Journal of Genetic Syndromes & Gene Therapy
ISSN: 2157-7412
OPEN ACCESS Freely available online
Commentary

Mitochondrial DNA Mutations and Multisystem Manifestations in Leber Hereditary Optic Neuropathy

Yuto Nakamori*

Department of Neurogenetics, Kyoto Medical University, Kyoto, Japan

DESCRIPTION

Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited mitochondrial disorder characterized by acute or subacute loss of central vision. The condition is caused by point mutations in mitochondrial Deoxyribonucleic Acid (DNA), most commonly affecting genes encoding subunits of complex I of the respiratory chain, including *MT-ND1*, *MT-ND4*, and *MT-ND6*. These mutations impair oxidative phosphorylation, leading to reduced Adenosine Triphosphate (ATP) production and increased oxidative stress, particularly in retinal ganglion cells.

Unlike nuclear gene disorders, LHON is transmitted exclusively through maternal lineage due to the inheritance pattern of mitochondrial DNA. All children of an affected mother inherit the mutation, but not all individuals develop symptoms. This incomplete penetrance suggests the involvement of additional genetic, epigenetic, and environmental factors that influence disease expression. Mitochondrial heteroplasmy, the coexistence of mutated and normal mitochondrial genomes within a cell, plays a significant role in determining disease severity.

The primary pathological event in LHON is dysfunction of retinal ganglion cells, which are highly dependent on mitochondrial energy production due to their long axons and high metabolic demand. When complex I activity is impaired, electron transport becomes inefficient, leading to reduced ATP synthesis and increased production of reactive oxygen species. These changes trigger apoptosis of retinal ganglion cells, resulting in progressive optic nerve degeneration. Clinically, LHON typically presents in young adult males, although females can also be affected. Vision loss is usually painless and begins in one eye, followed by involvement of the second eye within weeks or months. Central vision is predominantly affected, leading to the development of a central scotoma. Color vision defects, particularly involving red-green discrimination, are also common early features. Fundoscopic examination may reveal hyperemia of the optic disc and telangiectatic vessels during the acute phase.

The disease course can vary depending on the specific mitochondrial mutation. The *MT-ND4* mutation is the most frequently associated variant and is often linked to more severe visual impairment. However, environmental factors such as smoking and alcohol consumption significantly increase the risk of disease expression in genetically predisposed individuals. These factors are thought to exacerbate mitochondrial oxidative stress, thereby accelerating retinal ganglion cell damage. Diagnosis of LHON is based on clinical presentation and confirmed through mitochondrial DNA sequencing. Detection of primary pathogenic mutations in *MT-ND1*, *MT-ND4*, or *MT-ND6* supports the diagnosis. Optical coherence tomography and visual evoked potentials are used to assess structural and functional damage to the optic nerve. These diagnostic tools are important for distinguishing LHON from other causes of optic neuropathy.

Currently, there is no definitive cure for LHON, but several therapeutic approaches aim to improve mitochondrial function and slow disease progression. One approved treatment in some regions is idebenone, a synthetic analog of coenzyme Q10. Idebenone acts as an electron carrier within the mitochondrial respiratory chain, partially bypassing complex I dysfunction and reducing oxidative stress. Clinical studies have shown variable improvement in visual recovery, particularly when treatment is initiated early. Gene therapy represents a major area of active investigation in LHON. One experimental approach involves the use of adeno-associated viral vectors to deliver functional copies of the *MT-ND4* gene directly into retinal cells. This strategy aims to restore complex I function and improve cellular energy production. Early-phase clinical trials have demonstrated partial visual improvement in some patients, although results remain variable and long-term efficacy is still under evaluation.

Another emerging strategy involves allotopic expression, in which mitochondrial genes are engineered into nuclear DNA and targeted back into mitochondria. This approach attempts to overcome the limitations of direct mitochondrial gene delivery. However, challenges such as proper protein import and mitochondrial targeting remain significant technical barriers. Antioxidant therapies are also being explored to counteract oxidative damage associated with mitochondrial dysfunction. Compounds such as alpha-lipoic acid and vitamin-based

Correspondence to: Yuto Nakamori, Department of Neurogenetics, Kyoto Medical University, Kyoto, Japan, E-mail: daniel.kovalenko.sma@utoronto.ca

Received: 01-Dec-2025, Manuscript No. JGSGT-25-41632; **Editor assigned:** 03-Dec-2025, PreQC No. JGSGT-25-41632 (PQ); **Reviewed:** 17-Dec-2025, QC No. JGSGT-25-41632; **Revised:** 24-Dec-2025, Manuscript No. JGSGT-25-41632 (R); **Published:** 31-Dec-2025, DOI: 10.35248/2157-7412.25.16.475

Citation: Nakamori Y (2025). Mitochondrial DNA Mutations and Multisystem Manifestations in Leber Hereditary Optic Neuropathy. J Genet Syndr Gene Ther. 14:475.

formulations have been studied, although evidence for their effectiveness remains limited. These interventions are generally considered supportive rather than curative.

Mitochondrial replacement techniques have been proposed as a preventive strategy for families at high risk of transmitting mitochondrial mutations. These methods involve replacing mutated mitochondria with healthy donor mitochondria during assisted reproductive procedures. While ethically and technically complex, such approaches have the potential to eliminate transmission of mitochondrial diseases in future generations. Psychosocial impact is an important aspect of LHON due to the sudden and profound loss of vision. Affected individuals often experience significant emotional distress, requiring psychological support and rehabilitation services. Low-vision aids, orientation training, and occupational therapy play essential roles in maintaining independence and quality of life. Genetic counseling is essential for affected families due to the maternal inheritance pattern. Counseling provides information on recurrence risk, disease variability, and reproductive options. It also helps individuals understand the influence of lifestyle factors on disease expression, allowing for preventive behavioral modifications.

CONCLUSION

Leber hereditary optic neuropathy is a mitochondrial genetic disorder caused by mutations in genes such as *MT-ND1*, *MT-ND4*, and *MT-ND6*, leading to impaired oxidative phosphorylation and selective degeneration of retinal ganglion cells. Advances in molecular genetics and gene therapy have improved understanding of the disease and opened new therapeutic possibilities. While current treatments remain limited, ongoing research into mitochondrial gene delivery and metabolic support offers potential for future improvement in visual outcomes and disease management.