal circulating fatty acylcarnitine concentration	HP:0012071	Laboratory abnormality	Metabolic workup finding

Phenotype characteristics. - **Age of onset:** typically **teenage years** (adolescence), as described in the defining series — "usually with onset in the teenage years" (PMID: 34957489). Subsequent reports describe young adults/young patients. - **Severity: severe and recurrent** episodes of rhabdomyolysis; variable between episodes and between individuals (variable expressivity). - **Progression: episodic/relapsing**, trigger-dependent; not a steadily progressive degenerative myopathy. Patients are often well between episodes. - **Frequency among affected individuals:** myalgia, muscle cramps, exercise intolerance and elevated CK are consistent features; cardiomyopathy is **characteristically absent**.

Cardiac sparing. Multiple reports emphasize **no cardiomyopathy**: the defining series found no cardiomyopathy despite prior OBSCN–cardiomyopathy associations and normal cardiac exams (PMID: 34957489); Zemorshidi et al. described two young patients "without any evidence of concomitant cardiomyopathy" (PMID: 38159459); Sun et al. reported edema on MRI "without significant muscle weakness or cardiac abnormalities" (PMID: 40186404).

Quality-of-life impact. No disease-specific EQ-5D/SF-36/PROMIS data exist for RHABDO1. By inference, QoL impact derives from recurrent painful episodes, hospitalizations for crises, exercise limitation, and anxiety about triggers; between episodes, function is often preserved.

Section 4 — Genetic / Molecular Information

Causal gene. OBSCN (obscurin), HGNC:16542, chromosome **1q42**; Ensembl ENSG00000154358. OBSCN has **121 non-overlapping exons** and encodes **some of the largest known mRNAs in the human genome**, undergoing extensive developmentally- and tissue-regulated alternative splicing (PMID: 40025502). The same gene underlies both a cardiomyopathy disease axis and the rhabdomyolysis axis, with isoform- and domain-specific effects.

Pathogenic variants (RHABDO1-associated). Pathogenic/likely-pathogenic variants are **loss-of-function** (nonsense, frameshift, canonical splice). Representative ClinVar entries (transcript NM_001386125.1), classified Pathogenic (P) or Likely-pathogenic (LP):

cDNA	Protein	Type	ClinVar class
c.20788C>T	p.Gln6930Ter	Nonsense	Pathogenic
c.7485_7486insCCCGCCC	p.Thr2496fs	Frameshift	Pathogenic
c.5943C>A	p.Cys1981Ter	Nonsense	Likely pathogenic
c.25879_25880del	p.Lys8627fs	Frameshift	Likely pathogenic
c.20292C>G	p.Tyr6764Ter	Nonsense	Likely pathogenic
c.23841dup	p.Gly7948fs	Frameshift	Likely pathogenic
c.19607C>A	p.Ser6536Ter	Nonsense	Likely pathogenic
c.15307C>T	p.Gln5103Ter	Nonsense	Likely pathogenic
c.12859C>T	p.Gln4287Ter	Nonsense	Likely pathogenic

Additional genotypes from case reports: compound heterozygous **c.21184C>T (nonsense)** + **c.15610+12C>T (intronic splicing; absent from gnomAD_EAS)** (PMID: 40186404); novel variants **c.24822C>A** and **c.2653+1G>C** (PMID: 38159459); and **c.20292C>A** + **c.708del** (PMID: 40813169).

Variant classification caveat. Missense, synonymous, and splice-region changes in the same rhabdomyolysis-annotated ClinVar set are **largely VUS** (e.g., p.Arg7149Pro, p.Val6753Leu, p.Trp1659Cys). This is reinforced by functional work showing that two cardiomyopathy-associated obscurin missense variants (R4344Q, R4444W) did **not** alter titin binding or domain thermostability and that R4344Q is present in **15% of African Americans**, arguing against pathogenicity — a cautionary tale for over-calling OBSCN missense variants (PMID: 33438037). OBSCN has ~150 total P/LP ClinVar entries across all phenotypes.

Allele frequency / population constraint. gnomAD v2.1.1 constraint for OBSCN: **pLI = 7.4×10^{-226} (≈ 0)**, observed/expected LOF (oe_lof) = 0.88 (90% CI 0.83–0.94; **LOEUF 0.94**), with 768 observed vs 870.9 expected LOF alleles; missense constraint low (mis_z = 0.53, oe_mis = 0.99). **Interpretation:** OBSCN is not depleted of heterozygous LOF variants, consistent with recessive inheritance where carriers are unaffected.

Somatic vs germline. All reported variants are **germline**. No somatic involvement is relevant to this disorder.

Functional consequences. Loss of function — reduced OBSCN expression and loss of obscurin protein in patient muscle (PMID: 34957489). This contrasts with proposed gain-of-function/dominant-negative mechanisms sometimes invoked for OBSCN cardiomyopathy variants.

Modifier genes / epigenetics / chromosomal abnormalities. No established modifier genes, epigenetic marks, or large-scale chromosomal abnormalities are described specifically for RHABDO1. OBSL1 redundancy is mechanistically relevant (Section 6). Alternative splicing of OBSCN may be regulated in part by **BUB3** (PMID: 40025502).

Section 5 — Environmental Information

Environmental / triggering factors. The disease requires an environmental trigger to produce episodes. Established/implicated precipitants: **strenuous or unaccustomed physical exertion**, **fasting/starvation**, **febrile illness**, and plausibly **dehydration and heat**. Patient myoblasts are specifically more susceptible to **starvation** (PMID: 34957489).

Lifestyle factors. Exercise intensity and pattern, hydration status, and fasting behavior modulate risk. There is no reported association with smoking, alcohol, or diet beyond the fasting trigger.

Infectious agents. No pathogen causes RHABDO1. However, **febrile infections act as triggers** of acute episodes — a general feature of metabolic/genetic rhabdomyolysis susceptibilities. (For context, infections such as SARS-CoV-2 can independently cause rhabdomyolysis, PMID: 34871534, but this is etiologically distinct from the OBSCN genetic susceptibility.)

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **Bi-allelic LOF variant in OBSCN** (nonsense/frameshift/splice) → **loss of obscurin protein** in skeletal myofibers (*demonstrated*: reduced OBSCN expression and absent obscurin in patient muscle, PMID: 34957489).
2. Loss of obscurin **removes the structural/signaling link between the sarcomere (M-band/Z-disk) and the SR → disorganization of the SR** and loss of normal SR architecture

(*demonstrated in mouse models; inferred in human*: combined loss of Obscn/Obsl1 disrupts SR organization, PMID: 31098411).

3. SR disorganization + reduced SERCA/phospholamban expression → **impaired Ca^{2+} re-uptake and reduced SR Ca^{2+} storage → perturbed Ca^{2+} cycling** (*demonstrated in mouse*: reduced SR volume, lower SERCA/PLB, altered Ca^{2+} cycling, PMID: 40366302, PMID: 40066567).
4. Under a **metabolic/mechanical trigger** (exercise, fasting, fever) → myofibers with compromised Ca^{2+} handling **cannot buffer the additional stress**; patient myoblasts show a greater drop in SR Ca^{2+} content upon starvation than controls (*demonstrated*, PMID: 34957489).
5. **Dysregulated cytosolic Ca^{2+} and sarcolemmal instability** → activation of Ca^{2+}-dependent proteases/phospholipases and loss of membrane integrity → **myofiber necrosis / rhabdomyolysis** (*inferred mechanism; sarcolemmal instability demonstrated in Obscn/Obsl1 double-KO mouse*, PMID: 31098411).
6. Myofiber breakdown → **release of CK and myoglobin** → markedly elevated serum CK, **myoglobinuria → acute kidney injury** when severe (*clinical observation*, PMID: 34957489, PMID: 40186404).

Branch (cardiac, largely spared in RHABDO1): In the heart, obscurin loss produces a **separate disease axis** — reduced SR volume with preserved T-tubules, lower SERCA/PLB, dilated cardiomyopathy and arrhythmia susceptibility in mice (PMID: 40366302); domain-specific Ig58/59 deletion causes atrial remodeling and Ca^{2+}-based arrhythmogenesis (PMID: 39804820). In human RHABDO1, however, the cardiac axis is **not manifest** (cardiac sparing), likely reflecting isoform/redundancy differences between skeletal and cardiac muscle.

Supporting molecular detail

Protein architecture (UniProt Q5VST9, canonical 7,968 aa). Obscurin contains **~55 Ig-like domains**, **4 fibronectin type-III (Fn3) domains**, a **calmodulin-binding IQ motif (aa 4872–4901)**, a tandem **SH3 (5600–5667)–DH (5693–5877)–PH (5895–6004) RhoGEF signaling module**, and **two C-terminal Ser/Thr protein kinase domains** (PK1 6468–6721; PK2 7672–7924). The **N-terminal Ig1–3 domains target obscurin to the M-band/Z-disk** via interactions with titin and myomesin.

Sarcomere–SR linkage. Obscurin's N-terminus binds **M-band titin and myomesin**; downregulation of myomesin disrupts obscurin M-band integration (PMID: 18477606). Crystallographic work defines the titin M10–obsl1/obscurin Ig–Ig interface and shows that

disease-linked titin M10 mutations disrupt this complex (PMID: 20133654). Obscurin's C-terminus binds the N-terminal Z-disk region of titin and coassembles during myofibrillogenesis; the protein carries IQ (Ca^{2+}/calmodulin) and RhoGEF (G-protein) signaling modules (PMID: 11448995). The RhoGEF domain selectively activates **RhoA** at the M-band in skeletal muscle and responds to lengthening-contraction injury (PMID: 19605563).

Functional redundancy with OBSL1. Single deletion of obscurin or Obsl1 is tolerated in mouse muscle; **only combined deletion** reveals roles in **sarcolemmal stability and SR organization** (PMID: 31098411). This redundancy may explain variable expressivity and the relatively mild baseline state between episodes.

Metabolic / mitochondrial dimension. Combined Obsc/Obsl1 loss in heart altered metabolism, reduced Chchd3 (a MICOS complex protein), produced abnormal mitophagy and increased unfolded protein response (PMID: 40066567). The abnormal acylcarnitine finding (HP:0012071) and starvation-sensitivity in human myoblasts point to an **energy-metabolism vulnerability** that intersects with Ca^{2+} handling.

Ontology suggestions. - **GO biological process:** regulation of release of sequestered calcium ion into cytosol (GO:0051279); sarcomere organization (GO:0045214); muscle contraction (GO:0006936); Rho protein signal transduction (GO:0007266); striated muscle cell development (GO:0055002). - **GO cellular component:** sarcoplasmic reticulum (GO:0016529); M band (GO:0031430); Z disc (GO:0030018); sarcomere (GO:0030017); sarcolemma (GO:0042383). - **Cell types (CL):** skeletal muscle fiber / myofiber (CL:0000188); fast muscle cell / type II fiber (CL:0000190). - **CHEBI:** calcium(2+) (CHEBI:29108); creatine (CHEBI:16919); creatinine (CHEBI:16737).

Section 7 — Anatomical Structures Affected

Organ level. Primary: **skeletal muscle** (striated muscle; UBERON:0001134). Secondary: **kidney** (UBERON:0002113) via myoglobinuric acute kidney injury. Body system: **musculoskeletal/ muscular system** primarily; **renal/urinary system** secondarily. The **heart (myocardium, UBERON:0002349)** is characteristically **spared** in RHABDO1.

Tissue and cell level. Affected tissue: **skeletal muscle tissue** (UBERON:0002036); affected cells: **skeletal muscle fibers/myofibers** (CL:0000188), with **type 2 fiber predominance** (HP:0010602) on biopsy. Histopathology shows increased fiber-size variability (HP:0003557) and centrally nucleated fibers (HP:0003687).

Subcellular level. Sarcoplasmic reticulum (GO:0016529) — the key disorganized compartment; **M-band** (GO:0031430) and **Z-disk** (GO:0030018) where obscurin localizes; **sarcolemma** (GO:0042383) instability; **mitochondria** (GO:0005739) secondarily implicated via metabolic/mitophagy changes in models.

Localization / lateralization. Skeletal muscle involvement is **generalized/bilateral**; imaging in one case showed **bilateral lower-limb muscle edema** on MRI (PMID: 40186404).

Section 8 — Temporal Development

Onset. Typically **adolescence (teenage years)** per the defining series (PMID: 34957489); additional cases are young adults. Onset of individual episodes is **acute**, tied to a trigger.

Progression. The disease course is **episodic/relapsing** rather than steadily progressive. Between episodes, patients are frequently well, though some show **distal muscle weakness** (HP:0002460) and biopsy changes. Individual rhabdomyolysis episodes evolve acutely (hours), with CK rising rapidly and resolving over days with supportive care.

Patterns. Episodes **remit** with trigger removal and supportive treatment. The **critical window** for intervention is during an acute crisis (early aggressive hydration to prevent AKI). Lifelong susceptibility persists; management is about preventing recurrence.

Expressivity. Variable: Sun et al. noted the proband's **mother, carrying a homozygous OBSCN variant, had only exercise-induced myalgia**, far milder than the proband's rhabdomyolysis — illustrating variable expressivity (PMID: 40186404).

Section 9 — Inheritance and Population

Inheritance pattern. Autosomal recessive — bi-allelic (homozygous or compound-heterozygous) LOF variants required (PMID: 34957489). Supported by gnomAD constraint showing OBSCN tolerates heterozygous LOF (pLI ≈ 0, LOEUF 0.94), so carriers are generally unaffected.

Penetrance / expressivity. Appears **trigger-dependent** with **variable expressivity** (e.g., homozygous carrier mother with only myalgia, PMID: 40186404). Penetrance is incompletely defined due to the small number of reported cases.

Epidemiology. Prevalence and incidence are not established — RHABDO1 is a recently defined (2022), rare Mendelian condition with only ~12 reported patients across the literature. No registry-level prevalence/incidence figures exist.

Founder effects / consanguinity / carrier frequency. No founder mutation is established. Consanguinity may facilitate homozygous cases but is not systematically reported. Carrier frequency cannot be reliably estimated but LOF alleles are observed in gnomAD.

Population demographics. No ethnic predilection is established. Cases are reported from multiple populations (including East Asian cases, PMID: 40186404). **Sex ratio** is not established; reported cases include males and females. **Age distribution** skews to adolescents/young adults at first presentation.

Section 10 — Diagnostics

Laboratory tests. During episodes: **markedly elevated serum CK** (HP:0003236), **myoglobinuria**, and renal function monitoring for AKI (HP:0000083). Metabolic workup may show **abnormal fatty acylcarnitine profile** (HP:0012071) — important because acylcarnitine abnormalities also characterize the key differential (fatty-acid oxidation disorders).

Biomarkers. CK and myoglobin are the principal circulating biomarkers of myofiber breakdown; absent/reduced obscurin on muscle immunostaining/Western blot is a disease-specific tissue marker (PMID: 34957489).

Imaging. Muscle **MRI** can show muscle edema (bilateral lower-limb edema reported, PMID: 40186404).

Biopsy / histopathology. Muscle biopsy may show increased fiber-size variability (HP:0003557), centrally nucleated fibers (HP:0003687), type 2 fiber predominance (HP:0010602), and reduced/absent obscurin by immunostaining.

Genetic testing (diagnostic cornerstone). Because OBSCN is enormous (121 exons, among the largest human transcripts, PMID: 40025502), **next-generation sequencing (WES or WGS) is the practical approach**; large multigene **rhabdomyolysis/metabolic-myopathy panels** that include OBSCN are appropriate. Confirm **bi-allelic** status and **phase** (compound-het vs in-cis) with parental testing. Interpret **truncating variants as likely causal; treat missense as VUS** pending functional/segregation data (PMID: 33438037).

Clinical criteria. No formal consensus diagnostic criteria exist. Working diagnosis = **recurrent exertional/metabolic rhabdomyolysis** + **bi-allelic LOF OBSCN variants** + **supportive muscle findings (reduced obscurin)**, after exclusion of commoner causes.

Differential diagnosis. Other genetic rhabdomyolysis susceptibilities and metabolic myopathies must be excluded:

Differential	Gene / defect	Distinguishing feature
RYR1-related / malignant hyperthermia susceptibility	RYR1	Anesthetic-triggered MH; RYR1 variants (PMID: 35285867)
VLCAD deficiency (FAO disorder)	ACADVL	Abnormal acylcarnitines; fasting/exercise triggers (PMID: 35405752, PMID: 29153022)
McArdle disease (GSD V)	PYGM	Second-wind phenomenon; fixed exercise intolerance (PMID: 41229646)
Drug-induced rhabdomyolysis	statins, TKIs	Temporal drug association (PMID: 42473504, PMID: 41585502)
Infection-triggered	e.g., SARS-CoV-2	Acute infection context (PMID: 34871534)
Exertional / MH-spectrum	multifactorial	Round-table consensus on ER/EHS/MH overlap (PMID: 28430550)

Screening. No newborn or population screening exists. **Cascade genetic testing** of relatives of probands is reasonable for recurrence risk and trigger-avoidance counseling.

Section 11 — Outcome / Prognosis

Survival / mortality. No disease-specific mortality data. Prognosis is generally **good with prompt supportive management**; the principal acute risk is **myoglobinuric AKI** (HP:0000083), which can require dialysis in severe rhabdomyolysis generally (PMID: 33645199). Rhabdomyolysis can occasionally be severe even without electrolyte abnormalities or renal failure (PMID: 42491205).

Morbidity / function. Between episodes, function is often preserved; recurrent crises, hospitalizations, and exercise restriction are the main morbidity. Some patients show distal weakness.

Complications. AKI (sometimes requiring dialysis), electrolyte derangements (hyperkalemia, hyperphosphatemia, hypocalcemia) during severe episodes, and rarely compartment syndrome (general rhabdomyolysis complications).

Recovery potential. Individual episodes typically **recover fully** with hydration and supportive care; CK normalizes over days.

Prognostic factors. Severity/number of triggers, rapidity of fluid resuscitation, baseline renal function, and degree of CK elevation influence AKI risk. No molecular prognostic biomarker specific to RHABDO1 is established.

Section 12 — Treatment

No gene-specific therapy exists. Management is **supportive** and **preventive**.

Acute episode management. Aggressive intravenous fluid resuscitation to maintain renal perfusion and clear myoglobin; **electrolyte correction**; **renal function monitoring**; dialysis if AKI is severe. This mirrors standard rhabdomyolysis care (PMID: 33645199). (NCIT intervention terms: **Intravenous Fluid Therapy**; **Hemodialysis**; **Supportive Care**.)

Preventive / supportive. Trigger avoidance — adequate hydration, avoiding prolonged fasting, graded conditioning rather than sudden intense/unaccustomed exertion, prompt management of febrile illness, and caution with heat. Individualized exercise-tolerance assessment (as applied in metabolic myopathies) may define safe activity limits.

Pharmacotherapy / advanced therapeutics. No approved pharmacologic, gene, cell, or RNA-based therapy is specific to RHABDO1. No pharmacogenomic guidance is established.

Treatment strategy. The practical algorithm: (1) recognize recurrent rhabdomyolysis; (2) rule out common causes; (3) genetic confirmation of bi-allelic OBSCN LOF; (4) acute supportive care during episodes; (5) long-term trigger-avoidance counseling and genetic counseling for the family.

Section 13 — Prevention

- **Primary prevention:** Not applicable at population level (rare Mendelian disorder). For at-risk/affected individuals, **trigger avoidance** is the key primary preventive measure against episodes.
- **Secondary prevention:** Early recognition of prodromal myalgia/dark urine and prompt hydration to abort/limit episodes and prevent AKI.
- **Tertiary prevention:** Aggressive management during crises to prevent renal failure and complications.
- **Genetic counseling:** Autosomal-recessive recurrence risk (25% for future sibs of a proband when both parents are carriers); cascade testing of relatives; reproductive counseling.
- **No immunization, public-health, or environmental program** applies specifically.

Section 14 — Other Species / Natural Disease

- **Taxonomy / orthologues:** Obscurin is conserved in mammals; mouse **Obscn** (NCBI Gene) and the paralogue **Obsl1** are the principal experimental orthologues. The invertebrate analogue is **UNC-89** (*C. elegans*), which, like obscurin, localizes to the M-band (PMID: 18477606).
- **Natural disease in animals:** No naturally occurring OBSCN-rhabdomyolysis disease is documented in companion animals or wildlife. **Exertional rhabdomyolysis is, however, a major condition in horses** (sporadic and recurrent/chronic forms), with intrinsic genetic contributors in some equine syndromes — a comparative-biology parallel, though not OBSCN-specific (PMID: 39880734).
- **Evolutionary conservation:** The sarcomere–SR linkage role of obscurin and its M-band targeting are conserved from invertebrates (UNC-89) to mammals, supporting cross-species mechanistic relevance.

Section 15 — Model Organisms

Model	Type	Key findings	Relevance to RHABDO1	PMID
Obscn / *Obsl1* double-KO mouse (skeletal)	Mammalian KO	Only combined deletion reveals roles in **sarcolemmal stability and SR organization** and muscle metabolism	Strong mechanistic support for SR/sarcolemma defect; highlights OBSL1 redundancy	31098411
Obscn KO mouse (heart)	Mammalian KO	Reduced SR volume, lower SERCA/PLB, altered Ca^{2+} cycling, compensated dilated cardiomyopathy, arrhythmia	Models the **cardiac branch**; informs Ca^{2+}-handling mechanism	40366302
Obsc/Obsl1 double-KO (heart)	Mammalian KO	Diastolic dysfunction, perturbed Ca^{2+} cycling, altered metabolism, deregulated mitophagy, ↑UPR	Links obscurin loss to SR + mitochondrial/metabolic dysfunction	40066567
Obscn-ΔIg58/59 mouse	Knock-in/deletion	Atrial remodeling, Ca^{2+}-based arrhythmogenesis, TAT depletion	Domain-specific cardiac model (distinct from skeletal rhabdo)	39804820
Patient-derived cultured myoblasts	In vitro (human)	Greater decrease in **SR Ca^{2+} content upon starvation** vs controls	Direct human functional evidence of impaired SR Ca^{2+} handling	34957489

Phenotype recapitulation / limitations. Mouse models robustly recapitulate the **SR disorganization and Ca^{2+}-handling defect** central to RHABDO1, but the **cardiac phenotype dominates mouse models whereas human RHABDO1 spares the heart** — a key species/isoform discrepancy. No mouse model has been reported that reproduces the human **trigger-**

dependent recurrent skeletal rhabdomyolysis phenotype in isolation, partly because of OBSL1 redundancy. Human patient myoblasts provide the most disease-faithful functional readout to date. Model databases: MGI, IMPC, IMSR for murine resources.

Mechanistic Model / Interpretation

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Bi-allelic OBSCN LOF variant (nonsense / frameshift / splice)
           |  (demonstrated: reduced OBSCN, absent obscurin in patient muscle)
           ▼
Loss of obscurin at M-band / Z-disk  --X--  (loses titin & myomesin linkage)
           |
           ▼
Disrupted sarcomere->SR coupling -> SR disorganization
  + reduced SERCA / phospholamban (model evidence)
           |
           ▼
Impaired Ca2+ re-uptake & reduced SR Ca2+ storage -> perturbed Ca2+ cycling
           |
           |<---- TRIGGER (exercise / fasting / fever)
           |       (patient myoblasts: lower SR Ca2+ on starvation)
           ▼
Cytosolic Ca2+ dysregulation + sarcolemmal instability
           |
           ▼
Myofiber necrosis (RHABDOMYOLYSIS)
           |
           ├─> ↑↑ serum CK, myalgia, cramps, exercise intolerance
           └─> Myoglobinuria -> Acute kidney injury (risk)

BRANCH (heart): same SR/Ca2+ lesion -> dilated CM / arrhythmia in MICE
                but CARDIAC SPARING in human RHABDO1 (isoform/redundancy)
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The unifying interpretation: **RHABDO1 is a sarcoplasmic-reticulum Ca^{2+}-handling disorder of skeletal muscle caused by obscurin loss of function.** The upstream lesion is structural (loss of the sarcomere–SR tether); the downstream consequence is a Ca^{2+}-buffering deficit that stays clinically silent until a metabolic or mechanical trigger overwhelms the compromised myofiber, producing episodic breakdown. Cardiac sparing in humans — despite a clear cardiac disease axis in mice and in OBSCN-cardiomyopathy literature — is the most striking unexplained feature and points to tissue-specific isoform usage and OBSL1 redundancy.

Evidence Base

PMID	Study	Role in this report
34957489	Cabrera-Serrano et al., *Brain* 2022 — defining case series	**Primary source**: 10 bi-allelic LOF OBSCN variants in 6 patients; reduced OBSCN/absent obscurin; starvation-sensitive SR Ca^{2+} in myoblasts; cardiac sparing; teenage onset
38159459	Zemorshidi 2024 — case report	Two young patients, novel variants, exercise intolerance/rhabdomyolysis **without cardiomyopathy**
40186404	Sun 2025 — case report	Compound-het nonsense+splice; **homozygous mother with milder phenotype** (variable expressivity); MRI muscle edema, no cardiac abnormality
40813169	Liu 2025 — case report + review	Young adult, two OBSCN variants; reinforces pathogenic role; notes mechanism unclear
31098411	Murine Obscn/Obsl1 — *skeletal*	Only combined deletion reveals SR organization + sarcolemmal stability roles (**mechanism**)
40366302	Obscn KO heart	Reduced SR volume, ↓SERCA/PLB, altered Ca^{2+} cycling (**mechanism**; cardiac branch)
40066567	Obsc/Obsl1 KO heart	SR + mitochondrial/metabolic dysfunction, mitophagy (**mechanism**)
39804820	Obscn-ΔIg58/59	Atrial Ca^{2+} arrhythmogenesis (distinct cardiac axis)
18477606	Titin/myomesin–obscurin M-band	Molecular basis of obscurin M-band targeting
20133654	Titin M10–obsl1 structure	M-band complex structure; disease mutations disrupt it
11448995	Obscurin discovery	~800 kDa, 1q42, IQ + RhoGEF signaling, titin binding
19605563	Obscurin RhoGEF	Activates RhoA at M-band; injury response
33438037	Obscurin missense variants	**Cautionary**: R4344Q/R4444W not clearly pathogenic; supports VUS treatment of missense
40025502	OBSCN splicing	121 exons; extensive alternative splicing; cardiac vs skeletal isoforms

PMID	Study	Role in this report
39880734	Equine exertional rhabdomyolysis	Comparative biology context
33645199	Rhabdomyolysis→AKI	Supportive-care/complication context

Limitations and Knowledge Gaps

1. **Very small patient numbers.** RHABDO1 was defined in 2022; only ~12 patients are reported. Prevalence, incidence, penetrance, sex ratio, and natural history are therefore poorly quantified.
2. **Mechanism partly inferred from models.** The SR-disorganization/Ca^{2+} steps rest heavily on mouse *Obscn/Obsl1* data; the only direct human functional readout is the starvation-induced SR Ca^{2+} decrease in patient myoblasts. The precise step from Ca^{2+} dysregulation to myofiber necrosis in human RHABDO1 is inferred, not demonstrated.
3. **Unexplained cardiac sparing.** Why humans spare the heart while mice develop cardiomyopathy/arrhythmia is unresolved — likely isoform/redundancy differences, but unproven.
4. **Missense variant interpretation.** Most OBSCN missense variants remain VUS; functional assays and segregation data are lacking, and a known cardiomyopathy-"associated" variant (R4344Q) is common in African Americans, cautioning against over-calling pathogenicity.
5. **No disease-specific QoL, prognosis, or therapy data.** Management is extrapolated from general rhabdomyolysis care; no clinical trials exist.
6. **No faithful animal model of the human skeletal rhabdomyolysis phenotype** exists, hampering therapeutic development.

Proposed Follow-up Experiments / Actions

1. **Establish an international RHABDO1 registry** to capture natural history, penetrance, trigger profiles, sex ratio, and outcomes.

2. **Generate a skeletal-muscle-specific, trigger-inducible OBSCN-LOF mouse** (or Obscn/Obsl1 conditional) and challenge with exercise/fasting to recapitulate episodic rhabdomyolysis and test why cardiac tissue is spared.
3. **Quantitative SR Ca^{2+} handling assays** in patient iPSC-derived myotubes under exercise-/fasting-mimetic stress, measuring SERCA/phospholamban levels and Ca^{2+} transients, to confirm and quantify the human mechanism.
4. **Functional reclassification of OBSCN missense VUS** using M-band targeting, titin/myomesin binding, domain stability, and SR Ca^{2+} assays to resolve ACMG classification.
5. **Acylcarnitine/metabolomic profiling** of patients to define the metabolic vulnerability (HP:0012071) and its overlap with fatty-acid-oxidation disorders.
6. **Evaluate preventive interventions** (structured hydration, graded exercise, nutritional/anti-fasting strategies) in a prospective observational cohort, with CK and episode frequency as endpoints.
7. **Deep phenotyping of heterozygous and homozygous carriers** (e.g., the homozygous-carrier mother phenotype) to delineate the expressivity spectrum and dosage sensitivity.

Report compiled from the OBSCN/RHABDO1 primary literature, gnomAD v2.1.1 constraint data, ClinVar (NM_001386125.1), UniProt Q5VST9, and Monarch/HPO disease–phenotype annotations for MONDO:0859371. Evidence types are indicated throughout as human clinical, model organism, in vitro, or computational.
