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**Case Report**

# ONCE Syndrome and MTO1-Related Mitochondrial Disease: A Case Report with Narrative Literature Review and Evaluation of Dichloroacetate as Adjunctive Therapy

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## Abstract

MTO1-related mitochondrial disease (Combined Oxidative Phosphorylation Deficiency type 10, COXPD10; OMIM #614702) is a rare autosomal recessive disorder caused by biallelic variants in the nuclear MTO1 gene, which encodes an enzyme that modifies mitochondrial transfer RNA so that mitochondria can synthesise their proteins correctly. It typically presents in infancy with lactic acidosis and hypertrophic cardiomyopathy and, in longer-surviving children, evolves into a multisystem disorder with intellectual disability, epilepsy and optic neuropathy, a pattern termed ONCE syndrome (Optic Neuropathy, Cardiomyopathy, Encephalopathy with lactic acidosis and combined OXPHOS deficiency). We report a 12-year-old girl, the third child of consanguineous parents, with global psychomotor delay and persistent mild hyperlactataemia from infancy. Brain imaging showed symmetric T2 hyperintensity in both dentate nuclei with a cerebral lactate peak on MR spectroscopy. Whole-exome sequencing identified a homozygous MTO1 missense variant (c.1402G>A; p.Ala468Thr), consistent with the molecular diagnosis of COXPD10, with both parents heterozygous carriers; an incidental heterozygous FBN1 variant (p.Arg609Cys) was classified as a variant of uncertain significance and judged unrelated. She developed myoclonic epilepsy at age 11, managed with lamotrigine, while echocardiography and ophthalmological examination remained normal at age 12. We review the molecular pathogenesis, genotype-phenotype correlations and treatment options for MTO1 deficiency, focusing on dichloroacetate as adjunctive therapy for lactic acidosis and cardiomyopathy, and place the case alongside the 2025 FDA approval of elamipretide for Barth syndrome and emerging gene-therapy approaches. Early genetic diagnosis and structured cardiac and ophthalmological surveillance are essential; prospective studies of dichloroacetate are needed.

**Keywords:** MTO1, COXPD10, ONCE syndrome, mitochondrial tRNA modification, lactic acidosis, hypertrophic cardiomyopathy, dichloroacetate, combined OXPHOS deficiency.



## INTRODUCTION

Mitochondrial disorders are among the most varied inherited metabolic diseases, both genetically and clinically. They come from problems in the mitochondrial respiratory chain (RC), the five protein complexes that carry out oxidative phosphorylation (OXPHOS) and make ATP. The causative variants can lie in mitochondrial DNA (mtDNA) or in any of the more than 1,100 nuclear genes that encode mitochondrial proteins (MitoCarta3.0 catalogues ~1,136). When the nuclear genes for the mitochondrial translation machinery are disrupted, the result is a combined OXPHOS deficiency. This happens because the mitochondrial ribosomes, ribosomal RNAs, and transfer RNAs (tRNAs) serve all mtDNA-encoded subunits at once, so a fault in one translation factor lowers the supply of subunits across several respiratory chain complexes.

The MTO1 gene (chromosome 6q13; OMIM *614667) encodes the mitochondrial tRNA Translation Optimization 1 protein. This enzyme sits in the mitochondrial matrix and works with GTPBP3 to add a 5-taurinomethyluridine ($\tau m^5U$) group at the wobble position ($U_{34}$) of at least three mitochondrial tRNAs: mt-tRNAGln, mt-tRNAGlu, and mt-tRNALys. This modification lets the anticodon read the codon accurately at pyrimidine-ending codons during mitochondrial protein synthesis. Without it, the unmodified mt-tRNAs

pair poorly and translate less efficiently. As a result, the cell makes fewer of the RC subunits that these tRNAs help encode, especially subunits of Complexes I, III, and IV.

Ghezzi *et al.,* [2012] first linked MTO1 to human disease when they found pathogenic variants in two siblings with infantile hypertrophic cardiomyopathy and lactic acidosis. Since then, researchers have described a broad clinical range. In children who survive infancy, the cardiomyopathy may partly stabilise, but neurological problems become clearer over time: intellectual disability, epilepsy, and, typically in the second decade, optic neuropathy. Martín *et al.,* [2017] created the acronym ONCE syndrome (Optic Neuropathy, Cardiomyopathy, Encephalopathy with lactic acidosis and combined OXPHOS deficiency) to describe this pattern in patients homozygous for the p.Arg504Cys (R504C) MTO1 allele. The wider MTO1-related disease is classified as COXPD10 (Combined Oxidative Phosphorylation Deficiency 10; OMIM #614702), which covers the full range of alleles.

Here, we describe a 12-year-old girl with a homozygous MTO1 p.Ala468Thr (A468T) variant and a presentation that fits within the COXPD10 and ONCE spectra. We review how MTO1 deficiency develops at the molecular level, the growing literature on genotype-phenotype links, and current treatment options, with a focus on dichloroacetate (DCA) for lactic acidosis and cardiomyopathy. We place this case alongside recent milestones in mitochondrial medicine, including the 2025 FDA approval of elamipretide (Forzinity) for Barth syndrome and early gene therapy data for related mt-tRNA modification disorders.

## CASE REPORT

### Patient Presentation and Family History

The proband is a 12-year-old girl, born in 2010, referred for a progressive neurodevelopmental disorder with metabolic problems. She is the third child of healthy first-cousin parents, and her two older sisters are unaffected (Figure 1). The wider family history shows consanguinity on the mother's side and several unexplained infant deaths, which raised the prior probability of an autosomal recessive metabolic condition. A maternal aunt has a severe, undiagnosed neurological disability and uses a wheelchair, but she has no established diagnosis.

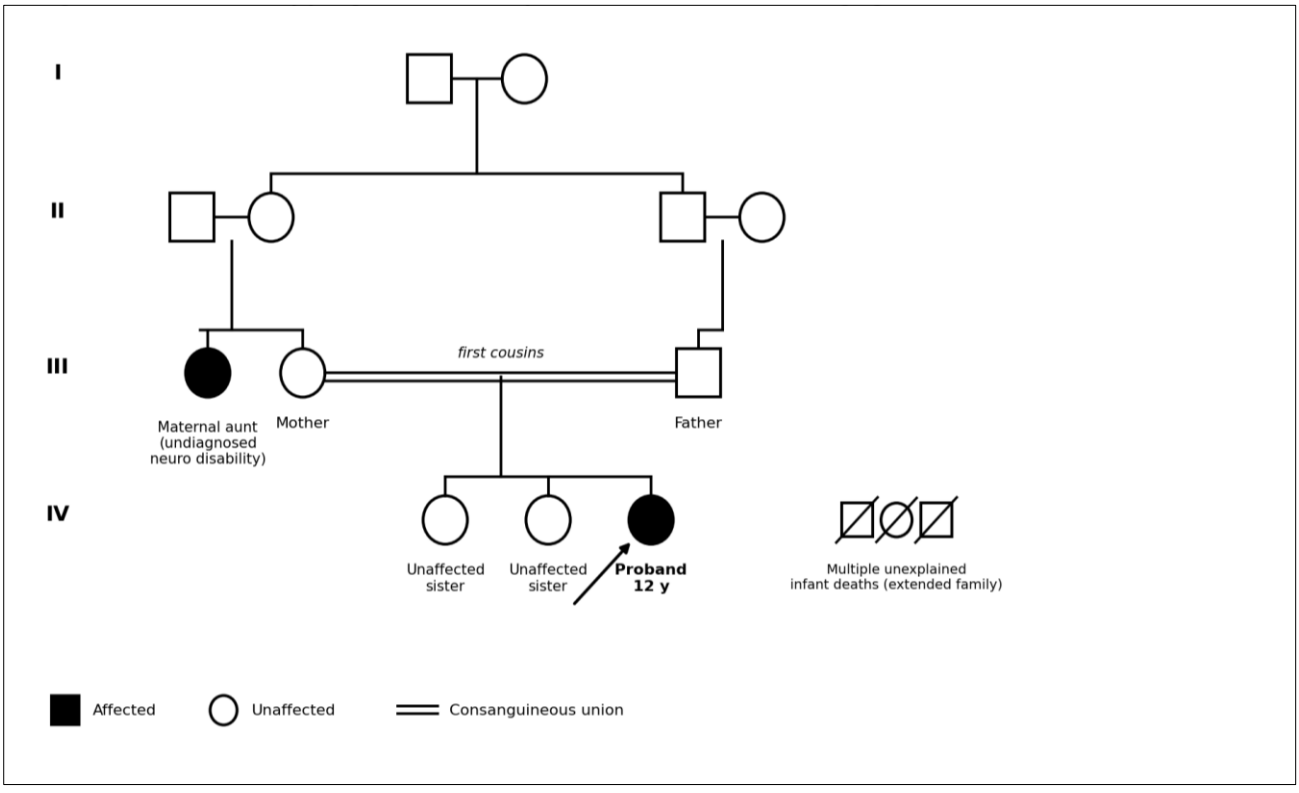


**Figure 1: Schematic family pedigree showing first-cousin parental union and autosomal recessive segregation. Extended structure is illustrative**

### Prenatal and Perinatal History

A second-trimester ultrasound at 20 weeks found a cystic lesion in the brain, possible poor skull ossification, intrauterine growth restriction (IUGR), and echogenic bowel. Chromosomal microarray analysis (array CGH) on amniocyte DNA was normal. Because of the echogenic bowel, both parents had CFTR variant testing, which was negative. Labor was induced at 37 weeks because of the IUGR. Birth weight was 2.47 kg (below the 10th centile), and birth length was 45 cm. The

newborn period was uncomplicated apart from mild axial hypotonia, with no respiratory distress, low blood sugar, or acute metabolic crisis.

**Developmental and Educational History**

Her psychomotor development was globally delayed from early infancy. She sat without support at about 12 months and walked on her own at 2.5 years, both well beyond the expected milestones. Her language developed slowly, too, so she has needed ongoing speech and language therapy. Neuropsychological testing showed intellectual disability. At age 7 she entered a specialised inclusive education unit (ULIS) with regular psychomotor and speech therapy. With this structured support, she has made gradual gains in motor skills and communication.

**Physical Examination**

At review at age 9 years (2018), her weight was 25.2 kg (+0.5 SD) and her height was 136.5 cm (+2.5 SD), which showed relative catch-up growth despite the IUGR. She had mild dysmorphic features: a high-arched palate and subtle synophrys. Although her tall stature (height +2.5 SD), high-arched palate and mild dorsal kyphosis are each counted in the systemic Ghent score, she had no other features of a connective tissue disorder: joint mobility and skin stretchiness were normal, the aortic root was normal on echocardiography, and there was no ectopia lentis. Her overall systemic score remained below the threshold for Marfan syndrome. The cardiovascular examination was normal, with no murmurs or signs of heart failure. The abdomen was normal, with no enlarged liver or spleen. On neurological examination she had mild diffuse hypotonia but no focal deficit. The eye review found moderate hypermetropia, corrected with glasses, and fundoscopy showed normal optic discs with no pallor or swelling.

**Biochemical Investigations**

Metabolic testing began in early childhood. Her blood lactate has been intermittently and mildly elevated. During a decompensation at age 6, lactate reached 2.7 mmol/L with a lactate to pyruvate (L/P) ratio of 22 and mild ketosis. A repeat test in 2016, when she was stable, showed lactate 1.7 mmol/L with an L/P ratio of 19 (reference <20). A high L/P ratio, when there is no hyperammonaemia, low blood sugar, or abnormal organic acid profile, points to an RC defect in which the cell cannot re-oxidise its reducing equivalents. This differs from a primary pyruvate dehydrogenase complex (PDC) deficiency, where the L/P ratio tends to be lower. Plasma amino acids showed a non-specific low pattern with no distinctive features. Urine organic acids were normal. Very-long-chain fatty acids and plasma cholestanol (to rule out cerebrotendinous xanthomatosis) were normal. A repeat high-resolution chromosomal microarray was normal. Together, these results pointed to a nuclear-encoded mitochondrial RC disorder as the cause of her intermittent mild hyperlactataemia.

**Neuroimaging**

Brain MRI at age 6 (2016) showed symmetric high T2 signal in both dentate nuclei and, to a lesser degree, in the thalami. The cerebellar folia looked prominent, which suggested mild cerebellar volume loss. MRS showed a lactate doublet at 1.33 ppm in the brain tissue, which indicated lactate build-up from OXPHOS failure. The cortex and white matter above the tentorium were structurally normal. Symmetric deep grey matter involvement with brain lactate on MRS is a typical imaging signature of mitochondrial encephalopathy, and it narrowed the differential diagnosis towards an RC cause.

**Molecular Genetic Findings**

Trio whole-exome sequencing (the proband and both parents) in 2018 found a homozygous variant in MTO1: c.1402G>A (p.Ala468Thr; A468T). Both parents were heterozygous carriers, and the variant was absent in the unaffected siblings. The A468T variant changes a residue in a conserved, functionally important region of MTO1. We classified it as likely pathogenic under the ACMG/AMP framework (criteria PM1, PM2_supporting, PP3 and PP4; Table 1): the in-silico tools agreed (SIFT: deleterious; PolyPhen-2: probably damaging; MutationTaster: disease-causing), Ala468 is highly conserved across vertebrates, and the variant is rare in gnomAD v4.0 with no reported homozygotes. Functional confirmation (respiratory-chain enzymology or direct measurement of $\tau m^5U$ modification) was not performed, so a definitive pathogenic classification is not yet established. Mitochondrial genome sequencing found no pathogenic mtDNA variants, which ruled out a primary mtDNA disorder.

**Table 1: ACMG/AMP evidence for MTO1 c.1402G>A (p. Ala468Thr)**

| Criterion | Strength | Evidence in this case |
|---|---|---|
| PM1 | Moderate | Located in a conserved, functionally important GidA-domain region adjacent to the catalytic core / GTPBP3 interface |
| PM2 | Supporting | Rare in gnomAD v4.0; no homozygotes reported |
| PP3 | Supporting | Concordant in-silico predictions (SIFT deleterious; PolyPhen-2 probably damaging; MutationTaster disease-causing) |
| PP4 | Supporting | Phenotype (combined OXPHOS deficiency, lactic acidosis, characteristic deep grey-matter MRI with cerebral lactate) highly specific for MTO1 disease |
| Segregation | Limited | Homozygous in proband, heterozygous in both parents, absent in unaffected sisters (single informative meiosis; insufficient for PP1 at full strength) |

| Criterion | Strength | Evidence in this case |
|---|---|---|
| PS3 | Not applied | No functional assay (respiratory-chain enzymology or $\tau m^5U$ quantification) performed |
| Resulting class | — | Likely pathogenic |

WES also found a heterozygous FBN1 variant (c.1825C>T; p.Arg609Cys) as a secondary finding. This variant was also present in her clinically unaffected mother and one sister, and it lacks strong published evidence of pathogenicity on its own, so we classified it as a variant of uncertain significance (VUS). She had no Marfanoid features: her aortic root diameter was normal on echocardiography, she had no ectopia lentis, and her body proportions were normal. We therefore judged the FBN1 VUS to be incidental and unrelated to her condition. We gave the family full genetic counselling about both findings, including the 25% recurrence risk for COXPD10 in future pregnancies.

**Clinical Evolution**

After the molecular diagnosis in 2019, her management stayed supportive: physiotherapy, occupational therapy, and specialised education. At age 11 (late 2021) she developed new myoclonic epilepsy, with brief, sudden jerks of the arms, head, and eyes and no loss of consciousness, which fit myoclonic seizures. EEG confirmed an epileptic cause. We started lamotrigine 50 mg twice daily, which gave partial seizure control, although occasional myoclonic episodes continue. We deliberately avoided valproic acid because of the MTO1 diagnosis.

At her most recent review (age 12, January 2022), she was walking and clinically stable. Her growth was normal. Echocardiography showed no ventricular hypertrophy and normal systolic function. The eye assessment, including fundoscopy, showed preserved visual acuity with corrected hypermetropia and normal optic discs. Her multidisciplinary care continues, and we have planned annual heart and eye surveillance because of the known risk of cardiomyopathy and optic neuropathy in the ONCE syndrome spectrum.

In summary, this patient has COXPD10 caused by homozygous MTO1 c.1402G>A (p.Ala468Thr). She presents with global intellectual disability, intermittent mild hyperlactataemia, typical neuroimaging, and myoclonic epilepsy that began in early adolescence (Figure 2). She has no cardiomyopathy or optic neuropathy at age 12, which fits the missense-variant phenotype of MTO1 deficiency, where these problems usually appear in later childhood and adolescence rather than in infancy.

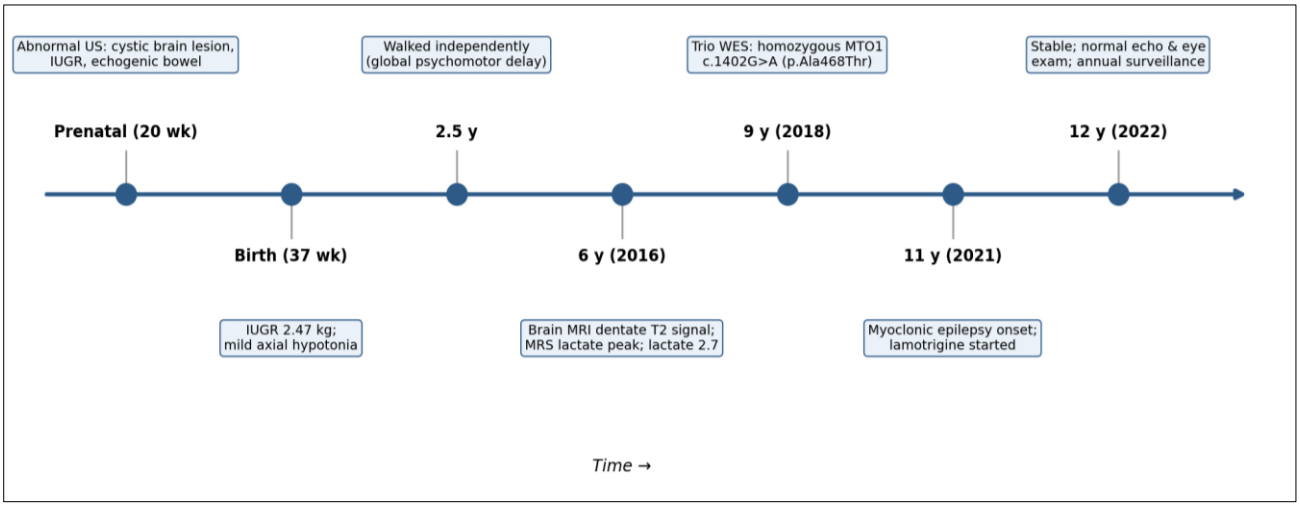


**Figure 2: Clinical timeline of the proband from the prenatal period to the most recent review at age 12**

**MTO1: Molecular Function and Pathogenic Mechanism**

**Molecular Biology of MTO1**

MTO1 (OMIM *614667; chromosome 6q13) encodes a 70 kDa protein in the mitochondrial matrix. It belongs to the GidA/MnmG family of flavoenzyme-dependent tRNA modification enzymes [Osawa T et al., 2009]. Together with GTPBP3 (the human version of bacterial MnmE), MTO1 forms an enzyme complex. This complex runs a two-step reaction that adds a taurinomethyl group to the 5-carbon of the wobble uridine ($U_{34}$) in at least three mt-tRNAs: mt-tRNAGln, mt-tRNAGlu, and mt-tRNALys. The resulting nucleotide, 5-taurinomethyluridine ($\tau m^5U_{34}$), is unique to human mitochondria. It serves as the wobble base in the anticodons of these three tRNAs, which decode the AA, GA, and CA codon families.

The $\tau m^5U_{34}$ modification does more than provide structure. It sets the correct shape of anticodon-codon pairing, prevents misreading at pyrimidine-ending codons, and improves aminoacylation. When it is

missing, as in MTO1-deficient cells, the unmodified mt-tRNAs misread codons or stall the mitochondrial ribosomes. Because these tRNAs serve all mtDNA-encoded transcripts, the translation defect is global: the cell makes fewer subunits for Complexes I, III, IV, and V, which produces a combined OXPHOS deficiency. Complex II is entirely nuclear-encoded, so it is usually spared.

**Functional Consequences of MTO1 Loss**

In human cell models, MTO1 deficiency lowers the oxygen consumption rate and reduces individual complex activities relative to citrate synthase, a marker of mitochondrial mass. Adding wild-type MTO1 cDNA fully corrects these defects [Ghezzi D *et al.,* 2012], which confirms that MTO1 loss is the cause rather than a secondary effect. The severity of the biochemical defect tracks with how much MTO1 protein remains. Frameshift and nonsense variants remove the protein and cause the greatest loss of enzyme activity, while missense variants usually leave some protein and partial function.

MTO1 deficiency does more than reduce OXPHOS; it also reprograms metabolism. Studies in patient fibroblasts and cell models show that the cell activates the HIF-1α (hypoxia-inducible factor) programme, lowers AMPK signalling, suppresses UCP2 and PPARγ, and shifts towards glycolysis. This creates a pseudohypoxic state even in normal oxygen [Boutoual R et al., 2018]. This metabolic shift probably adds to the chronic lactic acidosis seen in patients, on top of the pyruvate and lactate imbalance caused by RC impairment. In MTO1-deficient mice, the OXPHOS defect is tissue-specific and can be partly bypassed with a ketogenic diet [Tischner C et al., 2015].

**Pathogenicity of the p. Ala468Thr Variant**

The c.1402G>A change replaces a conserved alanine at position 468 with threonine. Ala468 sits next to the GidA-domain catalytic core, in a region important for binding tRNA or for the interaction with GTPBP3. Replacing the small, water-repelling alanine with a threonine that carries a hydroxyl group is predicted to disturb the local structure or the packing of this nearby functional domain. Ala468 is highly conserved across vertebrates, and the in silico tools agree on a damaging effect. The variant is absent in the homozygous state in gnomAD (v4.0) and occurs at a heterozygous frequency that fits a rare recessive allele.

It helps to separate A468T from the p.Arg504Cys (R504C) allele, for which Martín *et al.,* [2017] first coined the ONCE syndrome name. R504C changes a conserved arginine that probably sits directly in the MTO1 active site or at the GTPBP3 interface, while A468T affects a nearby but separate position. Clinically, the two alleles cause broadly similar disease. Both produce combined OXPHOS deficiency, lactic acidosis, and cognitive problems, and both carry a risk of cardiomyopathy and optic neuropathy in patients who survive longer. A468T should therefore be placed within the ONCE syndrome clinical spectrum, even though the acronym was first coined for R504C. A growing number of MTO1 reports, including a 2023 study that showed marked variability within one family carrying different compound heterozygous alleles [Almeida CM *et al.,* 2023], suggests that the COXPD10 spectrum is wider than any single defining allele implies.

**Literature Review: MTO1-Related Disease**

**Epidemiology and Genetic Architecture**

Since the first report by Ghezzi *et al.,* [2012], authors have described more than 35 patients with COXPD10. A systematic review collected 35 cases that carried 19 different pathogenic MTO1 variants across several ethnic backgrounds [O'Byrne JJ *et al.,* 2018]. The variants include missense changes, frameshift insertions and deletions, nonsense changes, and splice-site variants, all inherited in an autosomal recessive way. Many cases come from consanguineous families, where homozygous variants account for the whole allelic burden, but compound heterozygous genotypes are also common. The R504C (c.1510C>T) allele has been found in unrelated families of Spanish and French or German ancestry [Martín MÁ *et al.,* 2017], which suggests either a mutational hotspot at codon 504 or a low-frequency founder allele in these European populations. The A428T (p.Ala428Thr) allele has also been reported in homozygous and compound heterozygous states in several families.

**Clinical Spectrum**

The core clinical features of MTO1 deficiency are lactic acidosis, hypertrophic cardiomyopathy, and global developmental delay. A systematic review of 35 patients found that lactic acidosis eventually appeared in 100% of cases (35/35), hypertrophic cardiomyopathy in 79% (27/34), and global developmental delay or intellectual disability in 97% (28/29) [O'Byrne JJ et al., 2018]. The frequency, severity, and timing of each feature, however, vary widely by genotype and by the age at which patients are assessed.

Cardiomyopathy is the most striking early feature. In neonatal-onset cases, which usually carry truncating variants, hypertrophic cardiomyopathy can appear in the first weeks of life and cause death from arrhythmia or circulatory failure before doctors can assess neurological development. The two siblings in the Ghezzi *et al.,* [2012] report died at 19 and 40 days of age. Patients who carry a missense variant on at least one allele usually survive past infancy, and their cardiac hypertrophy may improve partly with supportive treatment. In the Martín *et al.,* [2017] group of R504C homozygotes, cardiomyopathy began between 22 months and the early teens.

Neurological involvement worsens over time. Hypotonia and global psychomotor delay are common in

infancy. As patients grow, intellectual disability, often moderate to severe, becomes the main functional problem. About half of longer-surviving patients develop epilepsy, mostly myoclonic and generalised tonic-clonic seizures [Martín MÁ *et al.,* 2017]. The most distinctive late feature is optic neuropathy. Charif *et al.,* [2015] first highlighted it when they described optic atrophy in patients who had homozygous MTO1 variants and also carried a homoplasmic mitochondrial MT-TF variant (m.593T>G). Martín *et al.,* [2017] then confirmed that optic atrophy occurs consistently in R504C homozygotes during the second decade of life; in one patient, visual acuity fell to about 10% of normal by age 16. The ONCE syndrome acronym captures this full set of features, optic neuropathy, cardiomyopathy, encephalopathy, and lactic acidosis, as the expected mature phenotype in survivors.

Almeida *et al.,* [2023], writing in the Egyptian Journal of Medical Human Genetics, showed how broad the COXPD10 phenotype can be. They described two siblings with compound heterozygous MTO1 variants (c.413delT/c.1450C>T [p.M138Sfs*6 / p.R484W]) and very different courses. One sibling died at 16 years after progressive myoclonic encephalopathy and repeated metabolic decompensations. Her brother, diagnosed at 15, had only mild persistent hyperlactataemia, psychomotor delay, dilated cardiomyopathy, and epilepsy. This variability within one family, despite the same primary genotype, suggests that environmental or genetic modifiers strongly shape the course and make individual prognosis difficult.

**Genotype-Phenotype Correlations**

The clearest and most useful genotype-phenotype link is between the type of variant and disease severity (Table 2). Truncating variants, such as frameshifts, nonsense variants, and splice changes that abolish the protein, are linked to death in the neonatal period. Missense variants keep variable amounts of MTO1 function and are linked to later onset and longer survival with supportive care. When both alleles carry missense changes, as in homozygous R504C or A468T, the phenotype usually includes cognitive impairment from childhood, a risk of cardiomyopathy that develops gradually in childhood or adolescence, and expected optic neuropathy by the second decade.

**Table 2: Representative MTO1 genotypes and associated phenotypes (selected reports)**

| Genotype | Variant type | Representative report | Key clinical features | Outcome |
|---|---|---|---|---|
| Biallelic truncating (frameshift/nonsense) | Loss of function | Ghezzi *et al.,* [2012] (two siblings) | Neonatal hypertrophic cardiomyopathy, severe lactic acidosis | Neonatal death (19 and 40 days) |
| p.Ala428Thr homozygous | Missense | Ghezzi *et al.,* [2012] (Case 3) | Early HCM, severe lactic acidosis; stabilised on dichloroacetate + cofactors | Survived with treatment |
| p.Arg504Cys (R504C) homozygous | Missense | Martín *et al.,* [2017] | Intellectual disability, lactic acidosis, cardiomyopathy (22 mo–teens), optic neuropathy in 2nd decade (ONCE) | Survival into 2nd decade |
| c.413delT / c.1450C>T (compound het) | Mixed | Almeida *et al.,* [2023] | Marked intrafamilial variability | One sib died 16 y; other mild |
| p.Ala468Thr (A468T) homozygous — present case | Missense | This report | Intellectual disability, mild intermittent hyperlactataemia, myoclonic epilepsy; no cardiomyopathy/optic neuropathy at 12 y | Stable at 12 y |

Some studies have suggested that mtDNA may act as a modifier. Charif *et al.,* [2015] proposed that a homoplasmic MT-TF variant (m.593T>G) in their patients may have worked together with the nuclear MTO1 defect to worsen RC function. However, the ONCE phenotype also appears in patients without such mtDNA variants, including the present case, which confirms that the nuclear MTO1 alleles alone can cause severe disease. Whether mtDNA background changes how strongly the disease is expressed remains an open question.

**Biochemical Findings**

The most consistent biochemical abnormality across reported cases is a high blood lactate, often with an L/P ratio above 20. A high L/P ratio supports a primary RC defect, because the cell cannot re-oxidise cytosolic NADH through the malate-aspartate shuttle. It argues against a proximal PDC deficiency or an organic acidaemia. When muscle biopsy or fibroblast studies are done, they typically show combined deficiencies of Complexes I and IV, with variable Complex III reduction. Citrate synthase activity is usually normal or high, which reflects compensatory mitochondrial biogenesis. Skeletal muscle may occasionally show COX-negative fibres, although this is less consistent in nuclear-encoded translation defects than in primary mtDNA disorders.

Two extra, treatable problems have been reported in individual cases. One patient in the Martín *et al.,* [2017] group had cerebral folate deficiency (low 5-methyltetrahydrofolate in CSF), which responded to folinic acid. Another had high homocysteine from vitamin B12 deficiency and needed parenteral supplementation. These were not direct effects of MTO1 dysfunction, but co-occurring deficiencies that can add

to neurological injury. They show why it is worth screening for folate and B12 status in these patients.

**Therapeutic Approaches**

**Supportive Care**

There is currently no curative or licensed disease-modifying treatment for MTO1 deficiency. Care is multidisciplinary and supportive, and it aims to limit the metabolic, cardiac, neurological, and developmental effects of the disease. Key principles are to avoid prolonged fasting, which raises lactate by increasing anaerobic glycolysis, to give high-calorie support during illness, and to start developmental help early, including physiotherapy, occupational therapy, and speech and language therapy.

For epilepsy, doctors must avoid valproic acid in all mitochondrial disease patients. It inhibits RC Complex I, can cause liver toxicity (especially in POLG-related disease), and can trigger hyperammonaemia. Levetiracetam, benzodiazepines (e.g., clonazepam) and lamotrigine are suitable alternatives; importantly, lamotrigine can occasionally aggravate myoclonic seizures, so levetiracetam is often preferred for myoclonus in mitochondrial disease. We manage our patient's myoclonic epilepsy with lamotrigine, which achieved partial control; a switch to levetiracetam would be reasonable if myoclonus persists.

For cardiac disease, standard cardiomyopathy treatments apply. Doctors can use beta-blockers (propranolol, bisoprolol) or verapamil for significant hypertrophy, and they should monitor electrolytes to lower the arrhythmia risk. Annual echocardiography and ECG are recommended for all COXPD10 patients, including those with no current cardiac findings, because the risk rises with age.

Many specialist centres also use mitochondrial cofactor supplements, even though the controlled evidence is limited. Common agents are coenzyme Q10 (100 to 400 mg/day), L-carnitine, riboflavin (vitamin B2), and thiamine (vitamin B1, an essential PDC cofactor). These supplements carry little risk and may give modest benefit in certain settings. They should add to, not replace, active monitoring for correctable deficiencies such as folate or vitamin B12.

**Dichloroacetate (DCA)**

Mechanism of Action. Dichloroacetate is a small molecule that inhibits pyruvate dehydrogenase kinase (PDK). By inhibiting PDK, DCA keeps the pyruvate dehydrogenase complex (PDC) in its active form. This pushes pyruvate towards acetyl-CoA and into the tricarboxylic acid cycle. The net effect is less conversion of pyruvate to lactate, lower blood and CSF lactate, and a shift away from anaerobic glycolysis. DCA is well absorbed by mouth, crosses the blood-brain barrier easily, and acts within minutes. Doctors have used it for congenital and acquired lactic acidosis since at least the early 1980s.

In RC disorders such as MTO1 deficiency, the rationale for DCA is indirect, because the main block is at the RC rather than at PDC. Even so, keeping PDC active sends as much pyruvate as possible into the TCA cycle, lowers toxic lactate, and may improve substrate supply to the parts of the OXPHOS system that work better. Lowering lactate in the body and brain may also protect organs from injury, especially the heart, which needs a lot of energy, and brain neurons, which also have high energy demands.

Clinical Trial Evidence. Stacpoole *et al.,* [2006] ran the first randomised controlled trial of DCA in congenital lactic acidosis. They enrolled 43 children with various causes, including PDC deficiency and several RC defects. The children received DCA (12.5 mg/kg twice daily) or placebo for six months. DCA lowered blood and CSF lactate significantly compared with placebo, and it was as well tolerated as placebo. However, it did not improve the main clinical outcomes, namely neurological function, growth, or quality of life. This likely reflects the fixed pre-existing deficits, the short follow-up, and the mixed patient group. In a long-term open-label safety study, Abdelmalak *et al.,* [2013] followed eight patients on DCA for 9.7 to 16.5 years. DCA kept lactate near normal in most of them and was well tolerated at paediatric doses (about 25 mg/kg/day). The main safety signal was mild, subclinical slowing of nerve conduction in some patients, without overt neuropathy. This was hard to attribute to DCA alone, because peripheral neuropathy is itself a known feature of mitochondrial disease.

DCA in MTO1 Deficiency. No randomised trial has tested DCA specifically in COXPD10, but there is supportive anecdotal evidence. Ghezzi *et al.,* [2012] described their Case 3 (Patient 3), who was homozygous for the missense MTO1 p.Ala428Thr allele and presented with early-onset hypertrophic cardiomyopathy and severe lactic acidosis. With permanent dichloroacetate together with thiamine, coenzyme Q10, and carnitine, the acidosis came under control and the cardiomyopathy stabilised. This is an instructive documented use of DCA in MTO1 deficiency, and it provides proof of concept that DCA can favourably change the disease course, particularly by stabilising the heart.

Bennett *et al.,* [2020] reported a similar benefit in a newborn with MTFMT deficiency, a defect in mitochondrial methionyl-tRNA formyltransferase, which is another nuclear-encoded mitochondrial translation factor. This infant had severe lactic acidosis and cardiomyopathy that looked like MTO1 disease. DCA at 30 mg/kg/day normalised lactate, reversed the cardiomyopathy, and supported developmental progress over two years. Sabouny *et al.,* [2019] reported a

comparable response in a child with FBXL4-related mtDNA depletion syndrome, in whom DCA improved the acidosis and reversed cardiac hypertrophy. In the laboratory, however, DCA corrected only the extracellular acidification and not the broader mitochondrial defect. Together these reports suggest that the benefit of DCA may extend across congenital lactic acidosis from nuclear-encoded mitochondrial disorders, not only MTO1 deficiency.

In practice, doctors usually start DCA in children at 25 mg/kg/day in two divided doses. They monitor blood lactate (aiming for normal values below 2 mmol/L), liver function, nerve conduction velocity (yearly or twice yearly for long-term use), and hearing. Children clear DCA faster than adults because they have higher GSTZ1 enzyme activity. As a result, children generally tolerate it better and have a lower risk of peripheral neuropathy than adults on the same weight-based dose.

**Emerging and Investigational Therapies**

In September 2025 the FDA granted accelerated approval to elamipretide (Forzinity; Stealth BioTherapeutics) to improve muscle strength in patients with Barth syndrome weighing at least 30 kg [U.S. FDA, 2025]. This is a milestone for mitochondrial medicine, because it is the first drug approved specifically for a mitochondrial disease. Elamipretide is a tetrapeptide that targets mitochondria and binds cardiolipin, a phospholipid found in the inner mitochondrial membrane. By doing so, it stabilises the cristae, lowers oxidative stress, and improves the efficiency of ATP synthesis. The approval is limited to Barth syndrome, which is caused by TAZ variants that disturb cardiolipin remodelling. Even so, it sets a regulatory and conceptual precedent for targeting mitochondria with drugs, which may extend to other RC disorders. Trials of elamipretide in primary mitochondrial myopathies are ongoing, and its protective effect on the heart is of theoretical interest for the hypertrophic cardiomyopathy of COXPD10.

Gene therapy for mt-tRNA modification disorders is a more distant but scientifically grounded direction. Zhang *et al.,* [2026] showed that virus-mediated re-expression of GTPBP3 in cell and mouse models of GTPBP3 deficiency corrected mt-tRNA modification, restored mitochondrial translation, and reversed the cardiomyopathy. GTPBP3 and MTO1 work together as an obligate enzyme pair, and GTPBP3 variants cause a clinically overlapping mitochondrial translation disorder [Kopajtich R *et al.,* 2014]. For these reasons, gene therapy developed for GTPBP3-related disease may serve as a template for MTO1-targeted approaches. In addition, Tomoda *et al.,* [2023] showed that overexpressing the $\tau m^5U$-modifying enzyme MTO1 restored wobble-uridine modification, mitochondrial translation, and respiration in cells from MELAS and MERRF patients. This points to another way to restore translational accuracy.

None of these investigational approaches is available outside clinical trials yet, but their rapid progress shows how quickly the treatment landscape for mitochondrial disease is changing. For the present patient, the most immediately usable option remains DCA, given its established safety in children, the anecdotal evidence of benefit in MTO1 disease, and her ongoing mild high lactate.

## DISCUSSION

This case shows several clinically important points about MTO1 deficiency, set against the published literature on COXPD10.

Diagnostic trajectory. The diagnosis took a long time, which is typical for nuclear-encoded mitochondrial disorders. No single biochemical test diagnoses them, and their genetic variety makes targeted sequencing impractical. The combination of IUGR, neonatal hypotonia, early developmental delay, and persistent lactic acidosis suggested an inborn error of metabolism from infancy. The first workup, however, was normal or negative (array CGH, CFTR, amino acids, and organic acids), which correctly ruled out the more common conditions. The key diagnostic step was the brain MRI. Symmetric dentate nucleus T2 change and a cerebral lactate peak on MRS are typical, though non-specific, features of mitochondrial encephalopathy. Together with the biochemistry and the family history, this imaging pattern pointed the team towards WES, which gave the molecular diagnosis. The case supports the current consensus that early, broad genomic sequencing, rather than step-by-step single-gene or panel testing, is the best diagnostic strategy in children with unexplained developmental delay, metabolic acidosis, and a consanguineous family background.

Genotype and phenotype. The homozygous A468T MTO1 variant is different from the R504C allele that gave ONCE syndrome its name, but the clinical picture is broadly consistent with ONCE-spectrum disease. We cannot tell from the clinical data alone whether A468T leaves slightly more MTO1 activity than R504C, which might explain her relatively mild early course and the absence of neonatal cardiomyopathy. A direct biochemical comparison of the two variants in patient fibroblasts would help, but it was not available for this case. Even so, comparing A468T with previously described alleles supports the view that missense MTO1 variants usually cause later-onset, milder-initial, but slowly progressive disease compared with truncating alleles.

Cardiomyopathy surveillance. The absence of cardiomyopathy on echocardiography at age 12 is notable and somewhat fortunate. Among published R504C homozygotes, Martín *et al.,* [2017] recorded cardiomyopathy onset between 22 months and about 12 to 19 years. Our patient is now entering this age window, so continued annual cardiac surveillance is essential. The

Ghezzi *et al.,* [2012] Case 3 experience is instructive: cardiomyopathy in MTO1 deficiency is an ongoing metabolic vulnerability, and sustained metabolic support with DCA can stabilise the heart over the long term. This supports a proactive approach. Because benefit on clinical outcomes is unproven, DCA might be considered only for refractory acidosis or established or progressive cardiomyopathy, under explicit informed consent and close monitoring, rather than started pre-emptively while she remains clinically stable with near-normal lactate.

Epilepsy. The myoclonic epilepsy that began at age 11 fits the natural history of MTO1 disease. Epilepsy affects about half of long-term survivors and is not specific to one genotype. Myoclonic seizures predominate and usually respond at least partly to standard anticonvulsants. Lamotrigine is a suitable choice. Her dentate nucleus MRI changes suggest ongoing neuronal vulnerability in the cerebellar deep grey matter, a region that is sensitive to metabolic stress. This means seizure monitoring and management should stay a priority throughout adolescence.

Optic neuropathy risk. Optic neuropathy is the one ONCE feature that has not yet appeared in this patient. Published series show that it usually emerges between ages 11 and 20 in R504C homozygotes, and at 12 she is entering this critical window [Martín MÁ et al., 2017]. Optical coherence tomography (OCT) of the retinal nerve fibre layer can detect early optic nerve involvement before visual acuity drops, so it should be part of the annual eye review. Pattern-reversal visual evoked potentials give a complementary electrophysiological measure of optic nerve function. No drug has been shown to prevent mitochondrial optic neuropathy specifically in COXPD10. Idebenone, used off-label and on weak, LHON-specific evidence, could be considered if early optic nerve changes appear, although its benefit in COXPD10 is unproven.

Therapeutic considerations: DCA. The most clinically actionable treatment question for this patient is DCA. Her lactate stays mildly high despite clinical stability, and as she enters the adolescent window for cardiomyopathy, the question of whether to start DCA arises. The available evidence, particularly the long-term MTO1 case from Ghezzi *et al.,* [2012] and the similar MTFMT case from Bennett *et al.,* [2020], gives a reasonable basis for a therapeutic trial at paediatric doses (25 mg/kg/day in two divided doses) with close monitoring. This evidence, however, is anecdotal and uncontrolled. The only randomised trial of DCA in congenital lactic acidosis lowered lactate but did not improve clinical outcomes [Stacpoole PW *et al.,* 2006], and DCA carries a dose-dependent risk of peripheral neuropathy [Abdelmalak M *et al.,* 2013]. The consent process should make clear that DCA is investigational here, and monitoring should include serial lactate measurements, annual nerve conduction studies, and hearing assessments. A specialist centre with experience in DCA is preferable.

FBN1 VUS and incidental findings. The FBN1 p.Arg609Cys VUS, found as a secondary finding, shows a well-known challenge of WES in practice: it produces variants whose significance cannot be settled. Its presence in clinically unaffected relatives is strong evidence against pathogenicity on its own. Her tall stature is nonetheless atypical for mitochondrial disease, which more often causes short stature, and this discordance is currently unexplained. Even so, it appropriately prompted targeted cardiac and connective tissue assessment, and it will be revisited as the evidence for this variant grows, in line with current ACMG/AMP guidelines on secondary findings.

**Limitations**

Several limitations should be acknowledged. This is a single case report combined with a narrative review rather than a systematic one, so it can generate hypotheses but cannot establish causation or general treatment effects. The pathogenicity of the proband's variant rests on in silico prediction, evolutionary conservation, and rarity in population databases. Functional validation in patient cells, for example direct measurement of respiratory-chain enzyme activities or of wobble-uridine ($\tau m^5U$) modification, was not available and would strengthen the genotype to phenotype link. The discussion of DCA is limited by its evidence base: the benefit in MTO1 deficiency rests only on anecdotal, uncontrolled observations; the single randomised controlled trial in congenital lactic acidosis improved the biochemical surrogate (lactate) without improving clinical outcomes; and DCA carries a recognised, dose-dependent risk of peripheral neuropathy. Finally, because the proband has not developed cardiomyopathy or optic neuropathy, her place within the ONCE-syndrome spectrum is still anticipatory, and long-term surveillance will be needed to confirm the phenotype over time.

## CONCLUSION

MTO1-related mitochondrial disease (COXPD10) is a rare but now well-characterised autosomal recessive disorder. Impaired mt-tRNA modification leads to combined OXPHOS deficiency, lactic acidosis, and progressive multi-organ involvement. The case presented here, a 12-year-old girl with homozygous MTO1 p.Ala468Thr, shows the key features of the ONCE syndrome spectrum: early global developmental delay, chronic lactic acidosis, typical mitochondrial neuroimaging, and myoclonic epilepsy that began in early adolescence. She has no cardiomyopathy or optic neuropathy at this age, which fits missense-variant disease, but this should not be mistaken for protection. Both complications are expected and must be actively monitored as she goes through adolescence.

Several broader lessons emerge from this case. Whole-exome sequencing is the most efficient diagnostic tool in children with unexplained developmental delay, metabolic acidosis, and consanguinity, given the genetic variety of mitochondrial translation disorders. Characteristic neuroimaging, particularly symmetric deep grey matter T2 change and cerebral lactate on MRS, should prompt metabolic and genomic testing even when the first biochemical screens are not diagnostic. Once COXPD10 is confirmed, structured, protocol-driven surveillance for cardiomyopathy and optic neuropathy is essential, with annual echocardiography and an eye review that includes OCT. Epilepsy should be treated with anticonvulsants that avoid mitochondrial toxicity, and valproic acid in particular should be avoided.

DCA is the most readily available add-on option for the metabolic part of COXPD10. It consistently lowers lactate, a biochemical surrogate, and has anecdotal, uncontrolled signals of cardiac benefit, with an established safety profile in children with MTO1 deficiency. The only randomised trial in congenital lactic acidosis, however, showed no clinical-outcome benefit, so DCA is best seen as a biologically plausible treatment that still needs prospective study. In individual patients, it may be considered for persistent high lactate, early cardiac changes, or repeated metabolic decompensations, with appropriate consent and monitoring. The recent FDA approval of elamipretide for Barth syndrome and the early gene therapy data in GTPBP3-deficient models point to a fast-changing treatment landscape, in which disease-modifying strategies for COXPD10 may become possible. For now, comprehensive multidisciplinary supportive care, guided by the molecular diagnosis and informed by the growing literature, remains the standard of care.

This patient's ongoing clinical course, particularly the expected cardiac and optic nerve changes over the next decade, will keep adding to our understanding of MTO1 deficiency and the ONCE syndrome spectrum.

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## REFERENCES


- Abdelmalak, M., Lew, A., Ramezani, R., *et al.,*(2013). Long-term safety of dichloroacetate in congenital lactic acidosis. *Molecular Genetics and Metabolism, 109*(2), 139–143.
- Almeida, C. M., Rodrigues, E., Campos, T. A., *et al.,* (2023). Novel MTO1 mutations associated with an intrafamilial phenotypic variability. *Egyptian Journal of Medical Human Genetics, 24*, 8.
- Bennett, J., Kerr, M., Greenway, S. C., *et al.,*(2020). Improved lactate control with dichloroacetate in a case with severe neonatal lactic acidosis due to MTFMT mitochondrial translation disorder. *Molecular Genetics and Metabolism Reports, 24*, 100616.
- Boutoual, R., Meseguer, S., Villarroya, M., *et al.,* (2018). Defects in the mitochondrial-tRNA modification enzymes MTO1 and GTPBP3 promote different metabolic reprogramming through a HIF-PPARγ-UCP2-AMPK axis. *Scientific Reports, 8*, 1163.
- Charif, M., Titah, S. M., Roubertie, A., *et al.,* (2015). Optic neuropathy, cardiomyopathy, cognitive disability in patients with a homozygous mutation in the nuclear MTO1 and a mitochondrial MT-TF variant. *American Journal of Medical Genetics Part A, 167A*(10), 2366–2374.
- Ghezzi, D., Baruffini, E., Haack, T. B., *et al.,*(2012). Mutations of the mitochondrial-tRNA modifier MTO1 cause hypertrophic cardiomyopathy and lactic acidosis. *American Journal of Human Genetics, 90*(6), 1079–1087.
- Kopajtich, R., Nicholls, T. J., Rorbach, J., *et al.,*(2014). Mutations in GTPBP3 cause a mitochondrial translation defect associated with hypertrophic cardiomyopathy, lactic acidosis, and encephalopathy. *American Journal of Human Genetics, 95*(6), 708–720.
- Martín, M. Á., García-Silva, M. T., Barcia, G., *et al.,* (2017). The homozygous R504C mutation in MTO1 gene is responsible for ONCE syndrome (Optic Neuropathy, Cardiomyopathy, Encephalopathy with lactic acidosis and combined OXPHOS deficiency). *Clinical Genetics, 91*(1), 46–53.
- O'Byrne, J. J., Tarailo-Graovac, M., Ghani, A., *et al.,* (2018). The genotypic and phenotypic spectrum of MTO1 deficiency. *Molecular Genetics and Metabolism, 123*(1), 28–42.
- Osawa, T., Ito, K., Inanaga, H., *et al.,* (2009). Conserved cysteine residues of GidA are essential for biogenesis of 5-carboxymethylaminomethyluridine at tRNA anticodon. *Structure, 17*(5), 713–724.
- Sabouny, R., Wong, R., Lee-Glover, L., *et al.,* (2019). Characterization of the C584R variant in the mtDNA depletion syndrome gene FBXL4, reveals a novel role for FBXL4 as a regulator of mitochondrial fusion. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1865*(11), 165536.
- Stacpoole, P. W., Kerr, D. S., Barnes, C., *et al.,*(2006). Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. *Pediatrics, 117*(5), 1519–1531.
- Tischner, C., Hofer, A., Wulff, V., *et al.,*(2015). MTO1 mediates tissue specificity of OXPHOS

defects via tRNA modification and translation optimization, which can be bypassed by dietary intervention. *Human Molecular Genetics, 24*(8), 2247–2266.

- Tomoda, E., Nagao, A., Shirai, Y., *et al.,* (2023). Restoration of mitochondrial function through activation of hypomodified tRNAs with pathogenic mutations associated with mitochondrial diseases. *Nucleic Acids Research, 51*(14), 7563–7579.
- U.S. Food and Drug Administration. (2025). FDA grants accelerated approval to elamipretide (Forzinity) for the treatment of Barth syndrome. Silver Spring, MD: U.S. Food and Drug Administration.
- Zhang, Y., Yao, S. Y., Li, J., *et al.,*(2026). Molecular pathogenesis and gene therapy-based intervention of GTPBP3-related mitochondrial disease. *Nature Communications, 17*, article s41467-026-71750-z.