

# Myopathy Due To Calsequestrin And SERCA1 Protein Overload — Comprehensive Disease Report

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**Disease:** Myopathy due to calsequestrin and SERCA1 protein overload **MONDO ID:** MONDO:0014546 | **OMIM:** 616231 ("Myopathy, vacuolar, with CASQ1 aggregates; VMCQA")  
**Causal gene:** *CASQ1* (calsequestrin-1), chromosome 1q21 **Category:** Mendelian (autosomal dominant) **Date:** 2026-10-15

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## Summary

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Myopathy due to calsequestrin and SERCA1 protein overload is an **ultra-rare, autosomal dominant, adult-onset, benign and slowly progressive skeletal-muscle disease** caused by heterozygous missense mutations in *CASQ1*, the gene encoding the fast-twitch skeletal-muscle isoform of calsequestrin. The disorder was first defined morphologically in 2006 as a "surplus protein myopathy" in which muscle fibers contained non-staining vacuolar inclusions immunoreactive for the sarco/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase SERCA1 (ATP2A1) and/or calsequestrin ([PMID: 16714317](#)). Eight years later the causal lesion was identified as the heterozygous missense mutation *CASQ1* **c.731A>G, p.Asp244Gly (D244G)**, segregating as a founder mutation in Italian families ([PMID: 25116801](#), [PMID: 26136523](#)).

Mechanistically, the Asp244 residue sits within a high-affinity  $\text{Ca}^{2+}$ -binding site in Domain II of calsequestrin. The mutation causes the protein to **lose  $\text{Ca}^{2+}$  binding and aggregate abnormally** into electron-dense sarcoplasmic reticulum (SR) vacuoles that co-sequester SERCA1 and the ryanodine receptor RyR1, predominantly within type II (fast) fibers. Aggregated calsequestrin **dissociates from the junctional SR**, reducing SR  $\text{Ca}^{2+}$  storage and impairing  $\text{Ca}^{2+}$  release — a defect that has been termed a "**CASQ1-couplonopathy**" ([PMID: 27196359](#)). The downstream clinical picture is exercise intolerance, myalgia, mild-to-moderate slowly progressive proximal weakness, and mild-to-moderate elevation of serum creatine kinase (hyperCKemia), often presenting in the sixth decade of life ([PMID: 30258016](#)).

The disease is benign in prognosis and does not shorten life expectancy. There is **no approved disease-specific therapy**; management is supportive and includes physiotherapy, cardiac surveillance (rare subclinical cardiac findings), and genetic counseling for the dominant trait. A theoretical malignant-hyperthermia/heat-sensitivity concern arises from the related *Casq1*-null mouse model, in which antioxidants and estrogens are protective; these pharmacologic strategies remain unproven in humans. The disease is modeled by D244G knock-in and *Casq1*-knockout mice.

## 1. Disease Information

**Overview.** This is a hereditary vacuolar myopathy of skeletal muscle characterized by intracellular accumulation ("overload") of two terminal-cisternae SR proteins — **calsequestrin-1 (CASQ1)** and **SERCA1 (ATP2A1)** — forming inclusions within muscle fibers. It was originally delineated purely by muscle biopsy morphology and immunohistochemistry as a "SERCA1 and calsequestrin storage myopathy" / "surplus protein myopathy" ([PMID: 16714317](#)), and later unified genetically under mutations in *CASQ1*.

### Key identifiers.

| Resource         | Identifier                                                  |
|------------------|-------------------------------------------------------------|
| MONDO            | MONDO:0014546                                               |
| OMIM (phenotype) | 616231 — "MYOPATHY, VACUOLAR, WITH CASQ1 AGGREGATES; VMCQA" |
| Orphanet         | ORPHA:88635                                                 |
| GARD             | 0016770                                                     |
| MedGen / UMLS    | 864061 / C4015624                                           |
| SNOMED CT        | 724095006                                                   |

**Synonyms / alternative names:** - Myopathy due to calsequestrin and SERCA1 protein overload - Vacuolar myopathy with CASQ1 aggregates (VMCQA) - CASQ1-related myopathy - SERCA1 and calsequestrin storage myopathy - Protein aggregate myopathy with CASQ1 aggregates - CASQ1-couplonopathy (mechanistic designation)

**Information source.** Knowledge is derived from **aggregated disease-level resources** (OMIM, Orphanet, MONDO) and from **individual patient reports/case series** in the primary literature (Italian and Chinese families), not from large EHR datasets. The total reported experience worldwide is on the order of 30–40 patients.

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## 2. Etiology

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**Disease causal factors.** The disease is **purely genetic (Mendelian, monogenic)**. It is caused by heterozygous gain-of-function/dominant missense mutations in *CASQ1*. There is no infectious or primary environmental cause.

**Genetic risk factors.** The principal causal variant is **CASQ1 p.Asp244Gly (c.731A>G)**, a founder mutation in Italian families sharing a common haplotype ([PMID: 26136523](#)). Additional pathogenic alleles at the same or nearby residues broaden the allelic spectrum: - **p.Asp244His (c.730G>C)** — reported in two unrelated Chinese families ([PMID: 41699400](#)), establishing residue 244 as a **mutational hotspot**. - **p.Gly103Asp** — reported in one Italian family, with a distinctive tubular-aggregate histology ([PMID: 30258016](#)). - **p.Met87Thr** — a separate variant *weakly* associated with malignant hyperthermia susceptibility rather than the overload myopathy ([PMID: 26416891](#)).

**Environmental risk factors.** None established as causal. Theoretical triggers relevant to muscle Ca<sup>2+</sup> handling — strenuous exercise, heat exposure, and volatile anesthetics — are implicated only from the *Casq1*-null mouse (see Section 15), not confirmed in the human overload myopathy.

**Protective factors.** No human genetic or environmental protective factors are established. In the *Casq1*-null mouse model, **estrogens** reduce oxidative stress and protect against lethal hyperthermic episodes ([PMID: 29062464](#)), and **antioxidants** (N-acetylcysteine, Trolox) are protective ([PMID: 26132720](#)) — but these pertain to the knockout MH phenotype, not the overload myopathy in humans.

**Gene–environment interactions.** Not formally characterized for the human disease. The mechanistic hypothesis — that a Ca<sup>2+</sup>-handling defect might be unmasked by heat/anesthetic/exercise stress — derives from the knockout model and remains inferred, not demonstrated, for patients.

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### 3. Phenotypes

The clinical spectrum is best defined by the largest cohort to date: 22 CASQ1-mutated patients from 12 families (21 with p.Asp244Gly, 1 with p.Gly103Asp) ([PMID: 30258016](#)).

| Phenotype                       | Type            | Onset      | Severity      | Progression        | Frequency                           | HPO suggestion                                           |
|---------------------------------|-----------------|------------|---------------|--------------------|-------------------------------------|----------------------------------------------------------|
| Exercise intolerance            | Symptom         | 6th decade | Mild–moderate | Slowly progressive | Common presenting feature           | HP:0003546 (Exercise intolerance)                        |
| Myalgia                         | Symptom         | 6th decade | Mild          | Fluctuating        | Common presenting feature           | HP:0003326 (Myalgia)                                     |
| Proximal muscle weakness        | Clinical sign   | Adult/late | Mild–moderate | Slowly progressive | Develops later in most              | HP:0003701 (Proximal muscle weakness)                    |
| Quadriceps atrophy              | Physical        | Adult/late | Mild–moderate | Progressive        | Characteristic                      | HP:0003327 (Axial muscle weakness)/quadriceps wasting    |
| Scapular winging                | Clinical sign   | Adult/late | Mild          | Progressive        | Characteristic                      | HP:0003691 (Scapular winging)                            |
| HyperCKemia (elevated serum CK) | Lab abnormality | Adult      | Mild–moderate | Stable/fluctuating | Very common; sometimes sole feature | HP:0003236 (Elevated serum creatine kinase)              |
| Subclinical cardiac abnormality | Lab/clinical    | Adult      | Mild          | Stable             | 3/22 (~14%)                         | HP:0011675 (Arrhythmia)/HP:0001637 (Abnormal myocardium) |

**Key quotes.** "Patients usually presented in the sixth decade with exercise intolerance and myalgias and later developed mild to moderate, slowly progressive proximal weakness with quadriceps atrophy and scapular winging" (PMID: 30258016). "Three patients presented subclinical cardiac abnormalities" (ibid.).

**Quality-of-life impact.** Because the disease is mild and slowly progressive, functional impact is limited; most patients remain ambulant. HyperCKemia may be the *only* manifestation, and many carriers are likely under-ascertained ("it is likely that CASQ1 mutations may remain undiagnosed if a muscle biopsy is not performed" — PMID: 30258016). No disease-specific QoL instrument (EQ-5D/SF-36/PROMIS) data are available.

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## 4. Genetic/Molecular Information

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**Causal gene — CASQ1 (calsequestrin-1):**

| Annotation  | Value                                      |
|-------------|--------------------------------------------|
| HGNC        | HGNC:1512                                  |
| OMIM (gene) | 114250                                     |
| NCBI Gene   | 844                                        |
| Ensembl     | ENSG00000143318                            |
| UniProt     | P31415 (CASQ1_HUMAN)                       |
| Cytoband    | 1q21 (GRCh38 chr1:160,190,212–160,201,886) |

**Pathogenic variants.**

| Variant (protein) | cDNA     | Type     | Population           | Phenotype                                      | Classification                   |
|-------------------|----------|----------|----------------------|------------------------------------------------|----------------------------------|
| p.Asp244Gly       | c.731A>G | Missense | Italian founder      | Vacuolar aggregate myopathy                    | Pathogenic                       |
| p.Asp244His       | c.730G>C | Missense | Chinese (2 families) | Vacuolar myopathy                              | Pathogenic/<br>likely pathogenic |
| p.Gly103Asp       | —        | Missense | Italian (1 family)   | Myopathy w/<br>tubular aggregates              | Pathogenic                       |
| p.Met87Thr        | —        | Missense | —                    | Weak MH susceptibility (not overload myopathy) | Risk variant                     |

**Variant classification notes.** The Domain-II residue Asp244 is highly conserved ("a highly conserved residue" — [PMID: 41699400](#)); recurrence across independent populations (Italy, China) supports pathogenicity under ACMG criteria (PS1/PM1/PM5 — same residue, different substitutions).

**Allele frequency.** These are private/ultra-rare variants, essentially absent from population databases (gnomAD); the Italian cases share a single founder haplotype.

**Somatic vs germline.** All reported variants are **germline**, segregating in an autosomal dominant fashion.

**Functional consequences.** The mutation is best characterized as a **dominant, toxic gain-of-function / dominant-negative aggregation defect** combined with loss of normal  $\text{Ca}^{2+}$ -buffering at the junctional SR: mutant CASQ1 loses high-affinity  $\text{Ca}^{2+}$  binding and aggregates abnormally, sequestering wild-type CASQ1 and partner proteins (SERCA1, RyR1).

**Modifier genes.** None established.

**Epigenetic information / chromosomal abnormalities.** Not applicable/not reported; this is a point-mutation monogenic disorder with no described epigenetic or structural chromosomal component.

## 5. Environmental Information

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**Environmental factors.** None causally established. The disorder is monogenic. As a theoretical consideration (extrapolated from the knockout model, not the human overload myopathy), **heat stress and volatile halogenated anesthetics** could stress skeletal-muscle  $\text{Ca}^{2+}$  homeostasis.

**Lifestyle factors.** Strenuous exercise is a presenting trigger of symptoms (exercise intolerance, myalgia) but is not a disease cause.

**Infectious agents.** Not applicable — no infectious etiology.

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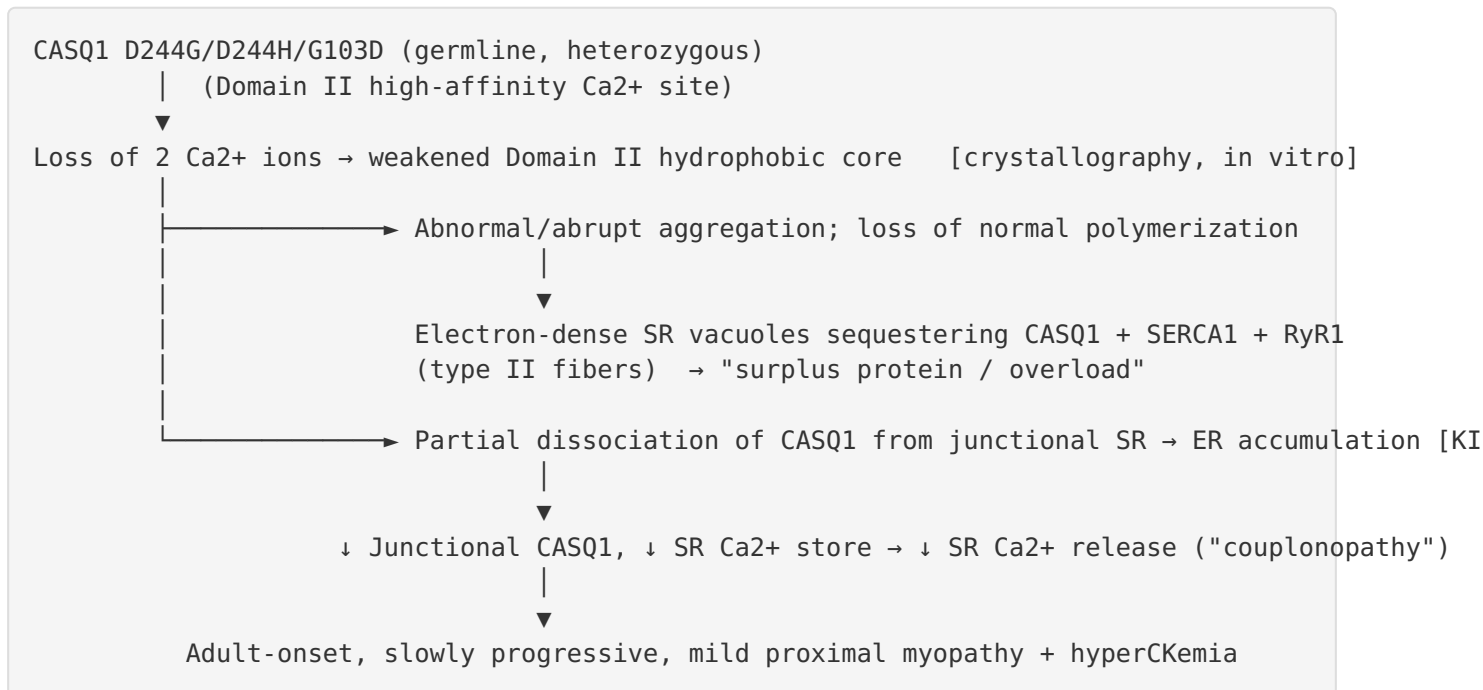
## 6. Mechanism / Pathophysiology

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### Ordered causal chain (initiating lesion → clinical manifestation)

1. A heterozygous **CASQ1 missense mutation** at/near a Domain-II high-affinity  $\text{Ca}^{2+}$ -binding site (p.Asp244Gly, p.Asp244His, or p.Gly103Asp) arises in the germline → **leads to** a structurally altered calsequestrin monomer.
2. Loss of two coordinating  $\text{Ca}^{2+}$  ions in the mutant structure **weakens the hydrophobic core of Domain II** (demonstrated crystallographically for D244G) → **results in** loss of high-affinity  $\text{Ca}^{2+}$  binding at elevated  $\text{Ca}^{2+}$  ([PMID: 26416891](#)).
3. Impaired  $\text{Ca}^{2+}$  binding **reduces the ability of CASQ1 to form normal elongated polymers** and instead **causes abrupt, abnormal aggregation** ([PMID: 26416891](#)).
4. Aggregated mutant (and co-recruited wild-type) CASQ1 **leads to** the formation of **electron-dense SR vacuoles** that co-sequester SERCA1 (ATP2A1) and RyR1, preferentially in **type II fibers** ([PMID: 25116801](#)).
5. In parallel (branch), the mutation **causes CASQ1 to partially dissociate from the junctional SR and accumulate in the ER** (shown in the D244G knock-in mouse) → **reduces junctional CASQ1 content and SR  $\text{Ca}^{2+}$  stores** ([PMID: 33786938](#)).
6. Reduced junctional calsequestrin and disrupted couplon architecture **result in less  $\text{Ca}^{2+}$  release from the SR** of mutant fibers compared with controls (patient-derived myotubes) → defining a "**CASQ1-couplonopathy**" ([PMID: 27196359](#)).

7. Chronically altered  $\text{Ca}^{2+}$  handling and protein overload **lead to** the clinical phenotype: **exercise intolerance, myalgia, mild proximal weakness, and hyperCKemia** (PMID: 30258016).



## Detail by category

- **Molecular pathways.** Excitation–contraction (EC) coupling: SR  $\text{Ca}^{2+}$  storage/release through the RyR1–DHPR couplon;  $\text{Ca}^{2+}$  reuptake via SERCA1. Calsequestrin is the principal luminal  $\text{Ca}^{2+}$  buffer that modulates RyR1 gating.
- **Cellular processes.** Protein aggregation / proteostasis failure in the SR; vacuole formation; altered intracellular  $\text{Ca}^{2+}$  signaling. GO suggestions: GO:0006874 (cellular calcium ion homeostasis), GO:0051209 (release of sequestered calcium ion into cytosol), GO:0005513 (detection of calcium ion), GO:0006457 (protein folding).
- **Protein dysfunction.** Loss of high-affinity  $\text{Ca}^{2+}$  binding, impaired polymerization, and toxic aggregation — a mixed loss-of-buffer + gain-of-aggregation mechanism. Normal CASQ1 binds ~80  $\text{Ca}^{2+}$  ions and polymerizes to form the SR terminal-cisternae matrix.
- **Metabolic changes.** Secondary; chronically impaired  $\text{Ca}^{2+}$  cycling can affect fatigue resistance/energy metabolism in fast fibers (exercise intolerance), though not directly profiled in patients.
- **Immune system involvement.** None; this is a non-inflammatory, non-autoimmune protein-aggregate myopathy.

- **Tissue damage mechanisms.** Chronic vacuolar accumulation and  $\text{Ca}^{2+}$  dysregulation in type II fibers; mild myofiber stress releasing CK. In the knockout MH model, oxidative stress is central — but that is the loss-of-function phenotype.
- **Biochemical abnormalities.** Defective luminal SR  $\text{Ca}^{2+}$  buffering (ion-handling defect) rather than an enzyme deficiency.
- **Subcellular localization.** SR terminal cisternae / junctional SR lumen (GO:0033018 sarcoplasmic reticulum lumen region, GO:0014701 junctional sarcoplasmic reticulum membrane); pathologic mislocalization to the ER (GO:0005783 endoplasmic reticulum).

**Cell types involved.** Skeletal muscle fibers, specifically fast-twitch type II fibers — CL:0000190 (fast muscle cell) / CL:0008002 (skeletal muscle fiber).

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## 7. Anatomical Structures Affected

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- **Organ/system level.** Primary: **skeletal muscle** (musculoskeletal system). Distribution is **proximal and bilateral/symmetric** — quadriceps (anterior thigh), scapular/periscapular muscles (scapular winging). Secondary: **heart** — subclinical cardiac abnormalities in ~14% (3/22) ([PMID: 30258016](#)).
  - **Tissue/cell level.** Striated **muscle tissue**; predominantly **type II (fast-twitch) fibers** contain the vacuolar aggregates.
  - **Subcellular level.** **Sarcoplasmic reticulum terminal cisternae / junctional SR**; abnormal accumulation in the **endoplasmic reticulum**.
  - **UBERON/CL suggestions.** UBERON:0001134 (skeletal muscle tissue), UBERON:0011907 (quadriceps femoris), UBERON:0000948 (heart, secondary), UBERON:0002349 (myocardium); CL:0000190 (fast muscle cell). GO cellular component: GO:0016529 (sarcoplasmic reticulum), GO:0033018, GO:0005783.
  - **Lateralization.** Bilateral, symmetric proximal involvement.
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## 8. Temporal Development

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- **Onset.** Adult, typically the **sixth decade**; onset is **insidious/chronic**. HyperCKemia may precede or exist without overt weakness.

- **Progression. Slowly progressive**; weakness remains mild-to-moderate; patients generally remain ambulant. Muscle MRI shows a recurrent fibrofatty substitution pattern (reported in 11 patients) ([PMID: 30258016](#)).
  - **Disease course.** Chronic, lifelong, but **benign**; no reported end-stage/wheelchair-dependent phase as a rule.
  - **Patterns.** No spontaneous remission; no relapsing-remitting pattern. Symptoms (myalgia, exercise intolerance) may fluctuate with activity. Critical periods for intervention are not defined because no disease-modifying therapy exists.
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## 9. Inheritance and Population

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- **Epidemiology.** Ultra-rare. The world literature totals roughly **30–40 reported patients**, concentrated in Italy (founder p.Asp244Gly) plus isolated Chinese families. Orphanet prevalence: unknown, <1/1,000,000. Likely under-ascertained because mild cases escape biopsy ([PMID: 30258016](#)).
  - **Inheritance pattern. Autosomal dominant** (heterozygous missense variants).
  - **Penetrance / expressivity.** Appears high but with **variable expressivity** (ranging from isolated hyperCKemia to symptomatic proximal weakness); formal penetrance estimates are not established.
  - **Genetic anticipation / mosaicism.** Not applicable (not a repeat-expansion disorder); germline mosaicism not reported.
  - **Founder effects.** Yes — a shared **Italian founder haplotype** for p.Asp244Gly ([PMID: 26136523](#)).
  - **Consanguinity / carrier frequency.** Not relevant to a dominant disorder; carrier frequency not meaningfully defined.
  - **Population demographics.** Italian (founder) and Chinese families reported; both sexes affected; adult age distribution (sixth decade typical).
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## 10. Diagnostics

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- **Laboratory.** Serum **creatine kinase** mildly-to-moderately elevated (hyperCKemia), sometimes the sole abnormality (HP:0003236).
  - **Muscle biopsy (diagnostic cornerstone).** Vacuoles in **type II fibers** appearing "**empty**" on H&E, Gomori trichrome, and NADH-tetrazolium reductase stains, but **strongly positive for SR proteins** (SERCA1/ATP2A1 and calsequestrin) by immunohistochemistry; immunoblot shows increased SERCA1 and calsequestrin (PMID: 16714317; PMID: 30258016). The p.Gly103Asp variant additionally shows NADH-positive **tubular aggregates**. Electron microscopy: electron-dense SR vacuoles.
  - **Imaging.** Muscle **MRI** shows a recurrent fibrofatty substitution pattern.
  - **Electrophysiology.** EMG may show myopathic features; patient-derived myotubes show reduced SR Ca<sup>2+</sup> release on Ca<sup>2+</sup> imaging/electrophysiology (research setting) (PMID: 27196359).
  - **Genetic testing.** Confirmatory. Recommended approach: **single-gene testing of CASQ1** (targeting the Asp244 hotspot) or a **myopathy/limb-girdle gene panel**; WES/WGS are useful for undiagnosed cases, especially given the characteristic biopsy. Chromosomal microarray, karyotyping, FISH, mtDNA testing, and repeat-expansion testing are **not applicable**.
  - **Clinical criteria / differential diagnosis.** No formal consensus criteria; diagnosis rests on the triad of (1) adult-onset mild proximal myopathy/hyperCKemia, (2) SR-protein-positive type II fiber vacuoles, and (3) a pathogenic CASQ1 variant. Differential diagnoses: **tubular aggregate myopathies** (STIM1/ORAI1), other **protein-aggregate/vacuolar myopathies**, limb-girdle muscular dystrophies, and idiopathic hyperCKemia.
  - **Screening.** Cascade genetic testing of at-risk relatives in known families. No population newborn/carrier screening (ultra-rare, dominant, benign).
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## 11. Outcome/Prognosis

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- **Survival/mortality.** **Benign**; life expectancy is not reported to be reduced; no disease-specific mortality established.

- **Morbidity/function.** Mild-to-moderate proximal weakness with slow progression; most patients remain ambulant and functionally independent. Rare subclinical cardiac abnormalities (~14%) warrant surveillance but have not been linked to adverse outcomes.
  - **Disease course/complications.** Chronic but stable-to-slowly-progressive. Theoretical anesthetic/heat risk is extrapolated from the knockout model and remains unproven in patients.
  - **Prognostic factors.** None validated. Genotype may influence histology (tubular aggregates with p.Gly103Asp) but not clearly prognosis.
  - **Supporting quote.** Patients "later developed mild to moderate, slowly progressive proximal weakness" ([PMID: 30258016](#)).
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## 12. Treatment

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- **Pharmacotherapy. No approved disease-specific or targeted drug.** Management is supportive.
  - **Advanced therapeutics (gene/cell/RNA).** None in clinical use; the dominant aggregation mechanism could in principle be amenable to allele-specific knockdown (ASO/siRNA) in the future, but no such program is reported.
  - **Supportive/rehabilitative.** Physiotherapy, graded exercise modification for exercise intolerance/myalgia, periodic **cardiac surveillance** given rare subclinical cardiac findings.
  - **Experimental / mechanistic leads.** From the *Casq1*-null mouse (loss-of-function MH model, distinct from the overload disease): **antioxidants** (N-acetylcysteine, Trolox) protected against lethal halothane/heat-triggered hypermetabolic episodes, reducing mortality from ~79–86% to ~20–33% ([PMID: 26132720](#)), and **estrogens** reduced oxidative stress and mortality ([PMID: 29062464](#)). These suggest antioxidant strategies and **anesthetic/heat precautions** as rational but unproven approaches in humans.
  - **Treatment outcomes / adverse events.** Not applicable (no disease-specific therapy).
  - **NCIT suggestions.** NCIT:C15336 (Supportive Care), NCIT:C15682 (Physical Therapy), NCIT:C98225 (Genetic Counseling), NCIT:C265 (Antioxidant) — all general/supportive.
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## 13. Prevention

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- **Primary prevention.** None for a Mendelian disorder.
  - **Secondary prevention.** Early detection via **cascade genetic testing** in known families; recognition of isolated hyperCKemia prompting biopsy/genetics.
  - **Tertiary prevention.** Cardiac surveillance; prudent **anesthetic and heat precautions** (theoretical, extrapolated from the knockout model).
  - **Immunization / public health / environmental interventions.** Not applicable.
  - **Counseling. Genetic counseling** for autosomal dominant inheritance (50% transmission risk); theoretical prenatal/preimplantation genetic testing is possible but rarely indicated given the benign course.
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## 14. Other Species / Natural Disease

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- **Taxonomy / orthologs.** Mouse ortholog **Casq1**: MGI:1309468, NCBI Gene 12372, Ensembl ENSMUSG00000007122. CASQ1 is highly conserved across mammals.
  - **Natural disease in other species.** No naturally occurring animal homolog of this specific overload myopathy is reported (OMIA). Disease knowledge in animals comes from engineered models (Section 15).
  - **Comparative biology.** Calsequestrin's role in SR  $\text{Ca}^{2+}$  storage and EC coupling is evolutionarily conserved, underpinning the translational relevance of mouse models.
  - **Transmission.** Not applicable (non-communicable genetic disease; no zoonotic potential).
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## 15. Model Organisms

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Two complementary mouse models anchor the mechanistic understanding, and cellular systems recapitulate the aggregation phenotype.

| Model                                                  | Type                                   | Key phenotype                                                                                                                                                                                                                                                                         | Relevance to human disease                                                                                     |
|--------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <b>D244G knock-in mouse</b>                            | Mammalian, knock-in                    | CASQ1 partially dissociates from junctional SR and accumulates in ER; reduced junctional CASQ1 and SR Ca <sup>2+</sup> ( <a href="#">PMID: 33786938</a> )                                                                                                                             | Directly models the human overload/couplonopathy mechanism                                                     |
| <b>Casq1-null (knockout) mouse</b>                     | Mammalian, knockout (loss of function) | Viable, normal motor activity, moderate atrophy; profound EC-coupling remodeling (shrunk jSR, proliferating SR/T-tubule contacts, ↑ RyR density); <b>lethal MH-like hypermetabolic episodes</b> on halothane/heat ( <a href="#">PMID: 22130610</a> ; <a href="#">PMID: 26132720</a> ) | Models malignant-hyperthermia/heat susceptibility; oxidative-stress mechanism; estrogen/antioxidant protection |
| <b>COS-7 cells, myotubes, patient-derived myotubes</b> | In vitro/cellular                      | Mutant CASQ1 forms electron-dense SR vacuoles with CASQ1/RyR1 aggregates; reduced polymerization; less SR Ca <sup>2+</sup> release ( <a href="#">PMID: 25116801</a> ; <a href="#">PMID: 27196359</a> )                                                                                | Recapitulates aggregation and the Ca <sup>2+</sup> -release defect                                             |
| <b>Recombinant protein / crystallography</b>           | Biophysical                            | D244G lacks two Ca <sup>2+</sup> ions, weakened Domain II core, abrupt aggregation ( <a href="#">PMID: 26416891</a> )                                                                                                                                                                 | Structural basis of the defect                                                                                 |

**Rescue evidence.** Re-introduction of wild-type CASQ1 by cDNA electrotransfer in *Casq1*-null muscle restores junctional SR targeting, terminal-cisternae ultrastructure, and Ca<sup>2+</sup> transient amplitude ([PMID: 22049211](#)) — confirming CASQ1's causal role in both Ca<sup>2+</sup> homeostasis and terminal-cisternae structure.

**Model limitations.** The *Casq1*-null mouse models **loss of function** and its dominant feature is MH/heat susceptibility, which is *not* the primary human overload phenotype; the knock-in D244G mouse better reflects the human dominant aggregation/couplonopathy. Resources: MGI (*Casq1*, MGI:1309468).

## Mechanistic Model / Interpretation

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The convergent human (biopsy, patient-myotube electrophysiology, 22-patient cohort), in vitro (crystallography, cell aggregation), and mouse (D244G knock-in, Casq1 knockout) evidence defines a single coherent model:

A heterozygous **CASQ1** missense mutation at/near a Domain II high-affinity  $\text{Ca}^{2+}$  site (D244G / D244H / G103D) → **loss of  $\text{Ca}^{2+}$  binding + abnormal aggregation** → **electron-dense SR/ER vacuoles sequestering CASQ1, SERCA1, and RyR1 in type II fibers** → **dissociation of CASQ1 from the junctional SR** → **reduced SR  $\text{Ca}^{2+}$  storage and release (CASQ1-couplonopathy)** → **adult-onset, slowly progressive, mild proximal myopathy with hyperCKemia.**

Upstream events are molecular/biophysical (the mutation, loss of  $\text{Ca}^{2+}$  coordination, aggregation); downstream events are physiological and clinical (impaired EC coupling, weakness, CK leak). The disease unifies two apparently opposite effects — a **gain** of toxic protein (the "overload"/surplus protein storage) and a **loss** of functional junctional buffering (the couplonopathy) — into one pathogenic cascade. Notably, calsequestrin dysfunction produces two divergent human phenotypes depending on the allele: the benign dominant **overload myopathy** (D244G/D244H/G103D) versus a weak **malignant-hyperthermia** association (M87T), with the knockout mouse illustrating the MH/heat-stress extreme of the loss-of-function axis.

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## Evidence Base

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| PMID                     | Title (abbrev.)                                   | Evidence type                | Supports                                                                         |
|--------------------------|---------------------------------------------------|------------------------------|----------------------------------------------------------------------------------|
| <a href="#">16714317</a> | SERCA1 and calsequestrin storage myopathy         | Human (biopsy)               | Original morphological definition (surplus SR-protein myopathy)                  |
| <a href="#">25116801</a> | CASQ1 mutation causes vacuolar myopathy           | Human genetics + cellular    | Causal D244G; vacuoles; altered Ca <sup>2+</sup> release                         |
| <a href="#">26136523</a> | CASQ1 founder mutation, 3 Italian families        | Human genetics               | Founder effect; benign evolution                                                 |
| <a href="#">41699400</a> | CASQ1 p.Asp244His, 2 Chinese families             | Human genetics               | Second hotspot variant; conserved residue                                        |
| <a href="#">26416891</a> | Characterization of two CASQ1 mutants             | Biophysical/ crystallography | Structural basis: loss of Ca <sup>2+</sup> , abnormal aggregation; D244G vs M87T |
| <a href="#">27196359</a> | CASQ1 mutation alters SR Ca <sup>2+</sup> release | Patient myotubes             | Reduced SR Ca <sup>2+</sup> release; "CASQ1-couplonopathy"                       |
| <a href="#">33786938</a> | Pathological mechanisms from Casq1 mutation       | D244G knock-in mouse         | jSR→ER mislocalization; reduced SR Ca <sup>2+</sup>                              |
| <a href="#">30258016</a> | Clinical spectrum of CASQ1 myopathy               | Human cohort (n=22)          | Onset, weakness distribution, histology, cardiac, MRI                            |
| <a href="#">22130610</a> | Lessons from Casq1 ablation                       | Knockout mouse               | EC-coupling remodeling                                                           |
| <a href="#">26132720</a> | Antioxidants protect Casq1-null mice              | Knockout mouse               | MH/heat phenotype; antioxidant protection                                        |
| <a href="#">29062464</a> | Estrogens protect Casq1-null mice                 | Knockout mouse               | Estrogen protection; sex difference                                              |
| <a href="#">22049211</a> | CASQ1 rescues Casq1-null muscle                   | Knockout + rescue            | Confirms CASQ1 role in Ca <sup>2+</sup> and structure                            |
| <a href="#">28465322</a> | Exercise triggers MH-like response                | Mouse (RyR1/MH)              | Exercise as a trigger in MH-susceptible muscle                                   |
| <a href="#">36311237</a> | Ablation of Calsequestrin-1                       | Mouse                        | CASQ1 ablation effects                                                           |

**Notable verbatim support.** - "The mutation affects a conserved aspartic acid in position 244 (p.Asp244Gly) located in one of the high-affinity Ca(2+)-binding sites of CASQ1 and alters the kinetics of Ca(2+) release in muscle fibers." (PMID: 25116801) - "D244G aggregates abruptly and abnormally ... D244G crystallized in low Ca(2+) concentrations lacks two Ca(2+) ions normally present in wild type that weakens the hydrophobic core of Domain II." (PMID: 26416891) - "Electrophysiological recordings and sarcoplasmic Ca<sup>2+</sup> measurements provide evidence for less Ca<sup>2+</sup> release from the SR of mutated myotubes when compared to that of controls." (PMID: 27196359) - "The DG mutation causes CASQ1 to partially dissociate from the junctional sarcoplasmic reticulum (SR) and accumulate in the endoplasmic reticulum (ER)." (PMID: 33786938)

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## Limitations and Knowledge Gaps

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1. **Small evidence base.** Only ~30–40 patients worldwide; cohort statistics (e.g., 22-patient series) dominate, so penetrance, true prevalence, and genotype–phenotype correlations are imprecise.
  2. **Ascertainment bias.** Mild/isolated-hyperCKemia cases likely under-diagnosed without muscle biopsy, so the spectrum may be broader and milder than reported.
  3. **Mechanistic duality unresolved in humans.** The human overload myopathy vs the knockout MH/heat-stress phenotype are modeled in different systems; whether human D244G patients carry a clinically meaningful anesthetic/heat risk is **not demonstrated** — the precaution is extrapolated.
  4. **No human therapeutic data.** Antioxidant/estrogen protection is only shown in Casq1-null mice; no trials in patients.
  5. **Cardiac involvement.** The significance of subclinical cardiac abnormalities (~14%) is unclear; CASQ1 is the skeletal isoform (cardiac CASQ2 is distinct), so the cardiac finding needs mechanistic clarification.
  6. **Omics gaps.** No transcriptomic, proteomic, metabolomic, or single-cell profiling specific to this disease is available.
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## Proposed Follow-up Experiments / Actions

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1. **Natural-history registry** across Italian and Chinese families (and new cases) to quantify penetrance, progression rate, and cardiac risk prospectively.
2. **Anesthetic/heat-stress risk assessment** in D244G knock-in mice and, cautiously, retrospective review of patient anesthetic exposures to test whether the MH/heat risk translates to the overload myopathy.
3. **Test antioxidant (NAC) and estrogen pathways** in the D244G knock-in (not only knockout) model to determine relevance to the overload phenotype.
4. **Allele-specific knockdown (ASO/siRNA)** proof-of-concept targeting mutant CASQ1 transcripts in patient myotubes to address the dominant aggregation mechanism.
5. **Deep muscle proteomics/transcriptomics** of patient biopsies to map the full "surplus protein" composition and secondary stress responses.
6. **Structural studies** of D244H and G103D (beyond D244G) to confirm shared loss-of-Ca<sup>2+</sup>-binding mechanism across the allelic spectrum.
7. **Cardiac evaluation protocol** to clarify whether skeletal CASQ1 variants have any genuine cardiac phenotype or whether findings are incidental.

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