

FDX2-Related Mitochondrial Myopathy (MEOAL) — Comprehensive Disease Report

Disease: FDX2-Related Mitochondrial Myopathy **Primary synonym:** MEOAL — *Mitochondrial myopathy, Episodic, with or without Optic Atrophy and reversible Leukoencephalopathy*
MONDO: MONDO:0020714 · **OMIM:** #251900 · **Gene:** FDX2 (alias FDX1L), 19p13.2 **Category:** Mendelian (autosomal recessive)

Autonomous literature-based research report. Evidence types indicated as: [HUMAN] clinical case/cohort; [IN VITRO] cell/biochemistry; [MODEL] model organism; [COMP] computational/database.

Summary

FDX2-Related Mitochondrial Myopathy, catalogued as **MEOAL (OMIM #251900; MONDO:0020714)**, is an ultra-rare autosomal-recessive inborn error of mitochondrial metabolism caused by biallelic loss-of-function variants in **FDX2 (FDX1L)** on chromosome 19p13.2. FDX2 encodes **mitochondrial ferredoxin-2**, a small [2Fe-2S] electron-transfer protein that serves as the dedicated electron donor for **iron-sulfur (Fe-S) cluster biogenesis**. When FDX2 function is lost, cells cannot efficiently assemble [2Fe-2S] and [4Fe-4S] clusters, crippling every Fe-S-dependent enzyme — most importantly respiratory chain complexes I, II and III, and the TCA-cycle enzyme aconitase. The downstream consequence is mitochondrial energy (ATP) failure accompanied by disordered cellular iron homeostasis and mitochondrial iron overload.

Clinically, the disease presents in childhood with **optic atrophy and nystagmus (by age ~3)**, followed within the first and second decades by an **episodic/progressive myopathy** featuring exercise intolerance, cramps, myalgia, and recurrent crises that can escalate to **severe rhabdomyolysis (CK up to ~320,000 U/L)**, **lactic acidosis**, and **acute kidney injury**. A **sensorimotor axonal neuropathy** and **reversible (or partially reversible) leukoencephalopathy** on MRI complete the characteristic multisystem picture. Muscle biopsy

shows a distinctive pattern of regional succinate dehydrogenase (complex II) and cytochrome c oxidase deficiency with iron accumulation. The disorder is genetically and biochemically related to, but distinct from, other Fe-S/ISC-biogenesis diseases such as FDXR-related neuropathy, ISCU myopathy, and Friedreich ataxia (FXN).

There is **no disease-specific or curative therapy**. Management is supportive and follows general mitochondrial-cytopathy principles: trigger avoidance (fasting, fever, intercurrent illness), graded low-intensity aerobic/resistance exercise, aggressive hydration and renal protection during rhabdomyolysis crises, empirical "mitochondrial cocktail" supplements, and genetic counseling for affected families. The evidence base is derived almost entirely from a small number of consanguineous/founder families plus mechanistic work in human cells, yeast (*Yah1*), and structural biology (cryo-EM of the ferredoxin-ISC complex); no dedicated vertebrate animal model of FDX2 disease has yet been published.

Key Findings

Finding 1 — Biallelic FDX2 (FDX1L) variants cause autosomal-recessive MEOAL [HUMAN]

FDX2-related disease is a classic Mendelian autosomal-recessive condition. The gene was first implicated by Spiegel and colleagues in 2014, who used **exome sequencing combined with homozygosity mapping** in a consanguineous family with adolescent-onset mitochondrial myopathy and identified a homozygous **c.1A>T** variant that disrupts the ATG start codon of FDX1L/FDX2 ([PMID: 24281368](#)). The abstract states: *"We employed exome sequencing combined with homozygosity mapping to identify a homozygous mutation, c.1A>T, in the FDX1L gene, which encodes the mitochondrial ferredoxin 2 (Fdx2) protein."*

Subsequent families confirmed the gene and broadened the allelic spectrum: a recurrent homozygous missense **c.431C>T (p.Pro144Leu / P144L)** was reported in **six patients from two unrelated Brazilian families** ([PMID: 30010796](#); mechanism in [PMID: 39467201](#), which notes *"the homozygous mutation c.431C>T (p.P144L) described in six patients from two unrelated families"*). A homozygous splice variant **c.200+4A>G** was described in a pediatric multiorgan case ([PMID: 41372147](#)), and an additional homozygous case presented with severe rhabdomyolysis ([PMID: 37565517](#)). The consistent requirement for two defective alleles, the frequent consanguinity, and the unaffected heterozygous parents all confirm recessive inheritance.

Finding 2 — Pathomechanism: FDX2 deficiency impairs Fe-S cluster biogenesis, disabling Fe-S-dependent respiratory complexes and aconitase [HUMAN / IN VITRO]

The core lesion is a failure of **iron-sulfur cluster assembly**. In patient skeletal muscle, FDX2 loss severely impairs the activities of the **Fe-S-dependent respiratory complexes I, II and III and mitochondrial aconitase** (PMID: 24281368: "*severely impaired activities of iron sulfur (Fe-S)-dependent complexes I, II and III and mitochondrial aconitase*"). FDX2 is the electron donor that promotes assembly of both **[2Fe-2S]** and **[4Fe-4S]** clusters (PMID: 39467201).

Structural work has defined precisely how FDX2 acts within the biogenesis machinery. Cryo-EM shows FDX2 binds the **core ISC complex (ISCU2–NFS1–ISD11/LYRM4–ACP1)** and **competes with frataxin (FXN) for overlapping binding sites**, delivering electrons to the nascent cluster (PMID: 39632806: "*FDX2 and FXN compete for overlapping binding sites*"). Patient cells carrying the c.200+4A>G splice allele show **impaired mitochondrial respiration, defects in many Fe-S proteins, enhanced mitochondrial iron accumulation, and reduced SOD2** (PMID: 41372147), tying the molecular defect directly to multisystem energy failure and redox imbalance.

Finding 3 — Clinical phenotype: childhood optic atrophy, episodic myopathy, neuropathy, reversible leukoencephalopathy [HUMAN]

The best-characterized cohort (two Brazilian families, 6 patients) defines the syndrome: **optic atrophy and nystagmus developing by age 3**, followed by **myopathy with recurrent episodes of cramps, myalgia and muscle weakness in the first or second decade**, a **sensory-motor axonal neuropathy** with progressive distal weakness, and a **reversible/partially reversible leukoencephalopathy** on MRI (PMID: 30010796: "*a complex neurological phenotype involving optic atrophy and nystagmus developing by age 3, followed by myopathy and recurrent episodes of cramps, myalgia and muscle weakness in the first or second decade of life*").

Muscle histopathology is distinctive: "*Muscle biopsy demonstrated an unusual pattern of regional succinate dehydrogenase and cytochrome c oxidase deficiency with iron accumulation*" (PMID: 30010796). Acute metabolic crises can be life-threatening: one patient showed **CK up to ~320,000 U/L, lactate 22.3 mmol/L, and acute kidney injury** during a rhabdomyolysis episode (PMID: 37565517), and multiorgan involvement has been documented in pediatric disease (PMID: 41372147).

Finding 4 — FDX2 is functionally distinct from FDX1 (adrenodoxin) [IN VITRO]

Humans possess **two mitochondrial ferredoxins**. RNAi depletion established that **FDX2 — not FDX1 — is essential for heme A and Fe/S protein biosynthesis**, whereas FDX1 (adrenodoxin) reduces P450 enzymes for steroidogenesis (PMID: 20547883: *"we identified a Fdx1-related mitochondrial protein, designated ferredoxin 2 (Fdx2) and found it to be essential for heme A and Fe/S protein biosynthesis"*). FDX2 cannot efficiently reduce P450s or convert steroids, explaining why FDX2 patients have a mitochondrial Fe-S disease rather than a steroidogenic disorder.

Crucially, FDX2 deficiency deranges iron homeostasis: *"Fdx2 deficiency had a severe impact, via impaired Fe/S protein biogenesis, on cellular iron homeostasis, leading to increased cellular iron uptake and iron accumulation in mitochondria"* (PMID: 20547883). Both ferredoxins receive electrons from the single ferredoxin reductase **FDXR** (NADPH → FDXR → FDX) (PMID: 28747430).

Finding 5 — Genomic/constraint data confirm a LoF-tolerant, recessive gene [COMP]

FDX2 (ENSG00000267673) maps to **chr19:10,310,045–10,316,015 (cytoband 19p13.2)**. gnomAD constraint metrics indicate the gene is **tolerant of heterozygous loss-of-function**: **pLI = 0.0006**, observed/expected LoF (oe_lof) = 0.70 (90% CI 0.46–1.12), missense oe = 0.95, mis_z = 0.34. This LoF-tolerance is exactly what is expected for an autosomal-recessive disorder in which single-allele carriers are unaffected and two defective alleles are required to produce disease. The protein (UniProt **Q6P4F2**, FDX2_HUMAN) is a **186-amino-acid mitochondrial [2Fe-2S] ferredoxin** with an N-terminal mitochondrial targeting presequence.

Finding 6 — Differential diagnosis: FDX2 disease within the ISC-biogenesis disorder spectrum [HUMAN]

FDX2 disease belongs to a broader family of **mitochondrial Fe-S/ISC-biogenesis disorders** with overlapping clinical features. The most important differential is **FDXR** (the upstream electron donor to FDX2), whose biallelic mutations cause auditory neuropathy and optic atrophy with mitochondrial iron overload (PMID: 28965846: *"FDXR encodes the mitochondrial ferredoxin reductase, the sole human ferredoxin reductase implicated in the biosynthesis of iron-sulfur clusters (ISCs) and in heme formation"*). Other differentials include **ISCU** (hereditary

myopathy with exercise intolerance / Swedish myopathy, with similar SDH/aconitase deficiency), **FXN** (Friedreich ataxia), and **NFU1/BOLA3/ISCA2/IBA57** (multiple mitochondrial dysfunctions syndrome with glycine elevation).

A pragmatic diagnostic strategy for suspected mitochondrial disease combines biochemical markers (plasma/CSF lactate, alanine, proline) and neuroimaging to predict disease, then applies **first-line clinical exome sequencing**, reserving muscle biopsy for urgent or inconclusive cases ([PMID: 34056100](#): *"apply first-line clinical exome sequencing to identify a definite diagnosis"*).

Finding 7 — Model organisms: yeast *Yah1* is the key ortholog; no dedicated vertebrate model [MODEL / IN VITRO]

The *S. cerevisiae* ortholog of FDX2 is **Yah1** (yeast adrenodoxin homolog). Yah1 depletion causes a strong decrease in de novo Fe/S cluster synthesis on the scaffold Isu1p ([PMID: 12970193](#): *"Depletion of the cysteine desulfurase Nfs1p, the ferredoxin Yah1p or the yeast frataxin homologue Yfh1p by regulated gene expression causes a strong decrease in the de novo synthesis of Fe/S clusters on Isu1p"*). The Yah1–Arh1 ferredoxin/ferredoxin-reductase pair is essential for heme A biosynthesis and FeSC assembly ([PMID: 15211518](#)). No dedicated mouse or zebrafish model of FDX2 disease has been published; mechanistic insight derives from RNAi knockdown in human cells, patient-derived fibroblasts/myoblasts, yeast complementation, and recombinant-protein biophysics/cryo-EM. The pathway framework is summarized by Braymer & Lill, who note *"some 30 proteins involved in the synthesis of cellular [2Fe-2S] and [4Fe-4S] clusters and their incorporation into numerous apoproteins"* ([PMID: 28615445](#)).

Finding 8 — Treatment is supportive/symptomatic; no curative therapy [HUMAN]

No gene-specific or curative treatment exists. Management follows general mitochondrial-cytopathy principles. **Endurance exercise training** increases VO₂max, respiratory chain enzyme activity, muscle strength, and quality of life, and is well tolerated ([PMID: 25008908](#): *"Endurance exercise training increases Vo2 max, respiratory chain enzyme activity, and improves quality of life."*). Patients are advised to avoid exercise during metabolic stress: *"not exercise on days they have fever, superimposed illness, muscle pain, or cramps, and/or if they have fasted for more than 12 hours"* ([PMID: 25008908](#)). Cochrane review found no evidence of harm from moderate training in muscle disease ([PMID: 20091552](#)); creatine monohydrate gives mixed/modest benefit in mitochondrial cytopathies ([PMID: 18652078](#)). Acute rhabdomyolysis crises require aggressive IV hydration and renal protection ([PMID: 37565517](#)).

Finding 9 — Verified identifiers [COMP]

EBI OLS4 confirms MONDO:0020714 = "**mitochondrial myopathy, episodic, with optic atrophy and reversible leukoencephalopathy**" (MEOAL), cross-referenced to OMIM:251900, GARD:0025221, MedGen:1679560 (UMLS C5193223).

The 15-Section Disease Knowledge Report

1. Disease Information

FDX2-Related Mitochondrial Myopathy (MEOAL) is an ultra-rare, autosomal-recessive mitochondrial disorder of **iron-sulfur cluster biogenesis**. It manifests as a multisystem neuromuscular syndrome combining optic atrophy, episodic/progressive myopathy with exercise intolerance and rhabdomyolysis, axonal neuropathy, and reversible leukoencephalopathy.

Key identifiers:

Resource	Identifier
MONDO	MONDO:0020714
OMIM	#251900
GARD	0025221
MedGen	1679560
UMLS	C5193223
Gene (HGNC)	FDX2 (alias FDX1L)
UniProt	Q6P4F2 (FDX2_HUMAN)
Ensembl	ENSG00000267673
ICD-10	G71.3 (mitochondrial myopathy, NEC) — closest applicable; no FDX2-specific code
ICD-11	8C73 / 5C53.1 (disorders of mitochondrial energy metabolism) — closest applicable

Synonyms / alternative names: MEOAL; mitochondrial myopathy, episodic, with optic atrophy and reversible leukoencephalopathy; FDX1L-related mitochondrial myopathy; ferredoxin-2 deficiency.

Information source: Disease-level, derived from aggregated case reports and small consanguineous/founder families (individual patient genotype–phenotype correlations) plus mechanistic in vitro and model-organism data — not from large EHR cohorts.

2. Etiology

Causal factor (genetic): Biallelic loss-of-function or hypomorphic variants in **FDX2/FDX1L**. Reported variants include start-loss **c.1A>T** ([PMID: 24281368](#)), missense **c.431C>T (p.P144L)** ([PMID: 30010796](#)), and splice **c.200+4A>G** ([PMID: 41372147](#)).

Genetic risk factors: The disease is monogenic; "risk" is fully determined by biallelic FDX2 genotype. **Consanguinity** and **founder effects** (e.g., the recurrent Brazilian p.P144L allele) are the principal population-level risk contexts.

Environmental risk factors: None cause the disease, but environmental/metabolic stressors act as **crisis triggers** — fasting (>12 h), fever, intercurrent infection, and strenuous exercise can precipitate rhabdomyolysis and metabolic decompensation ([PMID: 25008908](#); [PMID: 37565517](#)).

Protective factors: No specific genetic or environmental protective alleles are established. Trigger avoidance is protective against acute crises.

Gene–environment interactions: The underlying genetic Fe-S/energy deficit interacts with metabolic demand — energy-stress states (fasting, fever, exertion) unmask or worsen the biochemical defect, producing the episodic phenotype.

3. Phenotypes

Phenotype	Type	Onset	Severity / course	Frequency	Suggested HPO
Optic atrophy	Clinical sign	Early childhood (~age 3)	Progressive	Characteristic (majority)	HP:0000648
Nystagmus	Clinical sign	Early childhood	Stable/ progressive	Frequent	HP:0000639
Exercise intolerance	Symptom	1st–2nd decade	Episodic	Characteristic	HP:0003546
Myalgia / muscle cramps	Symptom	1st–2nd decade	Episodic	Frequent	HP:0003326 / HP:0003394
Muscle weakness (myopathy)	Clinical sign	1st–2nd decade	Progressive	Characteristic	HP:0003198
Rhabdomyolysis	Lab/clinical	Episodic (crises)	Severe when present	Reported (subset)	HP:0003201
Elevated creatine kinase	Lab abnormality	During crises	Severe (up to ~320,000 U/L)	Frequent in crises	HP:0003236
Lactic acidosis / elevated lactate	Lab abnormality	During crises	Severe (up to 22.3 mmol/L)	Frequent	HP:0003128
Sensorimotor axonal neuropathy	Clinical sign	Childhood–adolescence	Progressive, distal	Characteristic	HP:0007141
Reversible leukoencephalopathy	Imaging/lab	Variable	Reversible/ partially reversible	Characteristic	HP:0002352
Acute kidney injury	Lab/clinical	During rhabdomyolysis crises	Severe	Subset	HP:0001919

Quality-of-life impact: Progressive visual loss (optic atrophy), muscle weakness and exercise intolerance, and neuropathy impair mobility, education/employment, and independence. Acute crises are life-threatening and require hospitalization. Formal QoL instrument data (EQ-5D/SF-36) specific to FDX2 disease are not available given the rarity.

4. Genetic / Molecular Information

Causal gene: FDX2 (FDX1L), 19p13.2, ENSG00000267673; UniProt Q6P4F2; 186-aa mitochondrial [2Fe-2S] ferredoxin with N-terminal targeting presequence.

Pathogenic variants (ACMG-consistent, germline, homozygous in reported cases):

Variant (cDNA)	Protein	Class	Consequence	Reference
c.1A>T	start-loss (p.Met1?)	Pathogenic	Loss of function (no initiation)	PMID: 24281368
c.431C>T	p.Pro144Leu	Likely pathogenic/ Pathogenic	Missense, impaired function (founder, Brazil)	PMID: 30010796 , PMID: 39467201
c.200+4A>G	splice (exon 2 skip → 19 aa replaced by 21)	Pathogenic	Aberrant splicing, low FDX2 protein	PMID: 41372147

Allele frequency: All reported pathogenic variants are rare/private; FDX2 is LoF-tolerant in gnomAD (pLI = 0.0006; oe_lof = 0.70). **Origin:** germline (no somatic disease role). **Functional consequence:** loss of function — reduced protein level and/or impaired electron-donor activity. Notably, the P144L and c.200+4A>G mutant proteins may retain near-normal structure, implicating reduced abundance/activity rather than gross misfolding ([PMID: 41372147](#); [PMID: 39467201](#)).

Modifier genes / epigenetics / chromosomal abnormalities: None established; no large-scale structural variants reported.

5. Environmental Information

Not a primary driver of this monogenic disease. **Non-genetic triggers** of acute metabolic crises include fasting, fever, intercurrent illness, and strenuous/eccentric exercise. **No infectious agent** causes the disease (though infection/fever can precipitate crises). No toxic or occupational exposures are implicated.

6. Mechanism / Pathophysiology

Ordered causal chain:

1. **Biallelic FDX2/FDX1L loss-of-function variant** (c.1A>T start-loss, p.P144L missense, or c.200+4A>G splice) → reduced level/activity of mitochondrial ferredoxin-2 protein.
2. Reduced FDX2 **leads to** loss of the dedicated [2Fe-2S] electron donor within the core ISC assembly complex (ISCU2–NFS1–ISD11/LYRM4–ACP1), where FDX2 normally competes with frataxin for binding and feeds electrons to the nascent cluster ([PMID: 39632806](#)).
3. Loss of electron donation **results in** defective de novo assembly of **[2Fe-2S] and [4Fe-4S]** clusters on the scaffold (inferred from patient cells + yeast Yah1 depletion; [PMID: 41372147](#), [PMID: 12970193](#)).
4. Fe-S deficiency **leads to** loss of activity of Fe-S-dependent apoproteins — **respiratory complexes I, II, III and aconitase** ([PMID: 24281368](#)).
5. **Branch A (bioenergetic)**: Respiratory chain failure **results in** impaired oxidative phosphorylation and ATP deficit → exercise intolerance, myopathy, rhabdomyolysis, lactic acidosis.
6. **Branch B (iron homeostasis)**: Impaired Fe-S biogenesis is sensed as cellular iron deficiency (via IRP/IRE), **leading to** increased iron uptake and **mitochondrial iron overload** ([PMID: 20547883](#)); biopsy shows iron accumulation ([PMID: 30010796](#)).
7. **Branch C (heme A / redox)**: FDX2 loss impairs heme A biosynthesis (COX maturation) ([PMID: 20547883](#)) and reduces SOD2, **resulting in** altered ROS handling ([PMID: 41372147](#)).
8. Combined energy failure, iron overload, and redox imbalance in high-demand post-mitotic tissues (retinal ganglion cells/optic nerve, skeletal muscle, peripheral nerve, CNS white matter) **leads to** the clinical manifestations: optic atrophy, episodic myopathy/rhabdomyolysis, axonal neuropathy, and reversible leukoencephalopathy.

Molecular pathways: Mitochondrial ISC assembly pathway (NFS1/ISCU2/ISD11/ACP1/frataxin/ferredoxin); oxidative phosphorylation; TCA cycle (aconitase); heme A biosynthesis; cellular iron regulation (IRP1/IRP2–IRE). **Cellular processes (GO)**: iron-sulfur cluster assembly

(GO:0016226), [2Fe-2S] assembly (GO:0044571), mitochondrial electron transport (GO:0006120), cellular iron ion homeostasis (GO:0006879), oxidative stress response. **Protein dysfunction:** Loss of function — reduced abundance and/or electron-transfer capacity (not primarily aggregation). **Metabolic changes:** Impaired OXPHOS/ATP output, lactate accumulation, mitochondrial iron overload, reduced heme A. **Tissue damage mechanisms:** Bioenergetic failure + oxidative stress + iron-mediated injury in energy-demanding tissues. **Immune involvement:** None established (not autoimmune/inflammatory).

7. Anatomical Structures Affected

- **Organ/system level:** Nervous system (optic nerve/retinal ganglion cells, peripheral nerves, CNS white matter), musculoskeletal (skeletal muscle). Secondary: kidney (acute kidney injury during rhabdomyolysis).
- **Tissue/cell level:** Skeletal muscle fibers (CL:0000188 skeletal muscle cell / UBERON:0001134); retinal ganglion cells (CL:0000740); peripheral neurons/axons (CL:0000101 sensory neuron); CNS white matter / oligodendrocytes and myelin (UBERON:0002316).
- **Subcellular level (GO Cellular Component):** Mitochondrion (GO:0005739), mitochondrial matrix (GO:0005759), mitochondrial inner membrane/respiratory chain (GO:0005743).
- **Localization (UBERON):** skeletal muscle organ (UBERON:0001134), optic nerve (UBERON:0000941), peripheral nerve (UBERON:0001021), cerebral white matter (UBERON:0002437). **Lateralization:** bilateral/symmetric (optic atrophy, leukoencephalopathy, myopathy).

8. Temporal Development

- **Onset:** Pediatric. Optic atrophy/nystagmus by ~age 3; myopathy in the first-to-second decade. Onset of visual signs is insidious; muscle crises are acute/episodic.
- **Progression:** Chronic and progressive baseline course (progressive myopathy, distal neuropathy, optic atrophy) **punctuated by acute episodic crises** (rhabdomyolysis, metabolic decompensation). Leukoencephalopathy is notable for being **reversible/partially reversible**.
- **Patterns:** Episodic crises can resolve with supportive care; some white-matter changes reverse. **Critical periods** for intervention are the peri-crisis windows (prompt hydration/renal protection) and trigger avoidance. Lifelong, chronic disorder.

9. Inheritance and Population

- **Inheritance:** Autosomal recessive (biallelic FDX2). Unaffected heterozygous carriers.
- **Epidemiology:** Ultra-rare; fewer than ~15 genetically confirmed patients reported worldwide. No reliable prevalence/incidence estimates (Orphanet prevalence "unknown/<1/1,000,000").
- **Penetrance/expressivity:** Appears high penetrance in biallelic individuals; variable expressivity/severity across variants and families.
- **Anticipation:** Not applicable (not a repeat-expansion disorder).
- **Founder effects/consanguinity:** The p.P144L allele is a recurrent founder variant in Brazilian families; consanguinity underlies several reports. Carrier frequency not established but low (LoF-tolerant, rare alleles).
- **Demographics:** Reported in consanguineous Middle Eastern and Brazilian families; no strong sex predilection reported. Age distribution: pediatric onset with lifelong course.

10. Diagnostics

- **Laboratory:** Elevated serum/plasma **lactate** (markedly during crises, up to 22.3 mmol/L), elevated **creatine kinase** (up to ~320,000 U/L in rhabdomyolysis), elevated alanine; renal function monitoring during crises ([PMID: 37565517](#)).
- **Biopsy/histopathology:** Characteristic **regional succinate dehydrogenase (complex II) and cytochrome c oxidase deficiency with iron accumulation** on muscle biopsy ([PMID: 30010796](#)); reduced Fe-S-dependent complex I/II/III and aconitase activities ([PMID: 24281368](#)).
- **Imaging:** Brain MRI showing reversible/partially reversible leukoencephalopathy; MR spectroscopy may show a lactate peak.
- **Electrophysiology:** Nerve conduction studies/EMG consistent with sensorimotor axonal neuropathy; myopathic EMG features.
- **Genetic testing (definitive):** **Clinical exome/whole-exome sequencing** is first-line for suspected mitochondrial disease ([PMID: 34056100](#)); mitochondrial nuclear-gene panels including FDX2/FDX1L, or single-gene/targeted testing; homozygosity mapping is valuable in consanguineous families ([PMID: 24281368](#)). RNA/functional studies help classify splice variants ([PMID: 41372147](#)).
- **Differential diagnosis:** FDXR-related auditory neuropathy + optic atrophy ([PMID: 28965846](#)); ISCU myopathy (exercise intolerance); FXN/Friedreich ataxia; NFU1/BOLA3/

ISCA2/IBA57 multiple mitochondrial dysfunctions syndrome; other complex I–IV deficiencies and mtDNA disorders.

- **Screening:** No population newborn screening. **Cascade/carrier testing** in affected families and genetic counseling are appropriate.

11. Outcome / Prognosis

- **Survival/mortality:** No formal survival statistics. The chronic course is compatible with survival into adulthood, but **acute rhabdomyolysis crises with lactic acidosis and acute kidney injury are potentially life-threatening** (PMID: 37565517).
- **Morbidity/disability:** Progressive visual impairment (optic atrophy), muscle weakness/exercise intolerance, and distal sensorimotor neuropathy produce cumulative disability. Leukoencephalopathy may be reversible.
- **Disease course:** Chronic-progressive with superimposed episodic crises; recovery from individual crises is possible with supportive care.
- **Prognostic factors:** Severity/frequency of metabolic crises, degree of multiorgan involvement, and specific variant (residual FDX2 function) likely influence outcome. No validated prognostic biomarkers beyond lactate/CK trends.

12. Treatment

No curative or disease-specific therapy exists. Management is supportive (NCIT: Supportive Care, C15277):

- **Acute crisis management:** Aggressive **IV hydration** and renal protection for rhabdomyolysis; treat lactic acidosis; monitor/support kidney function (PMID: 37565517).
- **Exercise/rehabilitation (NCIT: Exercise Therapy, C16586):** Graded **endurance + resistance training** improves VO₂max, respiratory enzyme activity, strength, and QoL; start low-intensity and avoid exercising during fever, illness, muscle pain/cramps, or after fasting >12 h (PMID: 25008908). Cochrane: no evidence of harm from moderate training (PMID: 20091552).
- **Supplements (empirical "mitochondrial cocktail"):** CoQ10/ubiquinone, riboflavin, L-carnitine, antioxidants — no FDX2-specific trial evidence. Creatine monohydrate gives mixed/modest benefit (PMID: 18652078).
- **Trigger avoidance:** Avoid prolonged fasting, manage fever/illness promptly, pace activity.
- **Genetic counseling** for families.

- **Advanced/experimental therapeutics:** No gene therapy, RNA therapy, or targeted therapy in trials for FDX2 disease to date. **Pharmacogenomics:** none established.

13. Prevention

- **Primary prevention:** Not preventable at the individual level (monogenic). **Genetic counseling, carrier/cascade testing, prenatal/preimplantation genetic diagnosis** can prevent recurrence in at-risk families — especially relevant where consanguinity/founder alleles (p.P144L) are present.
- **Secondary prevention:** Early molecular diagnosis (exome-first) enables early supportive management and crisis-prevention education.
- **Tertiary prevention:** Trigger avoidance, prompt crisis management (hydration/renal protection), graded exercise, and multidisciplinary follow-up to limit complications.
- **Immunization/public health/environmental interventions:** Not applicable beyond general infection-prevention to reduce fever-triggered crises.

14. Other Species / Natural Disease

- **Taxonomy/orthologs:** Human FDX2 (NCBI Gene ID 614650). Functional ortholog in *Saccharomyces cerevisiae* (NCBI Taxon 4932) is **Yah1** (yeast adrenodoxin homolog), partnered with reductase Arh1 ([PMID: 12970193](#); [PMID: 15211518](#)). Mammalian orthologs exist (mouse *Fdx2*, *Mus musculus* NCBI Taxon 10090).
- **Natural disease in animals:** No naturally occurring FDX2 disease reported in companion animals or wildlife (no OMIA entry identified).
- **Comparative biology/conservation:** The ferredoxin-dependent ISC assembly pathway is **highly evolutionarily conserved** from yeast to humans, which is why Yah1 depletion recapitulates the core Fe-S assembly defect ([PMID: 12970193](#); [PMID: 28615445](#)).
- **Zoonotic/transmission:** Not applicable (genetic disease).

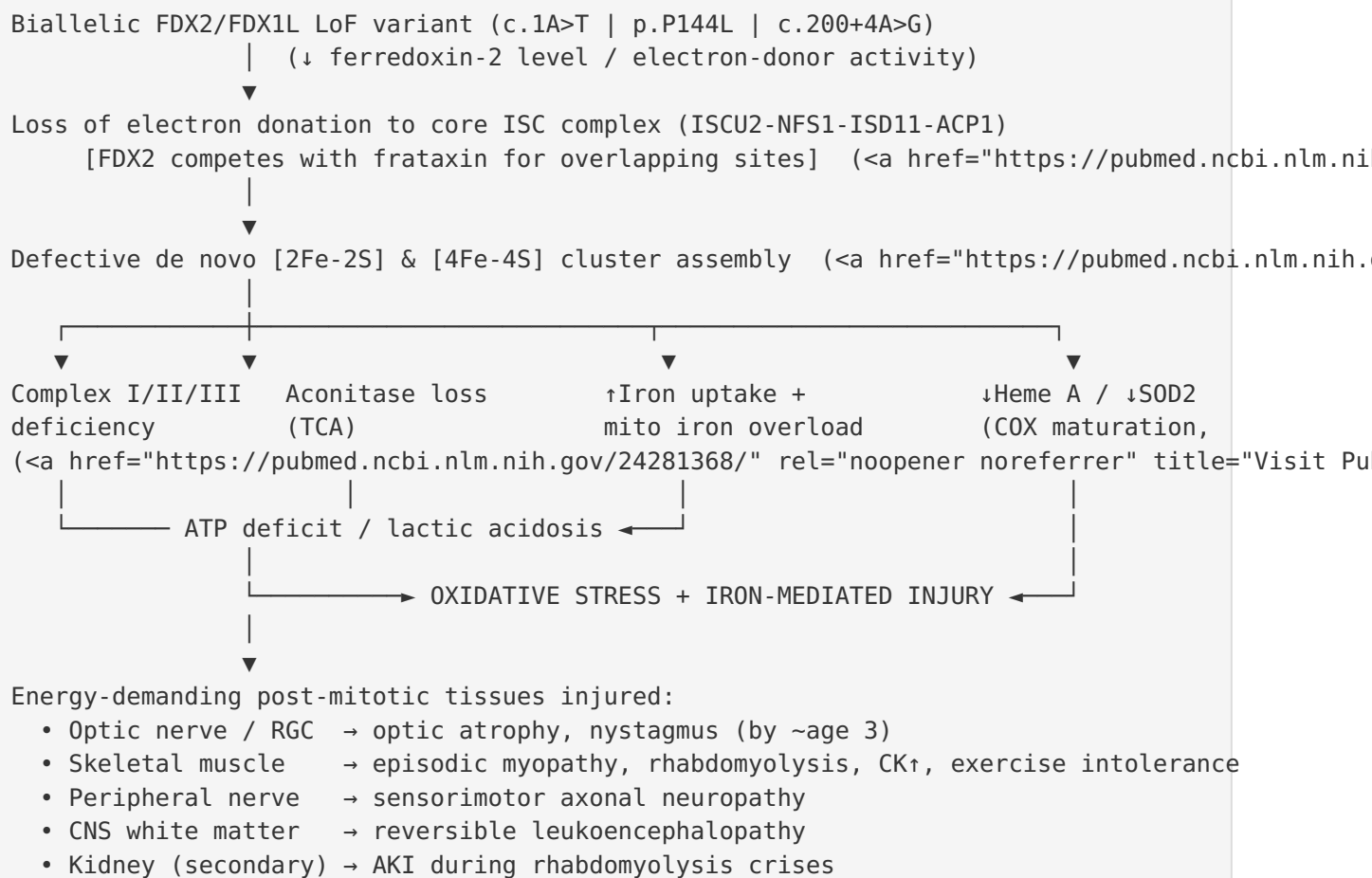
15. Model Organisms

- **Yeast (*S. cerevisiae*):** **Yah1** depletion is the principal genetic model, demonstrating that the ferredoxin is essential for de novo Fe-S cluster synthesis on Isu1p ([PMID: 12970193](#)) and for heme A biosynthesis with Arh1 ([PMID: 15211518](#)).
- **Human cell systems:** RNAi/CRISPR knockdown in human cells established FDX2's specific role in heme A and Fe/S biosynthesis and its iron-homeostasis phenotype ([PMID: 20547883](#));

patient-derived fibroblasts/myoblasts show impaired respiration, multiple Fe-S defects, mitochondrial iron accumulation, and reduced SOD2 (PMID: 41372147).

- **In vitro structural biology:** Recombinant FDX2 and cryo-EM of the FDX2–core-ISC complex define the electron-donation and frataxin-competition mechanism (PMID: 39632806; PMID: 39467201).
- **Phenotype recapitulation / limitations:** Cellular and yeast models faithfully reproduce the **biochemical core** (Fe-S assembly failure, respiratory/aconitase deficiency, iron overload) but **do not capture the multisystem organismal phenotype** (optic atrophy, episodic myopathy, neuropathy, leukoencephalopathy). **No dedicated mouse or zebrafish disease model of FDX2 has been published** — a notable gap.

Mechanistic Model / Interpretation



Upstream (initiating) events are the FDX2 mutation and the Fe-S assembly failure; downstream (effector) events are respiratory/TCA enzyme inactivation, iron mishandling, and tissue-specific energy failure. The **episodic** nature reflects gene–environment interaction: a chronically marginal bioenergetic reserve is tipped into crisis by metabolic stressors (fasting, fever, exertion).

Evidence Base

PMID	Study type	Contribution
24281368	Human clinical/ genetics	First gene identification (c.1A>T); complex I/II/III + aconitase deficiency
30010796	Human clinical (6 patients)	Defines phenotype (optic atrophy, episodic myopathy, neuropathy, leukoencephalopathy); SDH/COX + iron biopsy; p.P144L founder
41372147	Human + cellular	Novel c.200+4A>G splice variant; patient-cell respiration/Fe-S/iron/SOD2 defects
37565517	Case report	Severe rhabdomyolysis (CK ~320,000), lactic acidosis, AKI — crisis management
39467201	In vitro / structural	Molecular determinants of P144L; FDX2 donates electrons for [2Fe-2S]/[4Fe-4S]
39632806	Cryo-EM	Two-stage FDX2 binding to core ISC complex; frataxin competition
20547883	In vitro (RNAi)	FDX2 vs FDX1 functional distinction; iron-homeostasis phenotype
28965846	Human clinical	FDXR disease — key differential and upstream pathway partner
34056100	Review/ methodology	Exome-first diagnostic strategy for mitochondrial disease
12970193	Yeast model	Yah1 (FDX2 ortholog) essential for Fe-S assembly on Isu1p
15211518	Yeast/ computational	Yah1–Arh1 pair in heme A and FeSC assembly
28615445	Review	~30-protein ISC biogenesis pathway framework
25008908	Clinical review	Exercise therapy benefits + trigger-avoidance guidance
20091552	Cochrane review	Safety of strength/aerobic training in muscle disease
18652078	Clinical review	Creatine in mitochondrial cytopathies (mixed benefit)
28747430	In vitro	FDXR is sole reductase supplying both ferredoxins

Evidence source distribution: Human clinical/genetics (~5 reports, <15 patients total) + mechanistic in vitro/structural + yeast model. No RCTs, no large cohorts, no vertebrate disease model.

Limitations and Knowledge Gaps

1. **Extreme rarity:** Fewer than ~15 genotyped patients; all epidemiology (prevalence, incidence, sex ratio, survival) is anecdotal. No natural-history study or registry exists.
 2. **No vertebrate animal model:** Mechanism rests on yeast, human cell lines, and structural biology; organ-level pathophysiology (why optic nerve and white matter are vulnerable) is inferred, not demonstrated in vivo.
 3. **Genotype–phenotype correlation is immature:** Only a handful of variants; residual-function/severity relationships are not quantified. Some mutant proteins (P144L, c.200+4A>G) appear structurally near-normal, suggesting abundance/activity thresholds matter — but this is not fully resolved.
 4. **No disease-specific therapy or trials:** All treatment evidence is extrapolated from general mitochondrial-myopathy literature; no FDX2-specific interventional data.
 5. **Reversible leukoencephalopathy is mechanistically unexplained:** The basis for white-matter reversibility vs progressive optic atrophy is unknown.
 6. **ICD coding** is non-specific (mapped to general mitochondrial myopathy codes).
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Proposed Follow-up Experiments / Actions

1. **Establish a vertebrate model:** Generate a conditional/tissue-specific (muscle, retinal ganglion cell, oligodendrocyte) *Fdx2* knockout or knock-in (p.P144L) mouse and/or zebrafish to test phenotype recapitulation (optic atrophy, episodic myopathy, leukoencephalopathy) and to serve as a preclinical therapeutic platform.
2. **International patient registry & natural-history study:** Pool genotyped cases via GeneMatcher/consortia to define prevalence, penetrance, crisis frequency/triggers, survival, and validated outcome measures.

3. **Genotype–function mapping:** Systematically measure residual FDX2 electron-transfer activity and protein stability across variants (c.1A>T, p.P144L, c.200+4A>G, and new alleles) to build a severity-prediction model.
 4. **Biomarker development:** Evaluate plasma lactate/CK dynamics, FGF21/GDF15, and iron indices as diagnostic and prognostic biomarkers specific to FDX2 disease.
 5. **Targeted therapeutic exploration:** Test whether iron-chelation, antioxidant/SOD2-supporting strategies, or substrate/cofactor supplementation rescue the Fe-S/respiration defect in patient cells and the animal model; evaluate AAV gene-replacement feasibility given the small 186-aa cDNA.
 6. **Standardized crisis protocol:** Develop and disseminate a consensus acute-rhabdomyolysis management pathway (hydration, renal protection, trigger avoidance) for FDX2 and related ISC-biogenesis disorders.
 7. **Pathway-wide diagnostics:** Ensure FDX2/FDX1L is included on all mitochondrial and Fe-S/ISC gene panels, with reflex RNA/functional testing for splice and missense variants.
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Report compiled from 5 investigation iterations, 9 confirmed findings, and 30 reviewed papers. Evidence is weighted toward human case reports and mechanistic in vitro/yeast/structural studies; interpretations involving organ-level vulnerability and episodic triggering are mechanistically reasoned and explicitly flagged as inferred where direct in vivo demonstration is lacking.
