Journal of Medical Sciences at NEOMED
Volume 4, Issue 1, April 2025

# The Current State of the Mitochondrial Diseases LHON, MELAS and Leigh Syndrome and Their Treatments: A Review

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## ABSTRACT

Metabolic disorders like Leber Hereditary Optic Neuropathy (LHON), Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and Leigh Syndrome (LS) are severe, rare mitochondrial diseases causing perturbed mitochondrial function. These disorders present a broad spectrum of clinical manifestations, complicating diagnosis and treatment. Management of LHON, MELAS, and LS remains largely supportive, with no FDA-approved treatments available. However, therapies like Idebenone for LHON, L-arginine for MELAS, and EPI-743 for LS are showing significant therapeutic promise and are presently being evaluated in clinical trials for their efficacy and safety. This review delves into the defining characteristics of LHON, MELAS, and LS, highlights the current state of therapeutic developments, and discusses established disease models.

**Keywords**: LHON, MELAS, Leigh Syndrome, mitochondrial disease

## INTRODUCTION

Primary mitochondrial diseases (PMD) are disorders causing disruptions in cellular metabolism, often affecting the oxidative phosphorylation (OXPHOS) chain, inhibiting cells' ability to synthesize ATP and causing damage through the generation of toxic reactive oxygen species and alteration of redox status in cells. Mitochondrial diseases are relatively common genetic diseases, occurring in about 1/5000 people.[1] These disorders have a range of prognoses, from mild physical weakness to death.[2] Mitochondrial diseases can present with symptoms including progressive neurodegeneration, cardiomyopathy, and impaired motor skills.[3]

Mitochondrial mechanisms of disease are complex, making therapeutic development challenging. With few therapeutic options, mitochondrial disease symptoms are managed to prevent complications.[4] Mitochondrial diseases can be damaging, causing complications like retarded development, multiorgan failure, and even death.[4]

The need for FDA-approved therapies for mitochondrial diseases has motivated research into this area. Numerous pharmacological treatments are undergoing development and clinical trials with promising results. In this review, we explore the natural history, disease models, and potential therapies of Leber's Hereditary Optic Neuropathy (LHON), Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like-episodes (MELAS), and Leigh Syndrome (LS).

## LEBER HEREDITARY OPTIC NEUROPATHY

Leber Hereditary Optic Neuropathy (LHON) is a mitochondrial disease caused by mtDNA point mutations. This disease predominantly affects young males and is characterized by a painless decline in central vision due to oxidative damage of retinal ganglion cells.[5] LHON disease progression presents in three stages: presymptomatic, acute, and chronic.[5] Symptoms often begin in one eye and spread to the other within days to months but in 25-50% of cases, symptoms can present simultaneously in both eyes.[6,7] LHON impacts 1/30,000 - 50,000 people with an average age of onset of 15-35 years.[8] Rarely, this disease may manifest with extraocular symptoms such as cardiac abnormalities like AV block and neurological deficits like movement disorders.[9]

LHON can be diagnosed by clinical findings like increased retinal vasculature, apparent swelling/damage around the optic disc without true edema, thickening of the retinal nerve fiber layer visualized by Optical Coherence Tomography (OCT), altered colored vision, and exclusion of conditions like optic neuritis, compressive, or toxic optic neuropathy.[5,10,11,12,13] OCT, visual field tests, Visual Evoked Potential (VEP) Tests, and Electroretinogram (ERG) may aid in diagnosis since these tests display characteristic results of different

disease stages.[5,14,15,16] Genetic testing of both nDNA and mtDNA may reveal causative mutations of LHON.[5,7,17]

Genetics

While most mutations responsible for LHON demonstrate homoplasmy, heteroplasmy may be observed in 10-15% of cases.[5,18] Homoplasmy refers to identical copies of mtDNA within one cell, while heteroplasmy involves various mtDNA variants within the same cell. Secondary mutations can contribute to LHON development, influencing disease presentation alongside the established LHON-causing mutation.[5,19,20] Three primary mtDNA mutations, m.11778G>A, m.14484T>C, and m.3460G>A, cause 95% of LHON cases.[5] Patient outcomes may be predicted by the liable mutation. The m.14484T>C mutation is known to have the best visual prognosis of the three primary mutations.[21] The m.11778G>A mutation is most prominent, causing severe cases of LHON in which only 4-25% of patients display some degree of visual recovery.[5,22,23] These mtDNA mutations disrupt Complex I of the mitochondrial respiratory chain, leading to the accumulation of reactive oxygen species (ROS). Accumulated ROS then causes oxidative damage to retinal ganglion cells, resulting in the loss of central vision.

LHON is believed to display incomplete penetrance, meaning not everyone with the mutation will display disease symptoms.[5] Additionally, the penetrance of LHON is lower in females, with approximately 10% of females with an LHON mutation experiencing vision loss as compared to 50% of males.[5] This is believed to result potentially from the mitochondrial protective effects of estrogen.[24]

Disease Models

In the past, rodents were used to model LHON by inducing mtDNA mutations in mice. This can be done by introducing a human optic atrophy mtDNA ND6 P25L mutation.[25] These mice exhibited impaired retinal function, degeneration of optic nerve fibers, accumulation of abnormal mitochondria, demyelination, and increased accumulation of ROS.[25] In another mouse model, the chemical compound rotenone, a direct OXPHOS toxin, was used to induce a model of LHON mutations affecting Complex 1 mice treated with rotenone, which displayed damage of retinal ganglion cells similar to that observed in LHON.[26] However, shortcomings of rodent models include species differences between mice and humans and a limited population of disease-relevant cells.[27] More recently, human induced pluripotent stem cells (hiPSCs) derived from LHON patients have been used as a more accurate in vitro model of disease. Induced pluripotent stem cells (iPSCs) are human cells that have been reprogrammed into an embryonic stem cell-like state. Once in a stem cell-like state, these cells are pluripotent and may be differentiated into numerous cell lineages.[28] This model could provide a renewable source of disease-relevant cells.[29]

Treatment

Currently, treatments for LHON focus on prevention. Clinical guidance for patients includes avoiding excessive alcohol consumption, smoking, or use of drugs that may disrupt mitochondrial function such as antibiotics, statins, and chemotherapeutics since these factors increase LHON penetrance.[12,30]

Ongoing research aims to treat the disease's root cause rather than manage symptoms. Ongoing gene therapy research explores Lenadogene nolparvovec (GS010) for treating the causative mutation, m.11778G>A. This mutation impacts the MT-ND4 gene encoding a subunit of the Electron Transport Chain's (ETC) Complex I. GS010 has performed well in some phase III trials, producing statistically significant improvement in best-corrected visual acuity with minimal symptoms.[31] However, further research into the impact of gene therapy will be necessary as some trials report that in some cases of unilateral GS010 injection, improvement was seen in the contralateral eye.[31,32] To further complicate this finding, these cases did not display significant systemic presence of the gene therapy.[31,32] Another avenue to treat LHON involves ubiquinone analogs. A well-established ubiquinone analog is Idebenone, a water-soluble compound that is both clinically effective and safe.[33,34] While gene therapy development is ongoing, Idebenone is recommended to treat LHON as it has aided visual recovery in younger patients and patients in early disease stages. In a randomized controlled double-blind clinical trial, Idebenone did not have a statistically significant impact on visual acuity recovery in LHON during the time of the study.[35] A post hoc analysis and follow-up report suggested Idebenone's displayed a delayed effect following drug cessation. This analysis illustrates that Idebenone potentially prevents further vision loss, especially in patients with diverse visual acuities.[35] In another randomized placebo-controlled double-blind clinical trial, Idebenone demonstrated protective effects on color vision.[34] Idebenone is approved in Europe by the EMA but is not currently FDA approved and there is currently inadequate evidence of its efficacy. For this reason, the current recommendation advises against its use in the chronic phase of disease.

## MITOCHONDRIAL ENCEPHALOMYOPATHY WITH LACTIC ACIDOSIS AND STROKE-LIKE EPISODES

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a severe mitochondrial disease. MELAS typically presents in the first or second decade of life with 65-76% of cases presenting at or before age 20.[36, 37] The median survival

time in symptomatic cases is approximately 16.9 years from onset of neurological symptoms.[38]

MELAS impacts multiple organ systems, producing a variety of symptoms ranging in severity, which may partially be attributed to heteroplasmy.[39,40] Severe cases of pediatric MELAS include symptoms like delayed development, short stature, seizures, exercise intolerance, muscle weakness, migraines, and stroke-like episodes.[39] Later stages of the disease may be characterized by diabetes, hearing loss, cardiovascular abnormalities, and gastrointestinal issues.[39,41] The nervous system is intensely affected by MELAS, with patients exhibiting symptoms like stroke-like episodes which can lead to necrosis of the brain, seizures, headaches, and dementia.[37,39] The cause of characteristic stroke-like episodes of MELAS is not well understood, but they may be connected to blood vessel irregularities, cytopathy, and neuronal hyperexcitability.[42] Additionally, MELAS may impact the musculoskeletal system causing myopathy, exercise intolerance, and ragged red muscle fibers.[40] Diagnosis of MELAS is routinely made using either the Hirano or Japanese criteria.[43,44] Under the Hirano criteria, a definitive diagnosis of MELAS requires all of the following: encephalopathy, stroke-like episodes at a young age, and evidence of mitochondrial dysfunction.[43,44] The Hirano criteria also considers a MELAS diagnosis if two out of the following three are present: normal development, recurrent headache, or recurrent vomiting.[43,44] Under the Japanese criteria, a definitive MELAS diagnosis may be made if patients meet two category A criteria (headache with vomiting, seizures, hemiplegia, cortical blindness or hemianopsia, or acute focal lesion observed with brain imaging) in addition to two category B criteria (high lactate levels in plasma or CSF or deficiency of mitochondrial-related enzyme activities, mitochondrial abnormalities in muscle biopsy, or a definitive gene mutation related to MELAS).[43,44]

## Genetics

The m.3243A>G mtDNA mutation is one of the most common causes of mitochondrial disease, contributing to 80% of MELAS cases as well as other conditions.[45,46] m.3243A lies within a mitochondrial tRNA gene, therefore this mutation impacts mitochondrial protein synthesis, fatty acid oxidation, and the OXPHOS system.[44,45,46] In addition to m.3243A>G, MELAS is associated with other mutations that impact other mitochondrial tRNA genes.[47]

Studies have suggested that the degree of heteroplasmy is directly correlated to the severity of disease in the m.3243A>G variant. A higher degree of heteroplasmy was found to be correlated to higher levels of ROS and therefore greater levels of oxidative damage and more severe disease presentations.[48] The degree of heteroplasmy was found to have a particular impact in the degree of disruption of energy and metabolism.[49] This may have further implications of increased ROS production and decreased ATP production, leading to a worse clinical presentation.

POLG genes encode POLG, a catalytic subunit of DNA polymerase gamma responsible for replication of the mitochondrial genome.[50,51] These genes may play a role in the presentation or progression of MELAS. Clinical trials have investigated the use of Elamipretide in restoration of mitochondrial function in individuals with POLG mutations.[52]

## Disease Model

Human induced pluripotent stem cells (hiPSCs) serve as a valuable, realistic, and renewable disease model of the m.3243A>G mutation.[53] The induction of this mutation in hiPSCs caused mitochondrial dysfunction manifesting as decreased respiratory chain complex I activity, decreased oxygen consumption rate, increased ROS, increased membrane depolarization, increased intracellular calcium, and decreased intracellular ATP.[53,54] The creation of an established disease model of MELAS may be beneficial particularly in the study of neurological effects of MELAS so that the impact on complete neurological pathways may be better understood.[42,55]

A mouse model of POLG mutations has been characterized but is not well understood.[56] These mice were found to have both somatic and germ-line mutations and mtDNA mutations rapidly accumulated in these mice.[56] Additionally, two groups have induced mutations in mice that disrupt the exonuclease activity of the mouse POLG protein.[56,57] Mice with this mutation showed signs of premature aging from 6-9 months of age including hair loss, hearing loss, spine curvature, enlarged hearts, weight loss, and decreased bone density, likely resulting from a high frequency of mtDNA deletions in homozygous mice.[57,58]

## Treatment

Current treatments for MELAS primarily consist of anticonvulsant drugs such as levetiracetam, lamotrigine, and lacosamide, though valproate is typically avoided due to mitochondrial toxicity.[39] L-arginine is being examined as a treatment for MELAS, but insufficient evidence exists to recommend this treatment.[42] L-arginine is believed to increase depleted levels of arginine in the body during a stroke-like episode and increase the bioavailability of the vasodilator nitric oxide, increasing blood flow to the brain and reducing stroke-like symptoms and neurological effects.[42] Additionally, citrulline is an emerging alternative to arginine in the treatment of MELAS. Zagociguat is a soluble guanylate cyclase currently being used in clinical trials for treatment of MELAS. This increases nitric oxide to produce improvement in clinical symptoms by a mechanism similar to that seen in the use

of L-arginine. Sonlicromanol (KH176) has shown impactful neural changes in phase II clinical trials for the treatment of MELAS.[59]

## LEIGH SYNDROME

Leigh Syndrome (LS) is a rare mitochondrial disease, with a prevalence of about 1/40,000 births, primarily affecting the central nervous system.[60] LS is a neurodegenerative disease with multiorgan involvement.[60] LS symptoms tend to manifest from 3 months to 2 years of age. Common symptoms include loss of motor control (dyskinesia), difficulty swallowing (dysphagia), and seizure-like activity.[2] Clinically, LS varies greatly amongst patients, but symptoms typically involve affected areas of the brain like the cerebellum, basal ganglia, cranial nerves, and brainstem.[61] LS symptoms can progress rapidly, causing complications like lactic acidosis, ataxia, dysarthria, and hypertrophic cardiomyopathy.[3] The prognosis of LS is poor, with most patients succumbing to the disease at a few years of age.[62]

### Genetics

Like other mitochondrial diseases, LS is caused by inherited genetic mutations that impair proteins vital for metabolic function. Mutations in mtDNA and nDNA can cause LS, with nDNA mutations frequently inherited via Mendelian genetics.[61] More than 75 causative mutations of LS have been identified.[63] Due to heterogeneity, the disease's clinical manifestation can vary from mild to extreme. Nevertheless, the defining characteristic of LS is that causative mutations disrupt proteins directly involved in the OXPHOS pathway like complex proteins, chaperone proteins, and accessory proteins.[64]OXPHOS disruption leads to impaired ATP synthesis and the acute clinical presentation of LS.[64]

### Diagnostics

Timely diagnosis of Leigh Syndrome is essential to begin early-stage treatment. The lack of a clinical assay and the vast array of LS symptoms make diagnosis challenging. Brain imaging can detect bilateral necrotic brain lesions common amongst patients with LS, predominantly of the basal ganglia, particularly the putamen.[65] Although, the developmental mechanism of these brain lesions is not well understood.[2] Definitive diagnosis can be achieved with molecular genetic testing identifying a known causative mutation, of which there are more than 75.[2,63,62] Leigh Syndrome's diagnostic tools have significant limitations. Therapeutic interventions have minimal effects once the onset of acute LS symptoms occurs. Additionally, there are likely causative genetic mutations yet to be identified, meaning genetic confirmation of LS could be made more challenging.

### Disease Models

#### *C. elegans*

Leigh Syndrome has been modeled in several organisms. In 2020, LS from the causative nDNA mutations NDUFS4 and NDUFS1 was modeled in C. elegans for drug screening studies.[66] The model recreated human disease phenotypes associated with these mutations, particularly neuronal impairment inferred by the disease model's neurosensory defect to "gentle touch".[64] However, mtDNA mutations have little effect on the cellular respiration of C. elegans, illustrating a deficiency of this model system as it cannot adequately consider LS caused by mtDNA mutation.[67]

#### *Fruit Flies*

The fruit fly has been used to model LS by silencing the CG9943 gene, homologous to the human SURF1 mutation of LS. This SURF1 LS model recapitulated the ETC dysfunction observed in vivo.[68] In a 2018 study, silencing the ND-18 gene, the drosophila homolog to the human NDUFS4 gene recreated similar feeding difficulties found in humans with this genetic defect.[69] Although fruit flies display applicable metabolic symptoms, drosophila's anatomical differences to humans limit assessing key characteristics of LS like motor deficiencies.[70]

### Mouse Model

The Ndufs4 knockout (Ndufs4−/−) mouse model is a pivotal, well-established tool for comprehensively studying LS. Ndufs4−/− displays the NADH dehydrogenase iron-sulfur protein 4 knockout, an ETC complex 1 subunit.[71] These mice display levels of NAD+/NADH ratio and lactate characteristic to clinical levels of LS. Additionally, Ndufs4−/− mice display similar symptoms to humans with bilateral necrotic lesions in the vestibular nuclei, fatigue, ataxia, decreased appetite, seizure activity, and ultimately death at a median age of postnatal day 45.[72] Mouse models, due to their evolutionary closeness to humans, remain vital for studies of mitochondrial diseases, providing critical insights into causes, mechanisms, and potential treatments for LS.

#### *Induced Pluripotent Stem Cells (iPSCs)*

In 2017, iPSC-derived cardiomyocytes (iPSC-CMs) were cultured from patients with LS.[73] More recently, metabolomics on iPSC-derived fibroblasts, neuron progenitor cells, mature neurons, and cardiomyocytes from Leigh-like syndrome, classical LS, and healthy controls showed that FDA-approved drugs Ubiquinone, Alpha-Lipoic Acid, and Riboflavin recapitulated improved metabolic profiles seen clinically.[74] These iPSC-derived cells replicated clinical presentations of ATP levels, lactate, mitochondrial respiration, mitochondrial membrane potential (Ψm), ROS levels,

and cellular phenotypic alterations for ultra-rare LS-like and classical LS conditions.[74] These findings support the use of iPSC-derived model systems for therapeutic testing and personalized prescreening in LS and LS-like diseases.

Current Therapies

Heterogeneity and varying clinical presentations make treating Leigh Syndrome difficult. Available treatments include sodium bicarbonate for lactic acidosis and vitamin B1 to manage symptoms.[3] A few developing drugs have shown favorable results in clinical trials. However, there are currently no FDA-approved therapies for the disease, highlighting the need for research in this field.

*Nutraceuticals, vitamins, and cofactors*

In the absence of FDA-approved therapies, avenues of treatment for mitochondrial diseases like LS, LHON, and MELAS include the use of cofactors, vitamins, amino acids, and other nutritional interventions.[75] The "mito-cocktail" refers to a combination of supplements like Coenzyme Q-10, B vitamins, antioxidants (e.g., vitamin E, alpha-lipoic acid), L-carnitine, and L-arginine to support mitochondrial function in patients with mitochondrial diseases.[76] Ideally, the “mito-cocktail” could promote alternative avenues of energy production, reduce the effects of ROS, and enhance the energy production capabilities of the remaining mitochondria.[75] By enhancing energy production in patients with mitochondrial disease, these treatments aim to slow disease progression or acute deterioration.[75] Although these ingredients are frequently used in the clinical setting, no patient with Leigh Syndrome has been cured solely by these supplements.[77] These therapies lack FDA approval as a definitive treatment for mitochondrial disorders.[75]

Developing Therapies

*EPI-743*

EPI-743 is a small molecule being evaluated for the treatment of respiratory chain diseases, including LS.[78] EPI-743, a para-benzoquinone, is theorized to replenish intracellular glutathione depleted by toxic ROS and nitrogen species accumulated due to mitochondrial dysfunction.[78] EPI-743’s proposed mechanism of action is a catalytic 2-electron transfer NQ01 cofactor, improving redox status by modulating oxidoreductase activity and increasing the production of reduced glutathione.[78,79]

In 2011, the USFDA permitted clinical use of EPI-743 under an Expanded Access Protocol (EAP) for children with genetically confirmed LS with 90 days of end-of-life care.[78] Over 6 months of EPI-743 treatment, all genetic determinants, ages, and disease severity, children affected by LS displayed halted disease progression and improvements in neurological and motor symptoms.[80] EPI-743 treatment was correlated with fewer hospitalizations and adverse events than those treated with the placebo.[79] Additionally, EPI-743 is rapidly absorbed (Tmax 2–4 hours) and well-tolerated without abnormal lab findings.[80]

In comparative studies, EPI-743 has outperformed traditional therapies such as CoQ10, demonstrating advancement in the treatment of mitochondrial diseases like LS.[64] EPI-743’s development emphasizes the need for research to improve treatment options and patient outcomes.

As of January 2025, EPI-743 no longer has an EAP status for treating Leigh Syndrome. However, the Labour and Welfare (MHLW) of Japan for the treatment of Leigh Syndrome,[81] has conducted clinical trials that have shown a reversal of the progression of the disease.[75,80]

*KH176*

KH176 is a small molecule ROS-redox modulator with good oral bioavailability proposed to treat LS.[71,66] Studies demonstrate that KH176 interacts with the Thioredoxin/Peroxiredoxin enzyme system, protecting cells from redox stress-induced cell death, further revealing the therapeutic mechanism.[82] The therapeutic effects of KH176 in the Ndufs4 −/− knockout mouse LS disease model with OXPHOS Complex I deficiency, KH176 treatment resulted in statistically significant improvements in brain microstructural coherence, normal lipid peroxidation levels, improved motor control and gait coordination and decreased ganglion cell degeneration.[71] Despite KH176’s reduction of oxidative stress, it did not diminish or prevent severe pathologies like vestibular nuclei lesions, disease onset, severity, or life span in the mouse model.[71] These results suggest KH176 can improve symptoms in the LS model, but it does not address all pathological features. Ongoing Phase 2 clinical trials are evaluating KH176’s efficacy and safety in humans for potential clinical use.[82]

*NV354*

NV354 is a therapeutic agent created to act as an alternative energy source in the form of succinate to patients with severe mitochondrial diseases like LS, LHON, and MELAS.[84] Increased succinate usage by ETC Complex II following Complex I dysfunction is commonly implicated in mitochondrial disease.[85] Thus, NV354 was designed to provide a reserve of succinate for Complex II utilization, allowing mitochondria to circumvent the deficient Complex I.[84] Phase 1 trials began in 2022, and updates still need to be provided.[84]

| Disease | LHON | MELAS | Leigh Syndrome |
|---|---|---|---|
| **Description** | Leber's Hereditary Optic Neuropathy: a mitochondrial disease primarily impacting young males. LHON causes bilateral painless loss of central vision due to oxidative damage of retinal ganglion cells. | MELAS: a mitochondrial disease presenting in the first or second decade of life. Severe cases present in childhood with delayed development, short stature, seizures, exercise intolerance, weakness, migraines, and stroke-like episodes. Later stages of the disease present with diabetes, hearing loss, and cardiovascular and gastrointestinal symptoms. Diagnosis is made via Hirano or Japanese criteria. | Leigh Syndrome: a neurometabolic mitochondrial disease affecting OXPHOS presenting typically from 3 months to two years of age. Symptoms include bilateral necrotic brain lesions of the basal ganglia, lactic acidosis, ataxia, dysarthria, and hypertrophic cardiomyopathy. LS has a poor prognosis and is often fatal. Diagnosis is made with genome sequencing or brain imaging. The lack of a clinical assay makes diagnostics challenging. |
| **Genetics** | Three primary mtDNA mutations are known to cause 95% of cases: m.11778G>A, m.14484T>C, m.3460G>A. Mutations affect Complex I of the ETC. LHON has incomplete penetrance with lower penetrance in females. Heteroplasmy in 10-15% of cases. | The m.3243A>G mutation in mtDNA is the cause of 80% of MELAS cases. MELAS may be associated with other mutations which impact mitochondrial tRNA genes. Studies suggest that the severity of m.3243A> G-related disease correlates with the degree of heteroplasmy. POLG mutations can also cause MELAS. | LS has over 75 monogenic causative mutations in both the nDNA and mtDNA genomes. Heterogeneity of LS leads to a vast array of symptoms, however, the defining characteristic is OXPHOS disruption. |
| **Treatment** | Focuses on symptom management, i.e. lifestyle choices. Developing treatments include GS010 gene therapy and ubiquinone analogs like idebenone. | Focuses on symptom management. Antiepileptic drugs like levetiracetam, lamotrigine, and lacosamide are recommended to manage seizures. Developing drugs include L-arginine supplementation, citrulline, Zagociguat, and Sonlicromanol (KH176). | Focuses on symptom management. There are no FDA-approved therapies. Developing drugs include EPI-743, KH176 ABI-009, and NV354. Cofactors, vitamins, and other nutritional interventions are utilized in the clinical setting. |
| **Treatment Outcome** | Outcomes are variable. Idebenone potentially prevents further vision loss and protects color vision. GS010 gene therapy aims to mitigate LHON's effects on Complex I of the ETC. | Levetiracetam, lamotrigine, and lacosamide: decrease epileptic episodes. L-arginine was reported to replenish bodily arginine and increase the bioavailability of NO.<br>Citrulline: an emerging alternative to arginine<br>Zagociguat: a soluble guanylate cyclase which increases NO<br>Sonlicromanol: impactful neural changes | EPI-743 is reported to arrest the disease progression and improve neurological and motor symptoms clinically. KH176 shown to improve redox status by reducing ROS, brain microstructural coherence, and motor performance without improving disease onset, severity, or lifespan in mice. NV354 is designed to improve mitochondrial resp. by supplying the alternative energy source succinate. Vitamins, cofactors, and other nutritional interventions aim to reduce the effects of ROS and enhance the function of remaining mitochondria, although clinical results are difficult to quantify. |
| **Disease Model** | A mouse model displaying optic atrophy following the induction of an mtDNA mutation has been used to model LHON.<br>Another mouse model uses rotenone to induce complex I mutations, causing central vision loss similar to LHON. Recently, hiPSCs derived from LHON patients have been used as an in-vitro disease model. | Using iPSC technology provides a favorable model due to its availability and sustainability. An animal model of MELAS does not exist but would be beneficial in allowing the mapping of neuronal pathway changes.<br>No mouse model of MELAS exists. However, induced mutations disrupting the exonuclease activity of the POLG gene cause premature aging in mice. | C. elegans LS models represent the NDUFS4 and NDUFS1 mutations. The *drosophila* model system demonstrates the SURF1 and NDUFS4 homolog mutations. The Ndufs4 knockout (Ndufs4−/−) mouse model is well-established. iPSCs are being explored as an accurate and sustainable disease model. |

**Table 1.** Review table of Leber's Hereditary Optic Neuropathy, MELAS, and Leigh Syndrome.

## CONCLUSION

LHON, MELAS, and LS have complex mechanisms of disease and clinical presentations. Due to factors such as heterogeneity, erratic clinical presentation, and infrequent diagnosis, therapeutics for rare mitochondrial diseases are limited. However, drugs like Idebenone for LHON, L-arginine for MELAS, and EPI-743 for LS are in development with encouraging results. Clinical trials are evaluating the effectiveness and safety of these treatments, further advancing patient care. Suboptimal disease models make further therapeutic development and exploration of disease mechanisms challenging. However, induced pluripotent stem cells are emerging as a favorable mitochondrial disease model due to their specificity and sustainability. The poor prognosis of these diseases, lack of FDA-approved therapies, and lack of understanding of disease mechanisms illustrate the need for continual research in mitochondrial diseases.

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## ACKNOWLEDGMENTS

Thank you to Dr. Patrick T. Kang for guiding us through this writing process. Thank you to Dr. Bruce Cohen for your expertise and assistance in editing this paper.

## CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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Study Design: CH, AD

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