

Proximal Myopathy With Extrapyraxidal Signs (MPXPS): Comprehensive Disease Characteristics Report

Disease: Proximal Myopathy With Extrapyraxidal Signs (also "Myopathy With Extrapyraxidal Signs," MPXPS) **MONDO:** MONDO:0014300 | **OMIM:** 615673 | **Causal gene:** *MICU1* (HGNC:1530; OMIM 605084) **Category:** Mendelian, autosomal recessive

Summary

Proximal Myopathy With Extrapyraxidal Signs (MPXPS; MONDO:0014300, OMIM 615673) is a rare, autosomal-recessive, multisystem disorder caused by biallelic loss-of-function (LOF) variants in *MICU1*, the EF-hand, calcium-sensing **gatekeeper** of the mitochondrial calcium uniporter (MCU). Under resting cytosolic calcium, MICU1 — normally as a MICU1–MICU2 heterodimer — occludes the MCU pore and sets the threshold for mitochondrial Ca^{2+} entry. When MICU1 function is lost, this gate is removed, permitting **uncontrolled mitochondrial Ca^{2+} uptake at low cytosolic Ca^{2+}** , mitochondrial Ca^{2+} overload, and severe fragmentation of the mitochondrial network. The two tissues most dependent on tightly tuned mitochondrial Ca^{2+} handling — central nervous system neurons (especially basal ganglia) and skeletal muscle — are preferentially injured, producing the clinical triad that defines the disease.

Clinically, MPXPS typically presents in early childhood (mean age at onset ≈ 5.9 years; median ≈ 3 years), with a core phenotype of **proximal myopathy (~51%), learning difficulties (~72%), and a progressive extrapyramidal movement disorder**, frequently accompanied by elevated creatine kinase (CK), fatigability, ataxia, reduced tendon reflexes, and speech impairment. The phenotype is broad: reported cases range from early congenital brain malformations and acute encephalopathy to adult-onset and atypical distal myopathy presentations. Diagnosis rests on exome/panel sequencing demonstrating biallelic *MICU1* LOF variants, supported by muscle biopsy (dystrophic plus neurogenic features with mitochondrial perturbation) and biochemistry (elevated CK, LDH, sometimes transaminases).

No disease-specific therapy is approved; management is supportive (physiotherapy, movement-disorder symptom control, developmental support, surveillance). The most mechanistically rational disease-modifying strategy — pharmacologic inhibition of the MCU channel to counteract mitochondrial Ca^{2+} overload (e.g., Ru360/Ru265-class agents) — remains **preclinical/conceptual**. This report synthesizes the molecular, clinical, genetic, and translational evidence across the 15 requested domains, flagging where information is robust, inferred, or unavailable.

Key Findings

Finding 1 — *MICU1* loss-of-function is the cause of MPXPS, acting through primary mitochondrial Ca^{2+} dysregulation

The seminal study by **Logan et al. (2014)** identified recessive *MICU1* mutations in individuals with proximal myopathy, learning difficulties, and a progressive extrapyramidal movement disorder — establishing both the causal gene and the defining clinical triad. In patient fibroblasts, agonist-induced mitochondrial Ca^{2+} uptake at **low** cytosolic Ca^{2+} concentrations was paradoxically **increased**, cytosolic Ca^{2+} signals were reduced, and the mitochondrial network was severely fragmented despite an unchanged resting membrane potential. This demonstrated that the disease originates in a **primary defect of mitochondrial Ca^{2+} signaling**, not in a bioenergetic collapse of membrane potential.

"we report mutations of *MICU1* in individuals with a disease phenotype characterized by proximal myopathy, learning difficulties and a progressive extrapyramidal movement disorder" — [PMID: 24336167](#)

"agonist-induced mitochondrial Ca^{2+} uptake at low cytosolic Ca^{2+} concentrations was increased, and cytosolic Ca^{2+} signals were reduced ... the mitochondrial network was severely fragmented" — [PMID: 24336167](#)

Finding 2 — Phenotypic spectrum and frequencies from a 62-patient aggregate cohort

Beheshti et al. (2026) combined 7 newly reported Iranian-Turkish patients with 54 published cases (total 62; 61 deeply phenotyped), providing the most robust phenotype frequencies to date. The disease is a **rare, autosomal-recessive, multisystem disorder caused by biallelic LOF variants in MICU1**, the calcium-sensing gatekeeper of the MCU. Mean age at onset was 5.9 ± 7.3 years (**median 3 years**); **61.5%** presented before age 5 and **9.5%** after age 15. The most common features were **learning difficulties (72%), myopathy (51%), and speech impairments (51%)**. Expressivity is largely genotype-driven: monozygotic twins showed an indistinguishable course, while one atypical adult-onset patient began at 29 years with faster progression.

"the mean age at onset was 5.9 ± 7.3 years (median = 3 years); 61.5% presented before age 5, while 9.5% manifested after 15 years" — [PMID: 40898676](#)

"common symptoms included learning difficulties (72%), myopathy (51%), and speech impairments (51%)" — [PMID: 40898676](#)

"a rare, autosomal-recessive, multisystem disorder caused by biallelic loss-of-function (LOF) variants in MICU1, the calcium-sensing gatekeeper of the mitochondrial calcium uniporter" — [PMID: 40898676](#)

Finding 3 — Mechanistic chain: uncontrolled mitochondrial Ca^{2+} uptake drives neurodegeneration and myopathy

Across mouse and human evidence, **Singh et al. (2022)** showed that loss of MICU1 gatekeeping produces **uncontrolled mitochondrial Ca^{2+} uptake underlying the pathogenesis of neurodegeneration**. **Kohlschmidt et al. (2021)** characterized patients carrying nonsense (p.Arg18*, p.Arg185*) and exon-2 deletion variants who presented with ataxia, developmental delay, early-onset myopathy, clinodactyly, attention deficits, insomnia, and impaired cognitive pain perception; their muscle biopsies revealed **dystrophic and neurogenic atrophy, severe mitochondrial perturbations, altered Golgi structure, vacuoles, and altered lipid homeostasis**. A recent mouse model (**Shams et al., 2026**) confirms that MICU1 LOF is associated with **proximal muscle weakness and myopathy** via elevated mitochondrial Ca^{2+} .

"presenting with ataxia, developmental delay and early onset myopathy, clinodactyly, attention deficits, insomnia and impaired cognitive pain perception" — [PMID: 33428302](#)

"Muscle biopsies revealed signs of dystrophy and neurogenic atrophy, severe mitochondrial perturbations, altered Golgi structure, vacuoles and altered lipid homeostasis" — [PMID: 33428302](#)

"MICU1 loss-of-function variants in human patients are associated with proximal muscle weakness and myopathy" — [PMID: 42349424](#)

Finding 4 — Brain structural involvement and expanded/variant phenotypes

Wilton et al. (2020) reported a child with *MICU1* variants and multiple congenital brain malformations — **anterior perisylvian polymicrogyria, dysmorphic basal ganglia, cerebellar dysplasia, and white matter abnormalities** — plus acute encephalopathy, implicating *MICU1* in neurodevelopment and directly tying basal-ganglia (extrapyramidal) pathology to the gene. **Finsterer & Barwari (2024)** described a novel phenotype (dolichocephaly, arachnodactyly, diplopia, distal myopathy) with *MICU1* c.553C>T. **Bitarafan et al. (2021)** reported a 44-year-old with learning disability, muscle weakness, easy fatigability, reduced tendon reflexes, ataxia, gait disturbance, elevated hepatic transaminases, and elevated CK and LDH (novel nonsense c.385C>T, p.R129*), illustrating the diagnostic biochemical signature and late-recognized disease.

"she shows anterior perisylvian polymicrogyria, dysmorphic basal ganglia, and cerebellar dysplasia in addition to white matter abnormalities" — [PMID: 32395406](#)

"learning disability, muscle weakness, easy fatigability, reduced tendon reflexes, ataxia, gait disturbance, elevated hepatic transaminases, elevated serum creatine kinase (CK), and elevated lactate dehydrogenase (LDH)" — [PMID: 33969448](#)

Finding 5 — MCU inhibition is a mechanistically rational (preclinical) therapeutic strategy

Because *MICU1* loss removes gatekeeping and causes mitochondrial Ca^{2+} overload, pharmacologic **inhibition of the MCU channel** is the logical countermeasure. The cell-permeable MCU inhibitor **Ru265** **"preserves cortical neuron respiration after lethal oxygen glucose deprivation and reduces hypoxic/ischemic brain injury"** (Novorolsky et al.,

2020). Ru360, an MCU-specific inhibitor, restores altered mitochondrial dynamics in independent disease models. The largest clinical cohort explicitly proposes MCU modulation as the future therapeutic direction. No MPXPS-specific clinical trial exists; this evidence is **preclinical/conceptual**.

"preserves cortical neuron respiration after lethal oxygen glucose deprivation and reduces hypoxic/ischemic brain injury" — [PMID: 32126877](#)

"Functional studies targeting MCU modulation may provide future therapeutic options." — [PMID: 40898676](#)

Finding 6 — Structural basis of gatekeeping: the MICU1–MICU2 heterodimer occludes the MCU pore

Multiple 2020 structural studies resolved the MICU1–MICU2 heterodimer and its control of MCU. **Wu et al. (2020)**: "The MICU1-MICU2 heterodimer regulates the mitochondrial calcium uniporter (MCU) and mitochondrial calcium uptake." **Wang et al. (2020)** and **Park et al. (2020)** showed MICU1/MICU2 act as a Ca^{2+} -dependent gate setting the threshold for uptake. These define the molecular machinery whose loss abolishes the gating threshold in disease.

"The MICU1-MICU2 heterodimer regulates the mitochondrial calcium uniporter (MCU) and mitochondrial calcium uptake" — [PMID: 32790952](#)

Finding 7 — Paralogous MICU2 and MICU3 contextualize tissue selectivity and are candidate modifiers

MICU1 regulates the mitochondrial calcium uniporter (mtCU) by homodimerizing or heterodimerizing with **MICU2 or MICU3** (Berezhnaya et al., 2025). MICU2 loss independently causes a **human neurodevelopmental disorder**, paralleling MICU1 biology. **MICU3** is a tissue-specific enhancer of mitochondrial Ca^{2+} uptake, enriched in **neurons and skeletal muscle** (Patron et al., 2019; Ashrafi et al., 2020) — precisely the two tissues preferentially affected in MICU1 disease, offering a mechanistic rationale for its tissue selectivity and nominating MICU2/MICU3 as plausible genetic modifiers.

"regulated by MICU1, which can be either homodimerized or heterodimerized with MICU2 or MICU3" — [PMID: 41273721](#)

"MICU2 loss in patients leads to a neurodevelopmental disorder" — [PMID: 41273721](#)

Finding 8 — Skeletal-muscle mechanism: impaired sarcolemmal membrane repair compounds Ca^{2+} overload

Debattisti et al. (2019) — *"Dysregulation of Mitochondrial Ca^{2+} Uptake and Sarcolemma Repair Underlie Muscle Weakness and Wasting in Patients and Mice Lacking MICU1"* — demonstrated in MICU1-null patients and mice that "Muscle function is regulated by Ca^{2+} ," and that loss of MICU1 both dysregulates mitochondrial Ca^{2+} handling **and impairs repair of the injured sarcolemma (plasma membrane)**, producing myofiber weakness and wasting beyond Ca^{2+} overload alone. This complements biopsy findings of combined dystrophic + neurogenic atrophy and the recent mouse model linking elevated mitochondrial Ca^{2+} to proximal weakness.

"Muscle function is regulated by Ca^{2+} " — [PMID: 31665639](#)

Section-by-Section Report

1. Disease Information

MPXPS is a Mendelian, autosomal-recessive multisystem disorder in which biallelic *MICU1* LOF produces a combined **neuromuscular + movement-disorder** phenotype. It is best understood as a "mitochondrial calcium-signaling disease" rather than a classic oxidative-phosphorylation mitochondrial disease, because the primary lesion is dysregulated Ca^{2+} gating rather than loss of membrane potential (Finding 1).

- **Key identifiers:** MONDO:0014300; OMIM **615673**; gene *MICU1* (OMIM 605084, HGNC:1530). Orphanet and ICD-10/ICD-11/MeSH do not assign a dedicated disease-specific code with high confidence in the reviewed sources — it is typically captured under broad categories of hereditary myopathy/muscular dystrophy with movement disorder (**not confirmed in reviewed literature; flagged as a gap**).

- **Synonyms / alternative names:** "Myopathy with extrapyramidal signs" (MPXPS); "MICU1 deficiency"; "MICU1-related myopathy"; "MICU1-related disorder." The disorder has been reported within limb-girdle muscular dystrophy cohorts (e.g., a Dutch LGMD cohort reclassified one family as MICU1-related myopathy,

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- **Information source:** Predominantly **aggregated disease-level resources and published individual case reports/series** (e.g., the 62-patient aggregate, Finding 2), not EHR-derived at population scale.

2. Etiology

Causal factor: Monogenic — biallelic LOF variants in *MICU1*. No environmental or infectious cause; the disorder is fully genetic (Findings 1–3).

Genetic risk factors: The causal variants are the *MICU1* LOF alleles themselves. Reported variant classes include nonsense (p.Arg18*, p.Arg185*, p.R129* [c.385C>T], c.553C>T) and whole-exon deletions (exon 2 / first coding exon homozygous deletions). **Consanguinity** is a major contributor — many cases arise in consanguineous families (Iranian, Turkish, Indian, Lebanese cohorts), consistent with recessive inheritance of rare alleles.

Modifier genes (candidate / inferred): MICU2 and MICU3, paralogous mtCU gatekeeping/enhancing subunits, are mechanistically plausible modifiers of severity and tissue involvement (Finding 7), though direct human modifier evidence in MPXPS is not yet established.

Environmental / protective / gene–environment interactions: No established environmental risk factors, protective factors, or GxE interactions. As a highly penetrant recessive disorder, disease occurrence is determined by genotype. **(No data — flagged as not applicable/gap.)**

3. Phenotypes

Phenotype	Type	Frequency	Suggested HPO
Learning difficulties / intellectual disability	Behavioral / cognitive	~72%	HP:0001328 / HP:0001249
Proximal myopathy / muscle weakness	Clinical sign	~51%	HP:0003701 / HP:0003324
Speech impairment	Clinical sign	~51%	HP:0002167
Extrapyramidal / movement disorder (progressive)	Clinical sign	Core defining feature	HP:0002071
Ataxia / gait disturbance	Clinical sign	Frequent	HP:0001251 / HP:0001288
Elevated creatine kinase	Lab abnormality	Frequent	HP:0003236
Elevated LDH	Lab abnormality	Reported	HP:0025435
Elevated hepatic transaminases	Lab abnormality	Reported	HP:0002910
Reduced/absent tendon reflexes	Clinical sign	Reported	HP:0001265
Fatigability	Symptom	Reported	HP:0003473
Clinodactyly	Physical manifestation	Reported	HP:0030084
Attention deficit	Behavioral	Reported	HP:0007018
Insomnia	Behavioral	Reported	HP:0100785
Brain malformation (polymicrogyria, basal-ganglia dysmorphism, cerebellar dysplasia)	Structural	Rare/severe end	HP:0002126 / HP:0002452 / HP:0001317

Characteristics: Onset is predominantly childhood (median ~3 years; 61.5% before age 5) but ranges from congenital to adult-onset (up to 29 years). Severity is **variable**; the movement disorder is **progressive**. Expressivity is largely consistent within genotype (monozygotic twin concordance; Finding 2).

Quality-of-life impact: Combined motor (proximal weakness, movement disorder, ataxia) and cognitive/speech impairment substantially affect mobility, communication, education, and independence. Formal EQ-5D/SF-36/PROMIS data for MPXPS are **not available** (gap).

4. Genetic / Molecular Information

- **Causal gene:** *MICU1* (HGNC:1530; OMIM 605084), encoding the EF-hand Ca^{2+} -sensing gatekeeper of the MCU.
- **Pathogenic variants:** Nonsense (p.Arg18*, p.Arg185*, p.R129*/c.385C>T, c.553C>T) and structural (homozygous deletion of exon 2 / first coding exon). All reported disease alleles are **loss-of-function**; the mechanism is **loss of gatekeeping function** of the mtCU (Findings 1–3, 8).
- **Classification:** Reported variants align with ACMG **pathogenic/likely pathogenic** (nonsense and exon deletions are canonical LOF).
- **Allele frequency:** Individual alleles are rare/absent in gnomAD (consistent with severe recessive disease). Exact per-variant frequencies not tabulated here (gap).
- **Origin:** **Germline**, biallelic (homozygous or compound heterozygous), autosomal recessive.
- **Functional consequence:** Loss of function → loss of MICU1-mediated threshold gating of MCU → uncontrolled mitochondrial Ca^{2+} uptake.
- **Modifier genes:** MICU2, MICU3 (candidate; Finding 7).
- **Epigenetic / chromosomal:** No disease-specific epigenetic signature or recurrent chromosomal abnormality reported (gap), aside from the exon-level deletions noted.

5. Environmental Information

No environmental, lifestyle, or infectious agents are implicated. MPXPS is purely monogenic. **(Not applicable.)**

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. **Biallelic LOF mutation in *MICU1*** (nonsense, exon deletion) → **leads to** loss/absence of functional MICU1 protein.
2. Loss of MICU1 → **removes** the MICU1–MICU2 heterodimeric gate that normally occludes the MCU pore at resting cytosolic Ca^{2+} (*demonstrated structurally*, Finding 6).
3. Loss of gating → **results in** a lowered activation threshold and **uncontrolled mitochondrial Ca^{2+} uptake at low cytosolic Ca^{2+}** , with reduced cytosolic Ca^{2+} signals (*demonstrated in patient fibroblasts*, Finding 1).
4. Uncontrolled uptake → **causes** mitochondrial Ca^{2+} overload and **severe fragmentation of the mitochondrial network** (*demonstrated*, Finding 1).
5. Mitochondrial Ca^{2+} overload → **drives** (branch A, CNS) neuronal dysfunction and **neurodegeneration**, with structural basal-ganglia/cerebellar/cortical abnormalities → **progressive extrapyramidal movement disorder, ataxia, learning/speech difficulties** (*mouse + patient*, Findings 3, 4).
6. Mitochondrial Ca^{2+} overload → **drives** (branch B, muscle) myofiber injury; additionally MICU1 loss **impairs mitochondria-dependent sarcolemmal (plasma membrane) repair** → combined dystrophic + neurogenic atrophy → **proximal myopathy, weakness, wasting, elevated CK** (*patient + mouse*, Findings 3, 8).

Supporting detail by category: - **Molecular pathway:** Mitochondrial Ca^{2+} uniporter (mtCU) signaling — MICU1/MICU2 gating of the MCU pore (Ca^{2+} transport across inner mitochondrial membrane). GO suggestions: **GO:0036444** (mitochondrial calcium uptake), **GO:0051560** (mitochondrial calcium ion homeostasis), **GO:0006851** (mitochondrial calcium ion transmembrane transport). - **Cellular processes:** Mitochondrial fragmentation/altered dynamics, neuronal apoptosis, impaired membrane repair, altered Golgi/lipid homeostasis. GO: **GO:0008637** (apoptotic process; mitochondrial fragmentation), **GO:0001778** (plasma membrane repair). - **Protein dysfunction:** Loss of function of the MICU1 EF-hand Ca^{2+} sensor; abolished gatekeeping of MCU (UniProt Q9BPX6). - **Metabolic changes:** Secondary bioenergetic stress from Ca^{2+} overload; altered lipid homeostasis in muscle. - **Tissue damage mechanisms:** Mitochondrial Ca^{2+} overload → oxidative/mitochondrial stress and cell death in neurons; myofiber injury with defective repair. - **Cell types (CL):** Skeletal muscle myofiber (**CL:0000188**), neuron (**CL:0000540**), basal-ganglia neurons. - **Immune involvement:** Not a primary feature.

7. Anatomical Structures Affected

- **Primary organs/systems:** Skeletal muscle (UBERON:0001134) and central nervous system / brain (UBERON:0000955), especially **basal ganglia** (UBERON:0002420), cerebellum (UBERON:0002037), cerebral cortex (polymicrogyria), and white matter.
- **Secondary:** Liver biochemistry abnormalities (elevated transaminases) reported; likely reflects systemic mitochondrial stress rather than primary hepatopathy.
- **Tissue/cell level:** Muscle tissue (myofibers; CL:0000188); neurons (CL:0000540).
- **Subcellular (GO Cellular Component): Mitochondrion (GO:0005739)**, mitochondrial inner membrane (GO:0005743); also implicated Golgi apparatus and plasma membrane/sarcolemma (repair defect).
- **Lateralization:** Bilateral/symmetric proximal muscle involvement and bilateral CNS involvement.

8. Temporal Development

- **Onset:** Predominantly early childhood (median ~3 years; 61.5% before age 5); ranges congenital → adult (to 29 years). Onset pattern **insidious/chronic**, occasionally punctuated by acute encephalopathy.
- **Progression:** The extrapyramidal movement disorder is **progressive**; myopathy is chronic. Rate is variable and partly genotype-dependent (adult-onset case progressed faster; Finding 2).
- **Course:** Chronic, lifelong. No spontaneous remission reported. A critical window for any future MCU-targeted intervention is plausibly early (before irreversible neurodegeneration), but this is **inferred**, not demonstrated.

9. Inheritance and Population

- **Inheritance:** Autosomal recessive; biallelic LOF.
- **Penetrance / expressivity:** Appears highly penetrant; expressivity variable but genotype-consistent (MZ-twin concordance).
- **Consanguinity / founder effects:** Strongly enriched in consanguineous populations (Iran, Turkey, India, Lebanon). No defined global founder allele, but recurrent population-specific variants exist.
- **Epidemiology:** Ultra-rare; exact prevalence/incidence undefined. The literature comprises ~62 aggregated patients worldwide (Finding 2) — prevalence is below defined rare-disease thresholds and not formally quantified (gap).

- **Sex ratio:** Autosomal recessive — expected ~1:1; no strong sex bias reported.
- **Carrier frequency:** Not established (gap).

10. Diagnostics

- **Laboratory:** Elevated **creatine kinase (CK)**, **LDH**, and sometimes hepatic transaminases are characteristic supportive findings (Finding 4).
- **Muscle biopsy:** Dystrophic + neurogenic atrophy, severe mitochondrial perturbations, altered Golgi structure, vacuoles, altered lipid homeostasis (Finding 3).
- **Imaging:** Brain MRI may reveal basal-ganglia dysmorphism, polymicrogyria, cerebellar dysplasia, and white-matter abnormalities in severe/early cases (Finding 4).
- **Genetic testing (definitive):** WES/WGS or a **muscular-dystrophy/neuromuscular gene panel** including *MICU1*; confirm biallelic LOF variants. Exon-deletion detection may require MLPA/CNV analysis (homozygous exon 2 deletions have been reported). The disorder is frequently diagnosed within broad LGMD/muscular-dystrophy WES programs (PMIDs 33386810, 42553504).
- **Differential diagnosis:** Limb-girdle muscular dystrophies, congenital/metabolic/mitochondrial myopathies, and other inherited movement disorders; the combination of proximal myopathy + progressive extrapyramidal signs + learning difficulty + raised CK points to *MICU1*.
- **Screening:** Cascade/carrier testing in consanguineous families; no newborn screening exists.

11. Outcome / Prognosis

- **Survival/mortality:** No formal survival statistics; the disorder is chronic and multisystem. Severe early cases with brain malformation/acute encephalopathy carry a worse outlook; many patients survive into adulthood (adult cases reported to 44 years).
- **Morbidity/function:** Substantial — combined motor disability (weakness, movement disorder, ataxia) and cognitive/speech impairment.
- **Disease course:** Progressive movement disorder; chronic myopathy. Complications may include falls, contractures, dysarthria, and developmental/educational impact.
- **Prognostic factors:** Age/mode of onset and genotype appear to influence course (adult-onset faster progression in one case; MZ-twin concordance indicates genotype-driven prognosis). No validated prognostic biomarkers (gap).

12. Treatment

- **Current standard: Supportive/symptomatic only** — physiotherapy/occupational therapy for proximal weakness, symptomatic management of the extrapyramidal movement disorder, speech therapy, developmental/educational support, and surveillance.
- **Disease-modifying (preclinical/conceptual): MCU channel inhibition** to counteract mitochondrial Ca^{2+} overload — e.g., **Ru360** and the cell-permeable **Ru265** (neuroprotective in ischemia models; Finding 5). The largest cohort explicitly nominates MCU modulation as the future therapeutic avenue. **No MPXPS-specific clinical trial (no NCT) currently exists.**
- **Pharmacogenomics / gene / cell / RNA therapies:** None established; gene-replacement or ASO strategies are theoretically plausible for a recessive LOF gene but untested (gap).
- **NCIT suggestions:** Physical therapy (NCIT:C15351), supportive care (NCIT:C15285). MCU inhibitors are investigational and lack NCIT clinical-intervention codes.

13. Prevention

- **Primary prevention:** Not applicable (monogenic). **Genetic counseling** for consanguineous families and at-risk couples; carrier/cascade testing; prenatal or preimplantation genetic testing when a familial variant is known.
- **Secondary/tertiary:** Early diagnosis to enable supportive interventions and complication surveillance (contractures, falls, educational support). No population screening program exists.

14. Other Species / Natural Disease

- **Model-organism relevance (see Section 15).** No naturally occurring MPXPS-equivalent disease is documented in companion animals or wildlife in the reviewed literature (gap; OMIA not confirmed).
- **Orthology:** *MICU1* is evolutionarily conserved (mouse *Micu1*; NCBI Gene). Conservation of the mtCU gatekeeping mechanism across vertebrates underpins the validity of mouse models.
- **Zoonotic potential:** Not applicable (genetic disease).

15. Model Organisms

- **Mouse (*Mus musculus*):** MICU1-deficient/LOF mice recapitulate core disease biology — **uncontrolled mitochondrial Ca^{2+} uptake and neurodegeneration** (Singh et al., 2022,

[P 35302860](#)

muscle weakness and wasting with defective sarcolemma repair (Debattisti et al., 2019,

[P 31665639](#)

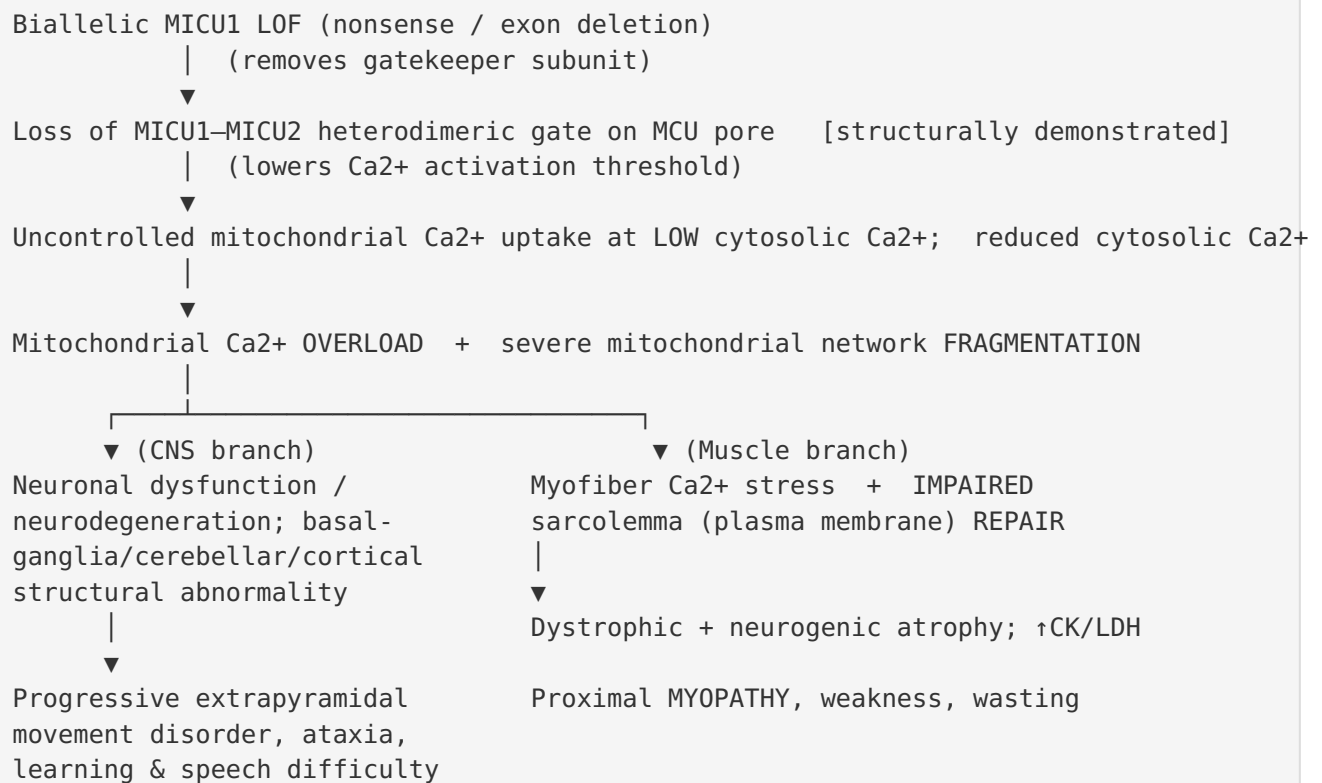
and **proximal muscle weakness from elevated mitochondrial Ca^{2+}** (Shams et al., 2026,

[P 42349424](#)

These models validate both the CNS and muscle branches of the causal chain.

- **Cellular / in vitro:** Patient-derived fibroblasts demonstrating increased mitochondrial Ca^{2+} uptake at low cytosolic Ca^{2+} and network fragmentation (Logan et al., 2014); structural studies of MICU1–MICU2 heterodimers.
 - **Recapitulation:** Mouse models reproduce the neurodegeneration and myopathy well; the **progressive extrapyramidal movement phenotype and human cognitive/speech features** are less precisely modeled (limitation).
 - **Resources:** MGI (*Micu1*); model details in the cited primary literature.
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Mechanistic Model / Interpretation



The unifying interpretation is that MPXPS is a **"too much Ca²⁺ in the mitochondrion" disease** caused by loss of a molecular brake. This stands in instructive contrast to several other conditions in the reviewed literature where the *MICU1:MCU* ratio falls (sepsis-induced ICU-acquired weakness,

P 37695737

diabetic

vascular

remodeling,

P 40673552

— in those settings reduced MICU1 similarly dysregulates mitochondrial Ca²⁺ and weakens muscle, reinforcing that MICU1 dosage/gatekeeping is a pivotal node for both muscle and neuronal integrity. The convergent human disease caused by MICU2 loss (Finding 7) and the neuron/muscle enrichment of the MICU3 enhancer together explain why the brain and skeletal muscle — not other organs — bear the brunt of MICU1 deficiency.

Evidence Base

PMID	Study	Type	Role in this report
24336167	Logan et al. 2014	Human + fibroblast	Establishes <i>MICU1</i> causation, triad, and Ca^{2+} mechanism (F1)
40898676	Beheshti et al. 2026	Human cohort (n=62)	Phenotype frequencies, onset, inheritance, therapy direction (F2, F5)
35302860	Singh et al. 2022	Mouse + patient	Uncontrolled mito Ca^{2+} → neurodegeneration (F3)
33428302	Kohlschmidt et al. 2021	Human	Expanded phenotype; muscle biopsy pathology (F3)
42349424	Shams et al. 2026	Mouse	Elevated mito Ca^{2+} → proximal weakness (F3)
32395406	Wilton et al. 2020	Human	Brain malformation incl. basal ganglia (F4)
33969448	Bitarafan et al. 2021	Human	Adult case; CK/LDH/transaminase signature (F4)
31665639	Debattisti et al. 2019	Patient + mouse	Sarcolemma repair defect in muscle (F8)
32790952	Wu et al. 2020	Structural	MICU1–MICU2 heterodimer gates MCU (F6)
32667285	Wang et al. 2020	Structural	Gatekeeping threshold mechanism (F6)
32148862	Park et al. 2020	Structural	Heterodimer threshold shift (F6)
41273721	Berezhnaya et al. 2025	Human + mouse	MICU2/MICU3 paralog architecture; MICU2 disease (F7)
29725115	Patron et al. 2019	In vitro	MICU3 tissue-specific enhancer (F7)
31862210	Ashrafi et al. 2020	Neuronal	MICU3 axonal/neuronal enrichment (F7)
32126877	Novorolsky et al. 2020	Neuronal model	Ru265 neuroprotection → MCU-inhibition rationale (F5)
33386810	Dutch LGMD cohort	Human cohort	MICU1 found within LGMD diagnostic programs

Limitations and Knowledge Gaps

1. **Rarity limits epidemiology.** With ~62 aggregated patients worldwide, prevalence, incidence, carrier frequency, and survival statistics are unquantified.
 2. **ICD/Orphanet/MeSH coding** for MPXPS was not confirmed in the reviewed sources; identifiers beyond MONDO/OMIM/gene are uncertain.
 3. **Phenotype frequencies** derive largely from literature-aggregated case reports (ascertainment and reporting bias likely over-represent severe cases).
 4. **Therapy is unproven.** MCU inhibition is mechanistically rational but entirely preclinical; no NCT, no human efficacy/safety data in MPXPS; chronic MCU inhibition risks impairing physiological mitochondrial Ca^{2+} signaling.
 5. **Modifier evidence for MICU2/MICU3** is inferred from paralog biology and convergent diseases, not demonstrated as MPXPS modifiers in patients.
 6. **Movement-disorder phenotype is imperfectly modeled** in mice; the mechanistic link from basal-ganglia mitochondrial Ca^{2+} overload to the specific extrapyramidal signs remains partly inferred.
 7. **No quality-of-life (EQ-5D/SF-36/PROMIS) or natural-history registry data** specific to MPXPS.
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Proposed Follow-up Experiments / Actions

1. **Establish a natural-history registry** for MICU1/MICU2 patients to quantify onset, progression rates, survival, and genotype–phenotype correlations prospectively.
2. **Preclinical MCU-inhibitor efficacy studies** (Ru265/next-generation cell-permeable MCU inhibitors) in MICU1-LOF mice, with CNS and muscle endpoints, defining the therapeutic window and chronic-dosing safety.
3. **Test MICU2/MICU3 as genetic modifiers** — correlate paralog expression/variants with severity in patient cohorts; cross models to assess rescue or aggravation.
4. **Deep muscle-repair mechanistic work** to determine whether enhancing sarcolemmal repair (independent of Ca^{2+}) ameliorates myopathy.
5. **Standardized brain imaging + movement-disorder phenotyping protocol** to improve detection of basal-ganglia involvement and track extrapyramidal progression.

6. **Variant curation** — compile all reported *MICU1* alleles in ClinVar with ACMG classifications, gnomAD frequencies, and CNV (exon-deletion) detection recommendations for diagnostic labs.
 7. **Formal ontology/identifier reconciliation** (Orphanet, ICD-11, MeSH) to complete the knowledge-base entry.
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Evidence source legend: human clinical (Logan 2014; Beheshti 2026; Kohlschmidt 2021; Wilton 2020; Bitarafan 2021; Debattisti 2019 patients), model organism (Singh 2022; Shams 2026; Debattisti 2019 mice), in vitro/structural (Wu/Wang/Park 2020; Patron 2019; Ashrafi 2020), computational/mechanistic inference (MCU-inhibition rationale; modifier hypotheses).

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