Mitochondrial Disorders: common clinical features, diagnosis, review of different syndromes with treatment/management, prognosis, and future perspectives.

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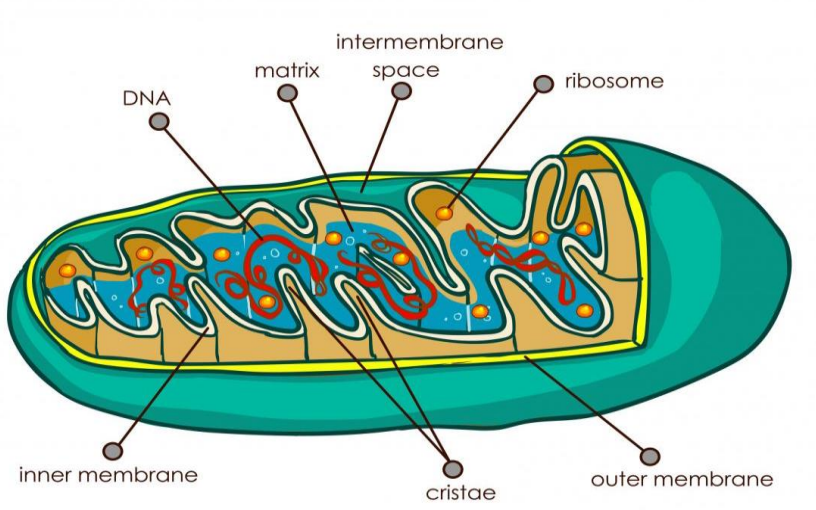
Mitochondrial disorders are a group of genetic conditions arising from mutations in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that impair mitochondrial function. These disorders can affect multiple organ systems and present with a wide range of symptoms due to the high energy demand of tissues like the brain, muscles, and heart.

BACKGROUND:

Mitochondria are often referred to as the powerhouses of the cell. Their main function is to generate the energy necessary to power cells. But, there is more to mitochondria than energy production.

Present in nearly all types of human cell, mitochondria are vital to our survival. They generate the majority of our adenosine triphosphate (ATP), the energy used by cells.

Mitochondria are also involved in other tasks, such as programming cell death: apoptosis.



- Mitochondria are small, often between 0.75 and 3 micrometers. Unlike other organelles (miniature organs within the cell), they have two membranes, an outer one and an inner one with different functions.
  Outer membrane: Small molecules can pass freely through the outer membrane. This outer portion includes proteins called porins, which form channels that allow proteins to cross. The outer membrane also hosts a number of enzymes with a wide variety of functions.
  Inner membrane: Because there are no porins in the inner membrane, it is impermeable to most molecules. Molecules can only cross the inner membrane in special membrane transporters. The inner membrane is where most ATP is created.
  Matrix: This is the space within the inner membrane. Containing hundreds of enzymes, it is important in the production of ATP. Mitochondrial DNA is housed here.
  Cristae: These are the folds of the inner membrane. They increase the surface area of the inner membrane, therefore increasing the space available for chemical reactions.
  Different cell types have different numbers of mitochondria. By example, mature red blood cells

have none at all, whereas liver cells can have more than 2,000. Around 40 percent of the cytoplasm in heart muscle cells is taken up by mitochondria. Cells with a high demand for energy tend to have greater numbers of mitochondria.
Although mitochondria are oval-shaped organelles, they are constantly dividing (fission) and bonding together (fusion). So, in reality, these organelles are linked together in ever-changing networks.

Mitochondrial vs. Nuclear DNA

- The mitochondrial genome is circular, whereas the nuclear genome is linear.
- The mitochondrial genome is built of 16,569 DNA base pairs, whereas the nuclear genome is made of 3.3 billion DNA base pairs.
- The mitochondrial genome contains 37 genes that encode 13 proteins, 22 tRNAs, and 2 rRNAs.
- The 13 mitochondrial gene-encoded proteins all instruct cells to produce protein subunits of the enzyme complexes of the oxidative phosphorylation system, which enables mitochondria to act as the powerhouses of our cells.
- The small mitochondrial genome is not able to independently produce all of the proteins needed for functionality; thus, mitochondria rely heavily on imported nuclear gene products.
- One mitochondrion contains dozens of copies of its mitochondrial genome. In addition, each cell contains numerous mitochondria. Therefore, a given cell can contain several thousand copies of its mitochondrial genome, but only one copy of its nuclear genome. The mitochondrial genome is not enveloped, and is it not packaged into chromatin.
- The mitochondrial genome contains few, if any, noncoding DNA sequences. (Three percent of the mitochondrial genome is noncoding DNA, whereas 93% of the nuclear genome is noncoding DNA).
- Some mitochondrial coding sequences (triplet codons) do not follow the universal codon usage rules when they are translated into proteins.
- Some mitochondrial nucleotide bases exhibit functional overlap between two genes; in other words, the same nucleotide can sometimes function as both the last base of one gene and the first base of the next gene.
- The mitochondrial mode of inheritance is strictly maternal, whereas nuclear genomes are inherited equally from both parents. Therefore, mitochondria-associated disease mutations are also always inherited maternally.

- Mitochondrial genes on both DNA strands are transcribed in a polycistronic manner: Large mitochondrial mRNAs contain the instructions to build many different proteins, which are encoded one after the next along the mRNA. In contrast, nuclear genes are usually transcribed one at a time from their own mRNA.

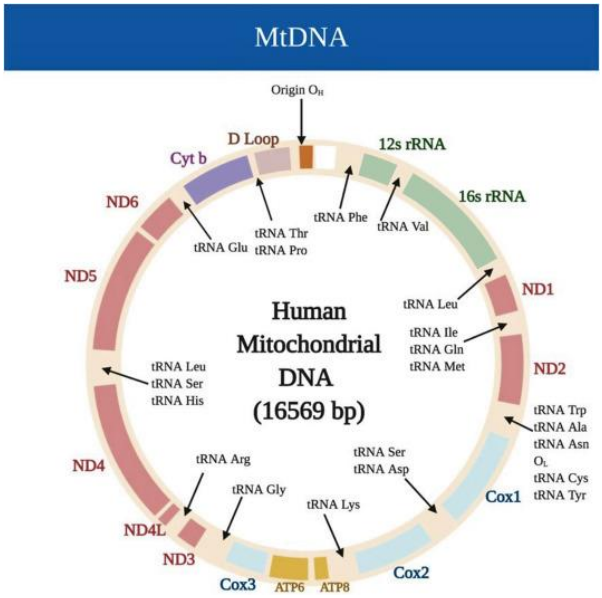
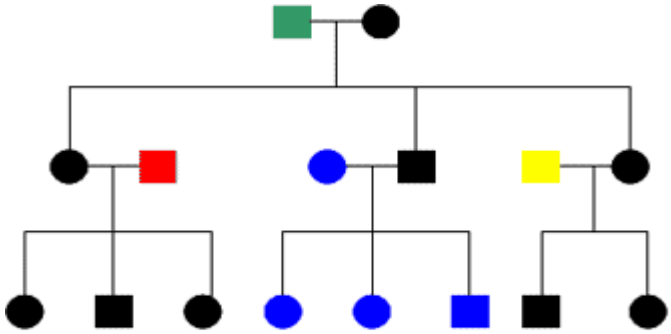


FIG. ON THE RIGHT: The mitochondrial genome is inherited from the mother in each generation.



Colors reflect inheritance of the same mitochondrial genome

1. Common Clinical Features:

Mitochondrial disorders are highly heterogeneous, but common clinical features, when they are present, may include:

1.1. Neurological Manifestations

- **Encephalopathy**: Developmental delay, cognitive impairment, or regression.
- **Seizures**: Often refractory to treatment.
- **Stroke-like episodes**: Especially in MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes).
- **Migraines** and **ataxia**.
- **Peripheral neuropathy**: Sensory or motor neuropathy.

1.2. Myopathy

- **Muscle weakness**: Proximal or generalized.
- **Exercise intolerance** and **fatigue**.
- **Ptosis** and **ophthalmoplegia** (e.g., in Chronic Progressive External Ophthalmoplegia = CPEO).

1.3. Ophthalmologic Features

- **Optic atrophy**: Vision loss (e.g., in Leber Hereditary Optic Neuropathy = LHON).
- **Retinopathy**.
- **Cataracts**.

1.4. Cardiac Involvement

- **Cardiomyopathy**: Hypertrophic or dilated.
- **Conduction defects**: Arrhythmias or heart block.

1.5. Endocrine Dysfunction

- **Diabetes mellitus**.
- **Hypoparathyroidism**.
- **Growth hormone deficiency**.

1.6. Gastrointestinal and Hepatic Features

- **Dysmotility**: Gastroparesis or constipation.
- **Liver dysfunction**: Hepatomegaly or liver failure.

1.7. Renal Involvement

- **Fanconi syndrome**: Renal tubular acidosis.
- **Nephrotic syndrome**.

1.8. Hearing Loss

- Sensorineural hearing loss (e.g., in Kearns-Sayre syndrome).

1.9. Multisystem Involvement

- Many mitochondrial disorders affect multiple systems, leading to complex phenotypes.

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2. Diagnosis of Mitochondrial Disorders

Diagnosis is challenging due to the heterogeneity of symptoms and overlap with other conditions. A combination of clinical, biochemical, imaging, and genetic tests is used.

2.1. Clinical Evaluation

- Detailed history and physical examination focusing on multisystem involvement.
- Family history (maternal inheritance suggests mtDNA mutations).

2.2. Biochemical Testing

- **Lactate and pyruvate levels**: Elevated lactate in blood or cerebrospinal fluid (CSF) is a hallmark.
- **Amino acid and organic acid analysis**: To detect metabolic abnormalities.
- **Creatine kinase (CK)**: May be elevated in myopathic forms.

2.3. Imaging

- **Brain MRI**: May show stroke-like lesions (MELAS), basal ganglia abnormalities (Leigh syndrome), or white matter changes.
- **Muscle MRI**: To assess muscle involvement.

2.4. Muscle Biopsy

- **Histopathology**: Ragged red fibers (seen with Gomori trichrome stain) or cytochrome c oxidase (COX)-negative fibers.
- **Electron microscopy**: Abnormal mitochondrial morphology.

2.5. Respiratory Chain Enzyme Analysis

- Measurement of mitochondrial enzyme activities in muscle or fibroblasts (e.g., complexes I–V).

2.6. Genetic Testing

- **mtDNA analysis**: To detect point mutations, deletions, or duplications.
- **Nuclear DNA analysis**: For mutations in nuclear genes encoding mitochondrial proteins.
- **Next-generation sequencing (NGS)**: Whole exome sequencing (WES) or whole genome sequencing (WGS) for comprehensive genetic diagnosis.

2.7. Functional Studies

- **Oxygen consumption assays**: To assess mitochondrial function in cultured cells.
- **Fibroblast studies**: For biochemical and genetic confirmation.

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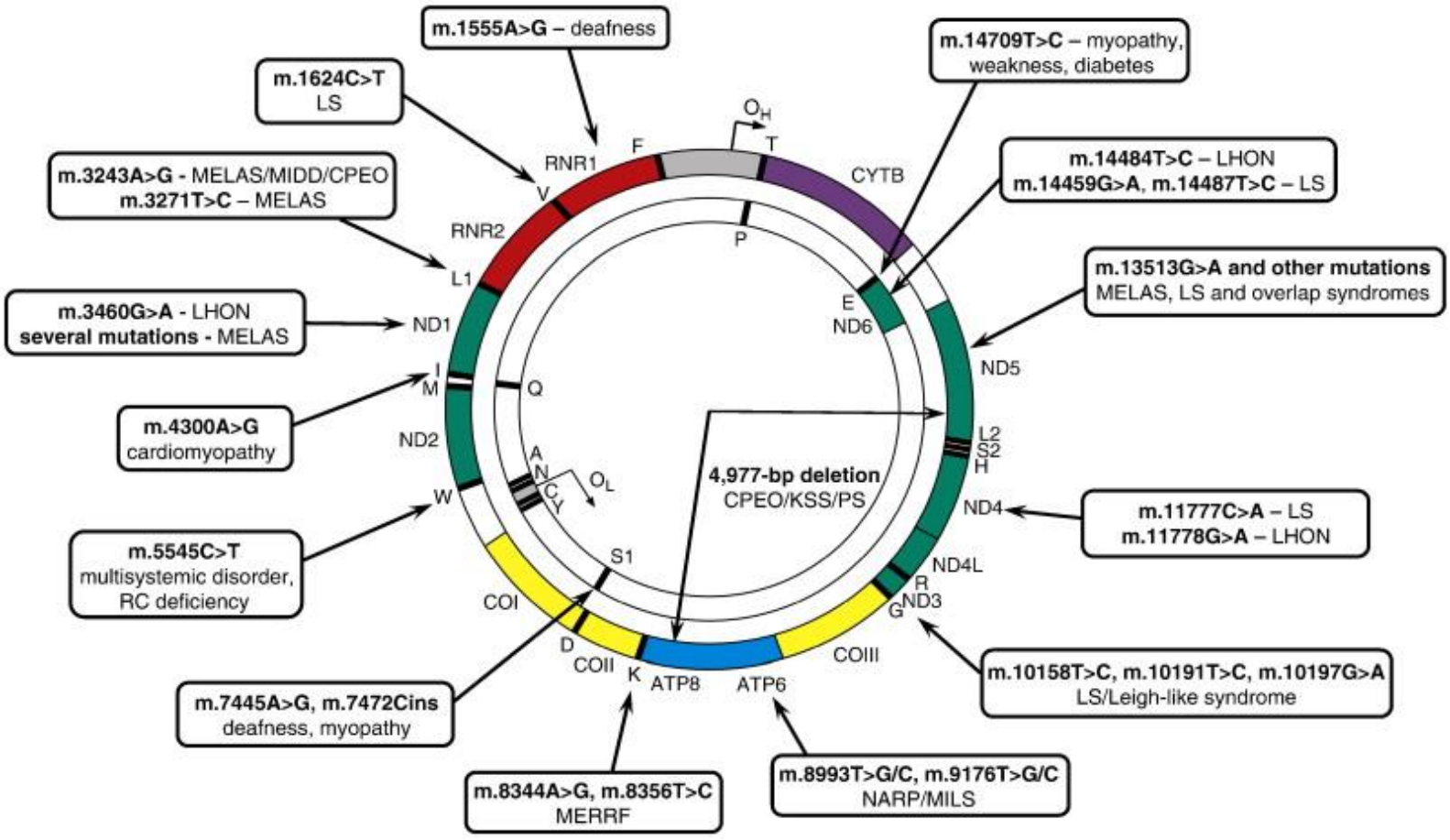
3. Mitochondrial Disorders:



Genotype:phenotype correlations in human mitochondrial disease

CPEO, chronic progressive external ophthalmoplegia; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy and ragged red fibres; MILS, maternally inherited Leigh syndrome; NARP, neurogenic weakness, ataxia, and retinitis pigmentosa; PS, Pearson syndrome.

3.1. Leber's Hereditary Optic Neuropathy (LHON)

- **Prevalence:** 1 in 30,000–50,000
- **Causal Genes:** mtDNA (MT-ND1, MT-ND4, MT-ND6)
- **Symptoms:** Painless, rapid vision loss due to optic nerve degeneration
- **Diagnosis:** Genetic testing, ophthalmologic exam, fundus photography
- **Treatment/Management:** Idebenone (antioxidant), supportive care
- **Prognosis:** Variable, some spontaneous recovery but often permanent vision loss
- **Future Perspectives:** Gene therapy trials, mitochondrial replacement strategies

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3.2. Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS)

- **Prevalence:** 1 in 4,000–10,000
- **Causal Genes:** mtDNA (MT-TL1, MT-ND5, MT-TK)
- **Symptoms:** Stroke-like episodes, seizures, muscle weakness, diabetes, hearing loss
- **Diagnosis:** Blood lactate, MRI, muscle biopsy, genetic testing
- **Treatment/Management:** Coenzyme Q10, arginine supplements, seizure control
- **Prognosis:** Progressive neurodegeneration, reduced lifespan
- **Future Perspectives:** Mitochondrial-targeted antioxidants, gene therapy

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3.3. Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

- **Prevalence:** Rare (~1 in 400,000)
- **Causal Genes:** mtDNA (MT-TK, MT-TL1, MT-TH)
- **Symptoms:** Myoclonus, epilepsy, ataxia, hearing loss, muscle weakness
- **Diagnosis:** Muscle biopsy (ragged red fibers), genetic testing
- **Treatment/Management:** Antiepileptic drugs, CoQ10, L-carnitine
- **Prognosis:** Progressive neurological decline
- **Future Perspectives:** Mitochondrial gene editing, stem cell therapy

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3.4. Kearns-Sayre Syndrome (KSS)

- **Prevalence:** 1-3 per 100,000
- **Causal Genes:** Large-scale mtDNA deletions
- **Symptoms:** Progressive external ophthalmoplegia, pigmentary retinopathy, cardiac conduction defects
- **Diagnosis:** Muscle biopsy, genetic testing
- **Treatment/Management:** Pacemaker for cardiac issues, CoQ10, folinic acid
- **Prognosis:** Variable, cardiac complications can be fatal
- **Future Perspectives:** Mitochondrial transfer therapies

3.5. Chronic Progressive External Ophthalmoplegia (CPEO)

- **Prevalence:** ~1 in 35,000
- **Causal Genes:** mtDNA deletions or nDNA (POLG, TWNK)
- **Symptoms:** Eyelid drooping, progressive weakness of extraocular muscles
- **Diagnosis:** Genetic testing, muscle biopsy
- **Treatment/Management:** Ptosis surgery, CoQ10, physiotherapy
- **Prognosis:** Slowly progressive but non-fatal
- **Future Perspectives:** Targeted molecular therapies

3.6. Leigh Syndrome (Subacute Necrotizing Encephalopathy)

- **Prevalence:** 1 in 40,000
- **Causal Genes:** mtDNA (MT-ND5, MT-ATP6), nDNA (SURF1, PDHA1)
- **Symptoms:** Neurodevelopmental delay, dystonia, breathing problems
- **Diagnosis:** MRI (bilateral basal ganglia lesions), genetic testing
- **Treatment/Management:** Thiamine, CoQ10, ketogenic diet
- **Prognosis:** Poor, often fatal in childhood
- **Future Perspectives:** Enzyme replacement, gene therapy

3.7. Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP)

- **Prevalence:** Rare (~1 in 100,000)
- **Causal Genes:** mtDNA (MT-ATP6)

- **Symptoms:** Peripheral neuropathy, ataxia, vision loss
- **Diagnosis:** Genetic testing, muscle biopsy
- **Treatment/Management:** Symptomatic treatment, CoQ10
- **Prognosis:** Progressive disability
- **Future Perspectives:** Mitochondrial replacement therapies

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3.8. Pearson Syndrome

- **Prevalence:** Extremely rare (~1 in 1,000,000)
- **Causal Genes:** Large-scale mtDNA deletions
- **Symptoms:** Sideroblastic anemia, pancreatic dysfunction
- **Diagnosis:** Bone marrow biopsy, genetic testing
- **Treatment/Management:** Blood transfusions, pancreatic enzyme replacement
- **Prognosis:** Often fatal in infancy, survivors may develop KSS
- **Future Perspectives:** Gene therapy, stem cell transplantation

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3.9. Mitochondrial DNA Depletion Syndrome (MDDS)

- **Prevalence:** Rare (~1 in 40,000)
- **Causal Genes:** nDNA (TK2, RRM2B, DGUOK)
- **Symptoms:** Muscle weakness, liver failure, encephalopathy
- **Diagnosis:** Muscle biopsy, genetic testing
- **Treatment/Management:** Supportive care, nucleoside therapy
- **Prognosis:** Poor, often fatal in childhood
- **Future Perspectives:** Gene therapy trials

3.10. Barth Syndrome

- **Prevalence:** ~1 in 300,000 (X-linked)
- **Causal Gene:** nDNA (TAZ)
- **Symptoms:** Cardiomyopathy, neutropenia, muscle weakness
- **Diagnosis:** Genetic testing, lipid analysis
- **Treatment/Management:** Cardiac support, antibiotics
- **Prognosis:** Variable, heart failure risk

- **Future Perspectives:** Enzyme replacement, gene therapy

3.11. Alpers-Huttenlocher Syndrome

- **Prevalence:** ~1 in 100,000
- **Causal Gene:** nDNA (POLG)
- **Symptoms:** Seizures, liver dysfunction, neurodegeneration
- **Diagnosis:** EEG, genetic testing
- **Treatment/Management:** Antiepileptics (avoid valproate)
- **Prognosis:** Fatal in early childhood
- **Future Perspectives:** Mitochondrial-targeted therapies

3.12. Progressive Infantile Poliodystrophy

- **Prevalence:** Rare
- **Causal Gene:** nDNA (SUCLA2, SUCLG1)
- **Symptoms:** Hypotonia, lactic acidosis, neurodevelopmental delay
- **Diagnosis:** Genetic testing, metabolic screening
- **Treatment/Management:** Symptomatic treatment
- **Prognosis:** Poor
- **Future Perspectives:** Genetic therapy

3.13. Sengers Syndrome

- **Prevalence:** Extremely rare
- **Causal Gene:** nDNA (AGK)
- **Symptoms:** Congenital cataracts, hypertrophic cardiomyopathy
- **Diagnosis:** Genetic testing, muscle biopsy
- **Treatment/Management:** Symptomatic care
- **Prognosis:** Poor, early death
- **Future Perspectives:** Gene therapy

3.14. Coenzyme Q10 Deficiency

- **Prevalence:** Rare

- **Causal Gene:** nDNA (COQ2, COQ9)
- **Symptoms:** Myopathy, ataxia, nephropathy
- **Diagnosis:** Muscle biopsy, genetic testing
- **Treatment/Management:** CoQ10 supplementation
- **Prognosis:** Improves with treatment
- **Future Perspectives:** Better delivery systems for CoQ10

3.15. Leigh-like Syndrome

- **Prevalence:** Rare
- **Causal Genes:** mtDNA (MT-ND3, MT-ND5), nDNA (PDHX, SURF1)
- **Symptoms:** Neurological decline, seizures, dystonia
- **Diagnosis:** MRI, genetic testing
- **Treatment/Management:** Supportive care
- **Prognosis:** Poor
- **Future Perspectives:** Gene editing, personalized medicine

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4. Conclusion:

This review offered up-to-date information on mitochondrial diseases, encompassing aspects such as prevalence, genetic causes, clinical manifestations, diagnostic methodologies, treatment options, and future research directions.
It discussed the complexities of diagnosing mitochondrial disorders, emphasizing the need for a multidisciplinary approach, and it highlighted the advancements in genetic testing and personalized management strategies.

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