Charcot-Marie-Tooth Disease Recessive Intermediate D (CMTRID)

A Comprehensive Disease Characterization Report

Prepared: 2026-08-29 | **Evidence base:** Primary literature (PubMed), OMIM/Orphanet/HGNC identifiers, and general CMT clinical literature.

> **Scope note:** CMTRID is an **ultra-rare Mendelian mitochondrial peripheral neuropathy** caused by biallelic *COX6A1* variants. Fewer than ~10 families/individuals are described in the literature worldwide. Consequently, many quantitative epidemiologic, prognostic, and treatment-trial parameters are **not established specifically for CMTRID**; where this is the case it is stated explicitly, and general CMT knowledge is used as the best available proxy and labeled as such.

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1. Disease Information

Overview. Charcot-Marie-Tooth disease Recessive Intermediate D (CMTRID) is a rare autosomal-recessive form of inherited peripheral neuropathy (hereditary motor and sensory neuropathy, HMSN). Clinically it presents as a length-dependent, slowly progressive distal sensorimotor neuropathy with the electrophysiological features of an **"intermediate"** neuropathy — i.e., motor nerve conduction velocities (NCV) that fall between the demyelinating (CMT1, <38 m/s) and purely axonal (CMT2, >38 m/s) ranges, or a mixed axonal-and-demyelinating picture. The disease is caused by loss-of-function variants in ***COX6A1***, a nuclear-encoded structural subunit of mitochondrial respiratory **complex IV (cytochrome *c* oxidase, COX)** (P 25152455).

Key identifiers. | Resource | Identifier | |---|---| | OMIM (phenotype) | **#616039** — Charcot-Marie-Tooth disease, recessive intermediate D (CMTRID) | | OMIM (gene) | ***602072*** — COX6A1 | | MONDO | **MONDO:0014467** (Charcot-Marie-Tooth disease recessive intermediate D) —

verified via EBI OLS4 | | Orphanet | **ORPHA:435998** — *verified via MONDO xref* | | DOID | **DOID:0110203** | | GARD | **GARD:0017723** | | UMLS | **C5569027** | | MedGen | **1800450** (C5569027) | | ICD-10 | **G60.0** (Hereditary motor and sensory neuropathy) | | ICD-11 | **8C20** (Hereditary motor and sensory neuropathy) | | MeSH | **D002607** (Charcot-Marie-Tooth Disease) | | HGNC (gene) | **HGNC:2277** (COX6A1) | | NCBI Gene | **1337** (COX6A1) | | Ensembl | **ENSG00000111775** | | UniProt | **P12074** (COX6A1_HUMAN) |

MONDO definition (verified): "Any Charcot-Marie-Tooth disease in which the cause of the disease is a mutation in the COX6A1 gene."

Synonyms / alternative names. - CMTRID; CMT Recessive Intermediate type D - Autosomal recessive intermediate Charcot-Marie-Tooth disease, COX6A1-related - COX6A1-related axonal/mixed Charcot-Marie-Tooth disease - Cytochrome c oxidase subunit VIa polypeptide 1-related neuropathy

Source type. Information is derived almost entirely from **aggregated, disease-level resources** (OMIM/Orphanet) and a small number of **individual case reports / small consanguineous-family studies** in the primary literature (P 25152455 ; 41044399). No EHR-scale cohort exists for this specific subtype.

HPO (disease-level suggestions): HP:0007141 (Peripheral axonal neuropathy), HP:0003477 (Peripheral sensory neuropathy), HP:0003693 (Distal amyotrophy), HP:0009830 (Peripheral neuropathy).

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2. Etiology

Primary cause — genetic. CMTRID is a **monogenic autosomal-recessive** disorder caused by **biallelic (homozygous or compound-heterozygous) pathogenic variants in *COX6A1***. The founding study mapped the locus to a 4.3 Mb region on **chromosome 12q24** (maximum multipoint LOD 4.23) in two consanguineous families and identified a homozygous 5-bp splice-region deletion **c.247-10_247-6delCACTC** in intron 2 of *COX6A1* (P 25152455).

> *"a disease-specific 5 bp deletion (c.247-10_247-6delCACTC) in a splicing element (pyrimidine tract) of intron 2 adjacent to the third exon of cytochrome c oxidase subunit VIa polypeptide 1 (COX6A1), which is a component of mitochondrial respiratory complex IV"* — Tamiya et al., 2014 (P 25152455)

Risk factors. - **Genetic:** The only established risk factor is inheritance of two pathogenic *COX6A1* alleles. **Consanguinity** is a strong contributing factor — the originally described families were consanguineous (P 25152455) — increasing the chance of homozygosity for a rare recessive allele. - **Environmental / lifestyle:** No environmental risk factors are established as *causal*. However, given the mitochondrial (oxidative-phosphorylation) basis, **metabolic stressors — especially febrile illness — can precipitate acute decompensation** in severe cases; a child with a *COX6A1* stop-loss variant died after a febrile illness at age 3.5 y (P 41044399). General CMT-relevant modifiers (potentially neurotoxic drugs such as vincristine, cisplatin; alcohol; vitamin B6 excess) are prudent to avoid but are not CMTRID-specific. - **Age / sex / family history:** Autosomal recessive; both sexes affected equally; positive family history and/or consanguinity increase risk.

Protective factors. None specifically established. Heterozygous carriers are clinically unaffected (recessive inheritance). No protective modifier alleles have been reported.

Gene–environment interactions. The most plausible interaction is between the **complex IV deficiency genotype and metabolic/energetic demand** (fever, catabolic stress, exercise), where increased ATP demand or mitochondrial stress may unmask or worsen the phenotype (inferred from). P 41044399 This is not yet formally quantified.

3. Phenotypes

Authoritative HPO clinical synopsis (HPO/Jax annotation network for OMIM:616039; verified iteration 3):

Phenotype	HPO term	Category
Peripheral neuropathy	**HP:0009830**	Nervous system
Distal sensory impairment	**HP:0002936**	Nervous system
Onion bulb formation (demyelination/remyelination hallmark)	**HP:0003400**	Nervous system
Hyporeflexia	**HP:0001265**	Nervous system
Areflexia	**HP:0001284**	Nervous system
Steppage gait (foot drop)	**HP:0003376**	Nervous system
Foot dorsiflexor weakness	**HP:0009027**	Limbs
Pes cavus	**HP:0001761**	Limbs
Childhood onset	**HP:0011463**	Clinical course
Slowly progressive	**HP:0003677**	Clinical course
Autosomal recessive inheritance	**HP:0000007**	Inheritance

> The co-annotation of **onion-bulb formation** (a demyelinating/remyelinating feature) with axonal signs provides the pathological basis for the **"intermediate/mixed"** electrophysiological classification.

Additional phenotype detail (from defining families and case reports;

P 25152455

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P 41044399

Phenotype	Type	HPO suggestion	Onset	Severity / Course	Frequency (in reported cases)
Distal muscle weakness & atrophy (legs > arms)	Clinical sign	HP:0007373 / HP:0009027	Childhood	Progressive	Typical / most
Distal sensory loss	Symptom/sign	HP:0002936	Childhood	Progressive	Common
Reduced/ absent deep-tendon reflexes	Clinical sign	HP:0001265 / HP:0001284	Childhood	Stable/ progressive	Common
Pes cavus / foot deformity	Physical manifestation	HP:0001761	Childhood	Progressive	Common
Steppage/gait disturbance	Symptom	HP:0003376	Childhood	Progressive	Typical
Intermediate/ mixed motor NCV + onion bulbs	Lab/ electrophysiology + pathology	HP:0003400	—	—	Defining feature
Elevated blood/CSF lactate	Lab abnormality	HP:0002151	Infancy (severe cases)	—	Severe variant (P 41044399)
Global developmental delay	Behavioral/ developmental	HP:0001263	Infancy	—	Severe variant only (P 41044399)
Neurogenic muscular atrophy	Pathology	HP:0003202	—	Progressive	Model + patients

Phenotype characteristics. - **Age of onset:** Typically **childhood** for the classic neuropathy; **infantile** (severe multisystem) presentation with the stop-loss variant (41044399). - **Severity: Variable** — from a relatively "pure" intermediate CMT to a severe infantile mitochondrial encephalo-neuropathy with fatal metabolic decompensation. - **Progression: Slowly progressive** in classic cases; **rapidly decompensating** in the severe infantile form. - **Frequency:** Given <10 reported individuals, frequencies are qualitative, not percentages.

Quality-of-life impact. No CMTRID-specific QoL data. In CMT and related rare long-term neurological conditions, HRQL is substantially reduced (mean **EQ-5D index 0.2–0.44**), with frequent pain, anxiety/depression, and problems with mobility, self-care, and usual activities (23001492).

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4. Genetic / Molecular Information

Causal gene. ***COX6A1*** (Cytochrome c Oxidase Subunit 6A1) — HGNC:2277, NCBI Gene 1337, OMIM *602072, Ensembl ENSG00000111775, chromosome 12q24.31, 3 exons; encodes an 85-aa mature protein (UniProt P12074, 12-aa mitochondrial targeting presequence) — the ubiquitous/"liver-type" isoform** of COX subunit VIa (the heart/muscle isoform is COX6A2) (7687470 ; 20307258).

Pathogenic variants (reported). | Variant (HGVS) | Type | Zygosity | Consequence | Reference | |---|---|---|---|---| | c.247-10_247-6delCACTC (intron 2) | Splice-region deletion (pyrimidine tract) | Homozygous | Aberrant splicing → reduced COX6A1 expression & COX activity | 25152455 | | c.329A>T, p.(Ter110Leuext*41)* | *Stop-loss** (missense of stop) | Homozygous | Protein +41

aa, markedly reduced protein level | P 41044399 |

- **ACMG/AMP classification:** The reported variants are **pathogenic**, supported by segregation in consanguineous families, functional assays (reduced mRNA/protein/enzyme activity), and absence from population databases (P 25152455, P 41044399).
- **Variant types:** splice-region and stop-loss; both act via **loss of function**.
- **Allele frequency:** Reported variants are **absent from gnomAD/population databases** (P 41044399), consistent with private/family-specific pathogenic alleles.
- **ClinVar landscape (queried iteration 4):** Of 50 COX6A1 ClinVar records, the vast majority are **VUS or likely-benign** missense/synonymous variants; the only "Pathogenic/Likely pathogenic" entries are large **12q24 contiguous-gene CNVs** (associated with intellectual disability), **not** COX6A1 point variants causing CMT. This confirms CMTRID alleles are private and documented chiefly in primary literature rather than variant repositories.
- **gnomAD constraint (queried iteration 4):** COX6A1 (ENSG00000111775) shows **pLI = 0.0023** and **LOEUF (oe_lof) = 0.875** (obs LoF 4 vs exp 4.57) — i.e., **heterozygous loss of function is tolerated** in the population, exactly as expected for a **recessive** disorder (carriers unaffected; two hits required).
- **Origin: Germline** (inherited recessive). No somatic role.
- **Functional consequence: Loss of function** — reduced COX6A1 protein → complex IV assembly/activity deficiency (P 25152455, P 20307258).

Modifier genes. None established. Mechanistically, **COX6A2** (heart/muscle isoform) can functionally substitute for COX6A1 in cell models (ectopic COX6A2 rescued holoenzyme and activity in COX6A1-knockdown cells;

), P 20307258 suggesting isoform expression could theoretically modify tissue vulnerability — but this is not demonstrated in patients.

Epigenetic information. No CMTRID-specific epigenetic data. *COX6A1* transcription is regulated by mitochondrial-biogenesis factors (e.g., NRF-1) and tissue-specific elements (P 7687470).

Chromosomal abnormalities. None; CMTRID is a single-gene point-variant/small-indel disorder, not a copy-number/structural syndrome. (Contrast with CMT1A, which is a 17p12/PMP22 duplication.)

Gene ontology (molecular): GO:0004129 (cytochrome-c oxidase activity, as complex), GO:0005751 (mitochondrial respiratory chain complex IV), GO:0009060 (aerobic respiration).

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5. Environmental Information

- **Environmental factors:** No environmental toxins are causal. As a mitochondrial disorder, exposure to **mitochondrial/neurotoxic agents** (e.g., certain chemotherapeutics, aminoglycosides, alcohol) is theoretically deleterious and should be avoided, though not CMTRID-specific.
- **Lifestyle factors:** No established lifestyle causes. Maintaining fitness/physiotherapy is beneficial for CMT generally; avoiding metabolic stress is prudent given OXPHOS deficiency.
- **Infectious agents:** Not causal. **Febrile/infectious illness can trigger metabolic decompensation** in the severe infantile form (P 41044399).

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6. Mechanism / Pathophysiology

Causal chain. Biallelic *COX6A1* LoF variants → reduced COX6A1 protein → **impaired assembly and reduced activity of mitochondrial complex IV (cytochrome c oxidase)** → deficient oxidative phosphorylation / ATP production and altered redox state → energetic

failure in metabolically demanding, long peripheral axons → **length-dependent axonal degeneration** (with secondary/mixed demyelinating features giving "intermediate" NCVs) → distal sensorimotor neuropathy and neurogenic muscle atrophy.

Molecular pathways / cellular processes. - **Oxidative phosphorylation / electron transport chain** (complex IV is the terminal oxidase transferring electrons to O_2). Loss of COX6A1 reduces CcO activity, lowers the enzyme's O_2 affinity, decreases holoenzyme and dimer levels, and perturbs respiratory **supercomplex** assembly (P 20307258).
- **Complex IV / supercomplex assembly** (COX6A1 is a late-assembling structural subunit) (P 20307258 ; supercomplex context P 27775717).
- Downstream: bioenergetic deficit, likely increased oxidative stress, and impaired axonal maintenance — the general theme of mitochondrial CMTs (cf. MFN2/CMT2A, GDAP1) in which axonal mitochondrial function/transport failure preferentially injures long peripheral nerves (P 32733278 P 20335458 P 33582224).

Protein dysfunction. Loss-of-function/reduced abundance of a structural subunit → **failure of complex IV holoenzyme assembly** rather than a gain-of-function or aggregation mechanism (P 25152455 P 20307258 P 41044399).

Metabolic changes. Reduced aerobic ATP synthesis; **lactic acidosis** in severe cases (elevated lactate; P 41044399), reflecting a shift to anaerobic metabolism from complex IV deficiency.

Immune system involvement. None described (non-inflammatory, non-autoimmune).

Tissue-damage mechanism. Energy-deprivation-mediated **axonal (Wallerian-like) degeneration**, most severe distally in long nerves; likely oxidative stress contribution.

Molecular profiling. Functional (not omics) evidence: reduced *COX6A1* mRNA in patient leukocytes and reduced COX activity in patient lymphoblastoid lines (P 25152455); reduced mutant protein by functional assay (P 41044399). No transcriptomic/proteomic/metabolomic dataset specific to CMTRID is published.

Upstream vs downstream. *Upstream:* COX6A1 loss → complex IV deficiency (primary). *Downstream:* bioenergetic failure → axonal degeneration → muscle denervation/atrophy → weakness, sensory loss, deformity.

Suggested ontology terms. GO:0006119 (oxidative phosphorylation), GO:0033617 (mitochondrial cytochrome c oxidase assembly), GO:0009060 (aerobic respiration), GO:0034599 (cellular response to oxidative stress), GO:0031667 (response to nutrient levels). Cell types (CL): CL:0000101 (sensory neuron), CL:0000100 (motor neuron), CL:0002573 (Schwann cell).

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7. Anatomical Structures Affected

- **Organ / system level (primary): Peripheral nervous system** — peripheral nerves (UBERON:0000010), especially long motor and sensory nerves of the limbs. Body system: nervous (peripheral).
- **Secondary:** Skeletal muscle (neurogenic atrophy; UBERON:0001134), skeleton/feet (pes cavus, deformity; UBERON:0002387 pes). In the severe infantile form, **CNS involvement** (developmental delay) and systemic metabolic derangement occur (P 41044399).
- **Tissue/cell level: Peripheral axons** (motor and sensory neurons), with mixed involvement implicating **Schwann cells/myelin** — supported by **onion-bulb formation (HP:0003400)** in the HPO synopsis, a hallmark of demyelination/remyelination that explains the

intermediate NCV. Cell Ontology: CL:0000100 (motor neuron), CL:0000101 (sensory neuron), CL:0002573 (Schwann cell).

- **Subcellular level: Mitochondrion** (GO:0005739) — specifically the **mitochondrial inner membrane** (GO:0005743) / **respiratory chain complex IV** (GO:0005751), with the protein localized to the mitochondrial inner-membrane face (UniProt P12074). Axonal mitochondria are the key affected compartment.
- **Localization / laterality:** Distal, **length-dependent** and **bilateral/symmetric** (legs affected earlier and more than arms), typical of CMT. UBERON:0002470 (pelvic limb), UBERON:0001021 (nerve).

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8. Temporal Development

- **Onset:** Usually **childhood** for the classic intermediate neuropathy; **infantile/early-childhood** with a severe multisystem phenotype in the stop-loss case (developmental delay from infancy)
(P 25152455). P 41044399
Pattern: **insidious/chronic** for the neuropathy; **acute decompensation** possible with intercurrent illness.
- **Progression: Slowly progressive** neuropathy in classic cases; **rapid decompensation and death** (age 3.5 y) reported in the severe infantile variant
(P 41044399).
Course is **chronic and lifelong**.
- **Stages:** No formal staging exists; general CMT trajectory = early (subtle distal weakness, foot deformity) → intermediate (functional gait/hand impairment, orthotic need) → advanced (marked distal atrophy, disability).
- **Patterns:** Progressive, not relapsing-remitting; no spontaneous remission. **Critical windows:** intercurrent febrile illness is a period of vulnerability for metabolic crisis in severe cases
(P 41044399).

9. Inheritance and Population

- **Inheritance: Autosomal recessive** (biallelic *COX6A1* variants) (PMID 25152455).
- **Penetrance:** Appears **complete** in biallelic individuals reported to date (small numbers). **Expressivity is variable** (mild intermediate CMT to severe infantile mitochondrial disease).
- **Genetic anticipation:** Not applicable (not a repeat-expansion disorder).
- **Germline mosaicism:** Not reported.
- **Founder effects:** None established; reported alleles are private/family-specific and absent from population databases (PMID 41044399).
- **Consanguinity: Important** — index families were consanguineous; homozygosity mapping was the discovery approach (PMID 25152455).
- **Carrier frequency:** Unknown/very low; pathogenic *COX6A1* alleles are essentially absent from gnomAD.

Epidemiology. - **Prevalence/incidence of CMTRID: Not established** — ultra-rare (<10 reported individuals). For context, all-CMT prevalence is ~1 in 2,500 (≈17–40/100,000; PMID 16775366), but CMTRID is a vanishingly small fraction. - **Populations / geography:** Reported cases include Japanese (original families; PMID 25152455) and Chinese (PMID 41044399) individuals; no ethnic predilection can be inferred from such small numbers. Recessive intermediate CMT overall is enriched in consanguineous populations. - **Sex ratio:** ~1:1 (autosomal recessive).

10. Diagnostics

Clinical / electrophysiology. - **Nerve conduction studies (NCS)/EMG:** cornerstone — reveal **intermediate motor NCV** (or mixed axonal + demyelinating) with reduced amplitudes; EMG shows chronic neurogenic changes/denervation (P 25152455 ; classification framework P 16775366). P 16775364 - **Laboratory: Elevated lactate** (blood/CSF) supports the mitochondrial/complex IV defect, particularly in severe cases (P 41044399). **Cytochrome c oxidase (COX) activity assay** in accessible tissue (lymphoblasts/fibroblasts/muscle) is reduced (P 25152455). - **Nerve/muscle biopsy (not routinely required):** neurogenic muscular atrophy; mixed axonal/demyelinating nerve pathology.

Genetic testing (definitive). - **Approach:** Because CMTRID is clinically indistinguishable from other intermediate/axonal CMTs, diagnosis rests on **molecular genetics**. Recommended: **NGS gene panel for CMT/inherited neuropathy** (including *COX6A1*), or **whole-exome/whole-genome sequencing** — the latter identified the founding variant (P 25152455). *COX6A1* is included in AR-CMT gene lists (P 26556829 lists "CMTRID/COX6A1"). - **Single-gene / targeted testing:** appropriate for at-risk relatives once a familial variant is known (cascade testing). - **CMA/karyotype/FISH/mtDNA/repeat-expansion testing:** generally **not applicable** (point/indel nuclear-gene disorder; *COX6A1* is nuclear, not mtDNA). - **Functional confirmation:** reduced *COX6A1* mRNA/protein and COX

enzyme activity support pathogenicity of novel variants (P 25152455). P 41044399

Differential diagnosis. Other intermediate/recessive CMTs — e.g., CMTRIA (*GDAP1*), CMTRIB (*KARS1*), CMTRIC (*PLEKHG5*), dominant-intermediate CMT (*DNM2*, *YARS1*, *INF2*), CMTX (*GJB1*), CMT2 subtypes, and mitochondrial neuropathies (*MFN2*/CMT2A). Distinguishing features: **elevated lactate and reduced COX activity** point toward *COX6A1*; genetics is definitive (P 16775364). P 16541790

Screening. No population/newborn screening exists for this ultra-rare disorder. **Cascade carrier testing** of relatives and **prenatal/preimplantation testing** are options once a familial variant is identified.

11. Outcome / Prognosis

- **Survival/mortality:** In classic CMT, life expectancy is generally near-normal; **however, the severe infantile *COX6A1* form can be fatal** — one child died at 3.5 y after febrile decompensation (P 41044399). No cohort mortality figures exist for CMTRID.
- **Morbidity/function:** Progressive distal weakness, sensory loss, foot deformity, gait impairment, and hand dysfunction cause **chronic disability**; substantial reduction in quality of life is expected (EQ-5D 0.2–0.44 in comparable rare neurological conditions; P 23001492).
- **Complications:** Foot ulcers/injuries from sensory loss, joint deformity, falls; in severe cases, metabolic crisis with intercurrent illness (P 41044399).

- **Recovery:** No spontaneous recovery; management is supportive and does not reverse the neuropathy.
- **Prognostic factors: Variant severity/genotype** (stop-loss with residual severe LoF and multisystem features vs milder splice variant), age of onset, presence of lactic acidosis/CNS involvement, and metabolic stability appear prognostically relevant (inferred from

P 25152455

vs 41044399).

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12. Treatment

No disease-modifying/approved therapy exists for CMTRID. Management is **symptomatic and supportive**, mirroring general CMT care (P 40014417).

- **Pharmacotherapy:** No targeted drug. Symptomatic management of **neuropathic pain** (e.g., gabapentinoids, duloxetine, tricyclics — NCIT clinical-intervention terms apply generically). **Avoid neurotoxic drugs** (vincristine and other CMT-hazardous agents).
- **Mitochondrial/supportive measures (rational, not proven for CMTRID):** aggressive management of intercurrent illness/fever, avoidance of catabolic/metabolic stress; "mitochondrial cocktail" supplements (e.g., riboflavin, coenzyme Q10, L-carnitine) are sometimes used empirically in complex IV deficiency but lack CMTRID-specific evidence.
- **Advanced therapeutics (investigational for CMT generally, none CMTRID-specific):** gene therapy/gene silencing, HDAC6 inhibitors, and metabolic agents are in trials for other CMT subtypes; govorestat (CMT-SORD) may become the first approved CMT drug (P 40014417). None target *COX6A1*.
- **Clinical-trial status (verified iteration 5):** A ClinicalTrials.gov API query returned **0 studies** mentioning *COX6A1*; no interventional or observational trial specifically addresses CMTRID. Patients may be eligible for general CMT natural-history/registry studies.
- **Surgical/interventional:** orthopedic correction of foot deformities (e.g., osteotomy, tendon transfer) as needed.

- **Supportive/rehabilitative (mainstay): physical therapy, occupational therapy, ankle-foot orthoses (AFOs), assistive devices, foot care, exercise**, and multidisciplinary support improve function and QoL
(P 40014417).
- **Treatment outcomes:** Supportive care improves function/QoL but does not alter the underlying neurodegeneration.

Suggested NCIT terms: Physical Therapy (C15327), Occupational Therapy (C15243), Orthotic Device (C50077), Supportive Care (C15417), Genetic Counseling (C15391).

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13. Prevention

- **Primary prevention:** No way to prevent occurrence in a conceived biallelic individual; **prevention is reproductive/genetic** — carrier identification, genetic counseling, and reproductive options (prenatal diagnosis, PGT) for at-risk couples (especially consanguineous families) (rationale: recessive inheritance,
P 25152455).
- **Secondary prevention:** Early diagnosis (NCS + genetics) enables timely orthotics, physiotherapy, and surveillance; in severe/infantile cases, **early recognition and aggressive management of febrile illness** to prevent metabolic decompensation
(P 41044399).
- **Tertiary prevention:** Prevent complications — foot-care programs to avert ulcers, fall-prevention, contracture prevention via therapy, deformity correction.
- **Immunization/public health/prophylaxis:** No vaccine or specific prophylaxis. Standard immunizations to reduce febrile illnesses may be prudent in severe cases (supportive rationale).
- **Counseling: Genetic counseling** is central — recurrence risk 25% for siblings of an affected child of carrier parents; carrier testing of relatives.

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14. Other Species / Natural Disease

- **Taxonomy:** *Homo sapiens* (NCBI Taxon **9606**). Experimental model: *Mus musculus* (NCBI Taxon **10090**).
- **Orthologous genes:** Mouse *Cox6a1* (NCBI Gene **12861**, **MGI:103099**; verified via mygene.info); *COX6A1* is highly conserved across mammals (bovine gene characterized in (P 7687470).
- **Natural disease in other species: No naturally occurring COX6A1-related CMT is documented in companion animals or wildlife** (OMIA search yields no established entry for this specific gene/phenotype as of this report). Inherited neuropathies do occur in dogs, but a *COX6A1* etiology is not established.
- **Comparative biology:** Complex IV/OXPHOS machinery is evolutionarily conserved from yeast to mammals, so the bioenergetic mechanism is broadly translatable; the *Cox6a1*-null mouse reproduces reduced COX activity and neurogenic muscular atrophy (P 25152455).
- **Zoonotic potential:** None (non-infectious genetic disease).

15. Model Organisms

- **Primary model — *Cox6a1*-null mouse (mammalian, knockout):** shows **significantly reduced COX activity and neurogenic muscular atrophy leading to difficulty walking**, recapitulating the core neuromuscular phenotype and confirming causality (P 25152455).

> *"Cox6a1-null mice showed significantly reduced COX activity and neurogenic muscular atrophy leading to a difficulty in walking"* (P 25152455).

- **Cellular / in vitro models:**

- Patient-derived **EBV-transformed lymphoblastoid cell lines** (reduced COX activity) and **peripheral leukocytes** (reduced *COX6A1* expression) (P 25152455).
- **HEK-293 RNAi knockdown** of *COX6A1*: reduced CcO activity, decreased holoenzyme/dimer, accumulation of assembly subcomplexes, altered supercomplexes; rescued by COX6A2 (P 20307258).
- Transfected cell lines demonstrating reduced mutant protein for novel variants (P 41044399).
- **Model characteristics:** The knockout mouse **recapitulates** COX deficiency and neurogenic atrophy/gait impairment. **Limitations:** murine models may not fully capture the human "intermediate" NCV pattern or the severe multisystem/lactic-acidosis infantile phenotype; small patient numbers limit genotype-phenotype modeling.
- **Applications:** Study of complex IV assembly, axonal bioenergetics, and preclinical testing of mitochondrial-supportive or gene-based therapies.
- **Resources:** MGI (mouse *Cox6a1*), IMPC/KOMP for engineered alleles, Cellosaurus for patient lines.

Supported and Refuted Hypotheses

Supported: 1. **CMTRID is caused by biallelic loss-of-function *COX6A1* variants** (splice-region deletion; stop-loss) — supported by linkage (LOD 4.23), WGS/WES, segregation, functional assays, and a knockout mouse (P 25152455, P 41044399).
2. **The mechanism is mitochondrial complex IV (cytochrome c oxidase) deficiency** impairing OXPHOS and causing length-dependent axonal degeneration (P 25152455, P 20307258).

3. **The phenotypic spectrum is variable**, extending from intermediate/axonal CMT to a severe infantile mitochondrial disease with developmental delay and lactic acidosis (P 41044399).

Refuted / not supported: - CMTRID is **not** a demyelinating-only or dominant disorder; **not** a chromosomal/CNV syndrome; **not** infectious/autoimmune. No founder effect or common population allele underlies it.

Limitations and Future Directions

- **Very small evidence base** (<10 individuals) → epidemiology, penetrance, natural history, and prognosis are poorly quantified.
- **No omics datasets** (transcriptomic/proteomic/metabolomic) specific to CMTRID; mechanistic detail beyond complex IV assembly is inferred.
- **No targeted therapy or clinical trials** for *COX6A1* CMT.
- **Future work:** patient registries; iPSC-derived motor/sensory neuron models; systematic genotype-phenotype correlation; testing of mitochondrial-support and gene-based therapies; clarification of why COX6A2 isoform substitution does not fully protect peripheral nerve in patients.

Key References

- P 25152455
  — Tamiya et al. 2014. *A mutation of COX6A1 causes a recessive axonal or mixed form of Charcot-Marie-Tooth disease.* (Founding gene-discovery study + Cox6a1-null mouse.)
- P 41044399
  — Cai et al. 2026. *A novel homozygous COX6A1 variant causes axonal CMT, developmental delays and mitochondrial dysfunction.* (First stop-loss variant; phenotype expansion.)
- P 20307258
  — Fornuskova et al. 2010. *Assembly and function of human nuclear-encoded COX subunits 4, 5a, 6a, 7a, 7b.* (COX6A1 in complex IV assembly; COX6A2 rescue.)

- P 7687470 — Smith & Lomax 1993. *Structural organization of the COX6A gene.* (Gene structure/regulation.)
- P 26556829 — Montecchiani et al. 2016. (Lists CMTRID/COX6A1 among AR-CMT genes.)
- P 16775366 / **16775364** — Houlden & Reilly 2006; Pareyson et al. 2006. (CMT classification, intermediate CMT concept, prevalence.)
- P 40014417 — De Grado et al. 2025. *CMT clinical developments and management — 2025.* (Management/therapeutic landscape.)
- P 23001492 — Calvert et al. 2013. (QoL/EQ-5D in CMT and rare neurological conditions.)
- P 27775717 — Cogliati et al. 2016. (Complex III–IV supercomplex assembly context.)