Congenital Myopathy 11 (CMYP11 / HACD1-related congenital myopathy) — Disease Characterization Report

Prepared: 2026-10-16 | **Target:** Congenital Myopathy 11 | **MONDO:0859264 Evidence base:** This is an **ultra-rare Mendelian disease**. Information is derived from **disease-level/ aggregated resources** (OMIM, gnomAD, UniProt) and a small number of **individual-patient case reports/series** (fewer than ~15 reported human families worldwide), supplemented by an extensively characterized **naturally occurring canine model** and **mouse/cell models**. There are **no registries, EHR cohorts, GWAS, or population epidemiology datasets** for this disease.

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1. Disease Information

Overview. Congenital Myopathy 11 (CMYP11) is an autosomal recessive congenital myopathy caused by biallelic loss-of-function (LoF) variants in **HACD1** (3-hydroxyacyl-CoA dehydratase 1; legacy symbol **PTPLA**). It presents at birth with generalized muscle weakness and hypotonia, motor developmental delay, and frequently respiratory distress, with a characteristic **improvement over time**. Muscle biopsy typically shows **congenital fiber-type disproportion (CFTD)**; the canine orthologous disease is classified as **centronuclear myopathy (CNM)**. First linked to humans in 2013 (P 23933735) and confirmed as a "bona fide" congenital myopathy gene in 2021 (P 33354762).

Key identifiers. - **OMIM (phenotype):** #619967 (Myopathy, congenital, 11) · **OMIM (gene HACD1):** 610467 - **MONDO:** MONDO:0859264 - **Gene:** HACD1 — **HGNC:9639**, Ensembl **ENSG00000165996**, UniProt **B0YJ81** (HACD1_HUMAN), **EC 4.2.1.134** - **Orphanet:** HACD1 congenital myopathy falls within "Congenital myopathy with fiber type disproportion"

(ORPHA:2020) group - **ICD-11:** 8C70.0 (Congenital myopathies) · **ICD-10:** G71.2 · **MeSH:** Myopathies, Structural, Congenital (D020914) - **Chromosome:** 10p13 (chr10:17,589,032–17,617,374, GRCh38)

Synonyms / alternative names. HACD1-related congenital myopathy; PTPLA-related myopathy; congenital myopathy with fiber-type disproportion (HACD1 type); (canine) autosomal recessive centronuclear myopathy / "Labrador myopathy" / type II fiber deficiency.

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2. Etiology

Primary cause — genetic (monogenic, autosomal recessive). Biallelic LoF variants in HACD1 are the sole established cause. There is **no environmental, infectious, or multifactorial contribution**; the disease is fully genetically determined.

Genetic risk factors. - **Causal variants (human, all biallelic LoF):** nonsense c.?? (first family, NMD reducing HACD1 mRNA to 31% — P 23933735); splice/deletion **c.373_375+2delGAGGT**; splice **c.785-1G>T**; nonsense **c.458G>A** (P 33354762); **biallelic LINE insertion** (P 32426512). (Canine) tRNA-derived **SINE insertion in exon 2** of PTPLA (P 15829503). - **Susceptibility loci / modifier genes:** none identified in humans. HACD2 (ubiquitous paralog) is a plausible genetic modifier via functional redundancy (inferred, not demonstrated). - **Family history / consanguinity:** affected individuals are typically from **consanguineous** families (Middle East/Asia; now Brazil); consanguinity is the major demographic risk factor for homozygosity.

Environmental risk / protective factors. None known. No toxins, diet, lifestyle, or exposures are implicated as causes, modifiers, or protectors. No protective genetic alleles described.

Gene–environment interactions. None established. (Not applicable for this monogenic disorder.)

3. Phenotypes

Phenotype frequencies are **qualitative** (small N). Core features, with suggested HPO terms:

Phenotype	Type	HPO term	Onset	Severity/Course	Frequency
Neonatal hypotonia	Clinical sign	HP:0001319	Neonatal/ congenital	Severe at birth, improves	Very frequent
Generalized muscle weakness	Clinical sign	HP:0003324	Neonatal	Severe→improving	Very frequent
Motor developmental delay	Clinical sign	HP:0001270	Infancy	Moderate, improves	Frequent
Respiratory distress / insufficiency	Clinical sign	HP:0002098 / HP:0002093	Neonatal	Severe, often transient	Frequent
Congenital fiber-type disproportion (biopsy)	Laboratory/ path	HP:0003749	Congenital	Static	Characteristic
Reduced fetal movements / feeding difficulty	Symptom	HP:0001558 / HP:0011968	Perinatal	Variable	Reported
Muscle fatty infiltration on MRI (pelvic/ posterior leg)	Imaging	HP:0009020	Childhood	Slowly evolving	3/3 imaged (P 42275936)
Normal/mildly elevated serum CK	Lab	HP:0003236	—	Static	Typical of congenital myopathies

Progression: Non-progressive/improving — the hallmark "temporally progressive improvement"
( ).
P 33354762
Severity: severe neonatal presentation, moderate residual weakness later. **Quality of life:** major early impact (respiratory/feeding/motor), substantially improving with age; most survivors become ambulant. Formal EQ-5D/SF-36/PROMIS data are **not available**.

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4. Genetic / Molecular Information

- **Causal gene: HACD1** (HGNC:9639; OMIM 610467). Sole gene.
- **Variant classification:** reported alleles are **pathogenic/likely pathogenic** (ACMG), acting as **loss-of-function**.
- **Variant types/classes:** nonsense, canonical splice-site, small deletion with splice disruption, and **transposable-element insertions (LINE in humans; SINE in dogs)** — a notable recurrent mutational mechanism for this gene.
- **Allele frequency (gnomAD):** HACD1 is **not LoF-constrained**: pLI ≈ 0 (1.8×10^{-17}), observed/expected LoF = **1.28** (41 obs / 32 exp), **LOEUF** = **1.66**, LoF Z = −1.35, missense Z = −0.35. Individual pathogenic alleles are rare/private; heterozygous carriers are asymptomatic.
- **Origin: germline** (constitutional); not somatic. **COSMIC/TCGA:** not applicable (non-oncologic).
- **Functional consequence: loss of function** (abolished dehydratase activity; NMD of transcript).
- **Modifier genes:** none proven (HACD2 redundancy inferred).
- **Epigenetics:** no disease-specific methylation/histone data.
- **Chromosomal abnormalities:** none (not a CNV/aneuploidy disorder).

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5. Environmental Information

Not applicable. No environmental, lifestyle, or infectious factors cause, trigger, or modify CMYP11. It is a purely genetic, congenital disorder.

6. Mechanism / Pathophysiology

Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic LoF variant in HACD1 → leads to** absent/non-functional HACD1 enzyme in striated muscle (NMD; splice/nonsense/insertion) *(demonstrated;*

   P *23933735* *).*

2. Loss of HACD1 dehydratase activity → **results in** a block at the **third (dehydration) step of the ER very-long-chain fatty-acid (VLCFA) elongation cycle** (ELOVL→KAR→**HACD**→TECR), reducing VLCFA (>C18) synthesis *(demonstrated in vitro/ patient muscle;*

   P *23933735*

   P *38422897* *).*

3. Reduced VLCFA/altered acyl chains → **leads to** remodeled membrane phospholipids: ↑ **lysophosphatidylcholine** and ↓ **≥C18/monounsaturated phospholipid fatty acids → increased plasma-membrane rigidity** *(demonstrated in dog, Hacd1-KO mouse, deficient myoblasts;*

   P *26160855* *).*

4. **Branch A (developmental):** membrane rigidity + LPC (a fusion inhibitor) → **impairs myoblast fusion → reduced myofiber diameter / fiber-type disproportion** → neonatal weakness/hypotonia *(demonstrated;*

   P *26160855* *).*

   PTPLA/HACD1 also supports myoblast proliferation/differentiation via **MyoG** and cell-cycle control *(in vitro;*

   P *22106411* *).*

5. **Branch B (structural/mature muscle):** membrane-composition defect → **progressive tubuloreticular & sarcolemmal membrane abnormalities, T-tubule dilation/ disorganization, mislocalized triads and mitochondria → defective excitation–**

contraction coupling → weakness; centronuclear histology in dogs *(demonstrated;* *27939133*).

6. Combined developmental hypotrophy + EC-coupling defect → **produces** the clinical phenotype (weakness, respiratory distress). Partial compensation (regeneration, growth, residual HACD2 activity) → **underlies the characteristic postnatal improvement** *(inferred from improving course + redundancy)*.

Supporting detail

- **Molecular pathways:** fatty-acid elongation (KEGG map00062; Reactome VLCFA synthesis). Myogenic regulatory network (MyoG; SRF upstream of PTPLA, 22106411).
- **Cellular processes:** myoblast fusion (GO:0007520), skeletal muscle fiber development (GO:0048741), excitation–contraction coupling (GO:0006941 muscle contraction), membrane organization.
- **Protein dysfunction:** loss of function of an ER-membrane dehydratase (EC 4.2.1.134); no aggregation/gain-of-function.
- **Metabolic changes:** VLCFA biosynthesis deficiency; lipid/phospholipid remodeling (lipidomics: ↑LPC). **Biochemical defect:** enzyme (dehydratase) deficiency.
- **Immune involvement / inflammation / fibrosis:** not a primary feature.
- **Molecular profiling:** lipidomic shifts documented (26160855); no human transcriptomic/proteomic/metabolomic disease datasets. CRISPR/RNAi screens: not disease-specific.
- **Cell types (CL):** skeletal muscle myoblast (CL:0000056), skeletal muscle fiber / myotube, type I vs type II fibers. **Subcellular (GO CC):** endoplasmic reticulum membrane (GO:0005789), T-tubule (GO:0030315), sarcoplasmic reticulum, triad.
- **Chemical entities (CHEBI):** very-long-chain fatty acid (CHEBI:27283), 3-hydroxyacyl-CoA, trans-2-enoyl-CoA, lysophosphatidylcholine (CHEBI:17504).

7. Anatomical Structures Affected

- **Organ/system level: Skeletal muscle / musculoskeletal system** (primary). **Respiratory system** (respiratory muscle weakness → neonatal respiratory distress). HACD1 is also highly expressed in **myocardium** (UniProt), but overt cardiomyopathy is **not** a reported human feature (potential monitoring target; the related canine CNM colony is used in CNM cardiac/neuromuscular studies).
- **Tissue/cell level:** striated **muscle tissue** (UBERON:0002036 skeletal muscle tissue); affected cells = **myoblasts/myotubes and mature myofibers**, with relative **type-1 fiber hypotrophy** (human CFTD) or **type II fiber atrophy / centronuclear** change (canine). Cell Ontology: CL:0000056 (myoblast), CL:0000188 (skeletal muscle cell).
- **Subcellular level: endoplasmic reticulum membrane** (site of enzyme), **T-tubules/triads**, **sarcolemma**, and **mitochondria** (mislocalized).
- **Localization:** generalized/axial and limb-girdle; MRI shows **symmetrical, bilateral** fatty infiltration predominantly in **pelvic girdle and posterior lower-limb compartments**, sparing anterior thigh/leg
  (P 42275936).
  Lateralization: bilateral/symmetric.
- **UBERON terms:** UBERON:0001134 (skeletal muscle tissue), UBERON:0001388 (gastrocnemius), UBERON:0002385 (muscle of pelvic girdle), UBERON:0000948 (heart, expression).

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8. Temporal Development

- **Onset: congenital/neonatal** (often antenatal — reduced fetal movements). Pattern: **subacute at birth**, clinically evident from the neonatal period.
- **Progression: non-progressive to improving**. Severe neonatal nadir (weakness + respiratory compromise) → **remarkable functional improvement** through infancy/childhood
  (P 33354762

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P 42275936

Disease duration: **chronic/lifelong** (residual weakness) but **not degenerative**.

- **Course pattern: stable/improving** (contrasts with progressive dystrophies).
- **Critical period / window of opportunity:** the **perinatal–early-infancy** period (respiratory support during the weakest phase is life-saving; developmental myogenesis window is where fusion defect manifests).
- **Remission:** functional improvement is **spontaneous** (natural history), not treatment-induced.

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9. Inheritance and Population

- **Inheritance: Autosomal recessive** (AR).
- **Penetrance: complete** in biallelic LoF individuals (reported); **expressivity** relatively **consistent** (comparable presentation across families,

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P 33354762

- **Epidemiology: ultra-rare**; prevalence/incidence **not quantified** (<15 reported human families; Orphanet "unknown/<1:1,000,000" range). No GBD/registry data.
- **Carrier frequency:** not formally estimated in humans; gnomAD indicates pathogenic alleles are individually rare and LoF is tolerated in heterozygotes (asymptomatic carriers).
- **Founder effects:** none established in humans; **striking founder effect in dogs** (single recent PTPLA SINE allele disseminated worldwide via popular sires,

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P 23071563

- **Consanguinity:** major driver of human cases (homozygosity in consanguineous Middle Eastern/Asian families; the c.373_375+2delGAGGT allele recurs, including in Brazil).
- **Germline mosaicism / anticipation:** not reported / not applicable (no repeat expansion).
- **Population demographics:** reported in Middle East, Asia, and Brazil. **Sex ratio:** ~1:1 (AR, no sex bias). **Age distribution:** presents at birth; patients survive into childhood/adulthood.

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10. Diagnostics

- **Muscle biopsy (key): congenital fiber-type disproportion** — smaller type-1 fibers without structural lesions (HP:0003749); canine counterpart shows centronuclear/type II features (P 20179953 P 27939133). P 42275936
- **Serum CK:** normal or mildly elevated (typical of congenital myopathies).
- **EMG/nerve conduction:** nonspecific myopathic changes; used to exclude neuromuscular-junction and neurogenic disorders.
- **Muscle MRI:** symmetrical pelvic-girdle/posterior lower-limb fatty infiltration sparing anterior compartments — an emerging supportive pattern (P 42275936).
- **Genetic testing (definitive): congenital-myopathy NGS gene panel → WES/WGS** to identify **biallelic HACD1 variants**; because splice/transposon insertions occur, **RNA sequencing** and **WGS** improve detection of non-canonical/structural alleles. Single-gene HACD1 testing applies for known familial variants / cascade testing. CMA, karyotype, FISH, mtDNA, and repeat-expansion testing are **not diagnostic** (used only to exclude mimics).
- **Clinical criteria:** no disease-specific consensus criteria; diagnosis = neonatal congenital myopathy phenotype + CFTD biopsy + biallelic HACD1 LoF.
- **Differential diagnosis:** other CFTD genes — **ACTA1, TPM3, TPM2, SELENON (SEPN1), RYR1** — and **congenital myotonic dystrophy (DMPK CTG expansion)**, which can mimic CFTD (P 20951040 P 20179953); P 24239060 also other congenital myopathies (nemaline, core, centronuclear/MTM1) and congenital muscular dystrophies.
- **Screening:** not part of newborn screening; **cascade carrier testing** in families and **carrier screening** for consanguineous couples are appropriate.

11. Outcome / Prognosis

- **Survival/mortality:** main risk is **neonatal respiratory failure**; with supportive care, survival is generally good and many patients improve. No formal survival statistics exist (small N). Life expectancy appears **near-normal** in survivors, but long-term data are limited.
- **Morbidity/function:** early severe disability (respiratory/feeding/motor) that **improves**; residual proximal weakness and possible orthopedic sequelae (contractures, scoliosis) typical of congenital myopathies.
- **Disease course: chronic but non-progressive/improving**. Complications: respiratory infections during the weak phase; potential orthopedic and (theoretically, given myocardial expression) cardiac surveillance.
- **Prognostic factors:** severity of neonatal respiratory involvement; **molecular diagnosis carries "impactful prognostic value"** (predicts the favorable improving trajectory) (P 33354762). No molecular prognostic biomarkers beyond genotype.
- **QoL tools:** none disease-specific reported.

12. Treatment

No curative or disease-specific (pharmacologic/gene/RNA) therapy exists. Management is **supportive and multidisciplinary** (NCIT: Supportive Care Intervention):

- **Pharmacotherapy:** none targeted. No pharmacogenomic guidance.
- **Supportive/rehabilitative (mainstay):**
- **Respiratory support** — neonatal ventilation, **non-invasive ventilation (NIV)**, airway clearance (NCIT: Respiratory Therapy).
- **Nutritional/feeding support** — assisted feeding for neonatal feeding difficulty (NCIT: Nutritional Support).
- **Physical & occupational therapy**, stretching to prevent **contractures**; orthopedic management of **scoliosis** (NCIT: Physical Therapy, Occupational Therapy).

- **Surgical/interventional:** orthopedic (scoliosis/contracture) procedures as needed.
- **Anesthesia:** caution advised in congenital myopathies; in the canine HACD1/CNM model, sensitivity to the non-depolarizing blocker **vecuronium was not increased** vs controls (P 25815571) — informative but not a substitute for standard neuromuscular-disease anesthetic precautions.
- **Advanced/experimental (future directions):** the recessive LoF mechanism and the **validated Labrador large-animal model** make **gene replacement/editing** conceptually attractive (the same canine platform enabled successful MTM1 gene therapy for X-linked CNM; P 31450509). **No clinical trials (ClinicalTrials.gov) are currently open for HACD1 myopathy.**
- **Personalized medicine:** genotype-guided counseling/prognosis; no genotype-directed drugs.

13. Prevention

- **Primary prevention: genetic counseling** for at-risk/consanguine families; **carrier screening**; **prenatal diagnosis** or **preimplantation genetic testing (PGT-M)** for couples with a known biallelic genotype (NCIT: Genetic Counseling).
- **Secondary prevention:** early recognition of neonatal hypotonia/respiratory compromise → prompt respiratory support; early molecular diagnosis to guide monitoring.
- **Tertiary prevention:** prevent complications — respiratory surveillance/vaccination against respiratory pathogens, orthopedic surveillance (scoliosis/contractures), aspiration precautions.
- **Immunization/public health/environmental:** no disease-specific vaccine or environmental intervention (not applicable).
- **Risk stratification:** family history/consanguinity + known familial variant enables **cascade testing**.

14. Other Species / Natural Disease

- **Taxonomy: Canis lupus familiaris** (NCBI Taxon **9615**) — dog; **Mus musculus** (NCBI Taxon **10090**) — engineered model.
- **Breed: Labrador Retriever** (naturally affected; VBO term for Labrador Retriever). Historically "Labrador myopathy" / type II fiber deficiency.
- **Orthologous gene:** canine/murine **Hacd1/PTPLA** (NCBI Gene orthologs).
- **Natural disease (veterinary):** autosomal recessive **centronuclear myopathy (CNM)** in Labradors — generalized weakness, exercise intolerance, type II fiber atrophy, centronuclear histology; onset in puppyhood. Driven by a **recent founder SINE insertion** in PTPLA exon 2, disseminated worldwide; carrier allele frequency ~1.8% in an Italian sample (~1/20,000 affected)
  (P 15829503 P 23071563). P 21217042
  Veterinary importance: significant inherited neuromuscular disease of a popular breed; **DNA carrier testing is used in breeding programs** to avoid carrier×carrier matings.
- **Comparative pathology:** dogs show CNM features (and progressive membrane/triad defects), humans show CFTD; both reflect the same VLCFA/membrane mechanism — strong **evolutionary conservation** of HACD1 function in striated muscle.
- **Transmission:** none — **not zoonotic/infectious**; purely inherited.

15. Model Organisms

- **Canine (natural, large-animal):** PTPLA/HACD1-deficient **Labrador Retriever** colony — the premier model; recapitulates weakness, exercise intolerance, fiber pathology, and progressive membrane/triad/EC-coupling defects
  (P 27939133);
  supports functional outcome measures (**6-minute walk test**,
  P 27012153)

and anesthetic/physiologic studies; a proven platform for CNM therapy translation (P 31450509).

- **Mouse: Hacd1-knockout** mice — reduced myofiber size, impaired myoblast fusion, altered membrane lipid composition/fluidity (P 26160855). Available via standard repositories (MGI/IMSR).
- **Cellular/in vitro:** HACD1-deficient primary myoblasts and PTPLA-knockdown myoblast lines — fusion failure, differentiation/cell-cycle defects (MyoG axis) (P 26160855 P 22106411). iPSC-derived myotubes are feasible but not yet reported for HACD1.
- **Phenotype recapitulation:** high — animal/cell models reproduce the core developmental (fusion/fiber-size) and structural (membrane/triad) defects and the lipid biochemistry.
- **Limitations:** canine disease is labeled CNM (vs human CFTD); the characteristic human postnatal improvement is less emphasized in models; no reported invertebrate (fly/worm/zebrafish) disease model.
- **Resources:** MGI (mouse Hacd1), IMSR; canine colony literature; Alliance of Genome Resources for orthology.

Summary (Answer to the Research Question)

Congenital Myopathy 11 is an **ultra-rare autosomal recessive congenital myopathy** caused by **biallelic loss-of-function variants in HACD1 (PTPLA)**, the muscle-enriched ER enzyme catalyzing the dehydration step of **very-long-chain fatty-acid elongation**. Enzyme loss remodels muscle-membrane phospholipids (↑lysophosphatidylcholine, ↑rigidity), **impairing myoblast fusion and triad/excitation–contraction architecture**, which produces **neonatal hypotonia, generalized weakness, and respiratory distress with congenital fiber-type disproportion on biopsy** — followed by a **characteristic clinical improvement**. Diagnosis is **molecular (biallelic HACD1 LoF) plus CFTD biopsy**; management is **supportive/multidisciplinary** (no curative therapy); and a **naturally occurring Labrador Retriever model** provides a validated platform for mechanism and future gene therapy.

Supported vs Refuted Hypotheses

- **Supported:** HACD1 LoF is the cause (H1); mechanism = VLCFA-elongation→membrane-lipid→fusion/triad defect (H2); AR inheritance with tolerant heterozygotes (H3, gnomAD); favorable improving prognosis (H4); robust canine model (H5).
- **Refuted/Excluded:** no environmental/infectious etiology; not a channelopathy, aggregation, or gain-of-function disorder; no somatic/oncologic component; HACD1 is **not** a functional tyrosine phosphatase despite the PTPLA name.

Limitations & Future Directions

- Very small human N → frequencies qualitative; no epidemiology, QoL, survival statistics, or human omics datasets.
- Possible cardiac involvement (myocardial HACD1 expression) is **untested** in humans and warrants surveillance studies.
- Natural history and genotype–phenotype correlation need prospective cohorts; **gene-replacement/editing** is a logical therapeutic avenue leveraging the canine model.

Key References (PMID)

23933735 (first human cause); 33354762 (bona fide confirmation, variant spectrum, prognosis); 42275936 (MRI, Brazilian cohort); 26160855 (membrane/fusion mechanism); 27939133 (triad/membrane defects, canine); 22106411 (MyoG/cell-cycle); 38422897 (VLCFA elongation machinery); 15829503, 23071563, 21217042, 27012153, 25815571, 31450509 (canine model); 20951040, 20179953, 24239060 (CFTD differential); 32426512 (LINE insertion).