# Epidemiology and Genetics of Mitochondrial Myopathies

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Mitochondrial myopathies represent a heterogeneous group of diseases caused mainly by genetic mutations to proteins that are related to mitochondrial oxidative metabolism. The International Workshop of Experts in Mitochondrial Diseases defined mitochondrial myopathies as a group of progressive muscle conditions, primarily caused by the impairment of oxidative phosphorylation (OXPHOS).

Keywords: mitochondria ; oxidative metabolism ; electron respiratory chain ; mutations

## 1. Introduction

In 1988, Wallace et al. showed that a mitochondrial DNA mutation was associated with Leber's hereditary optic neuropathy. Specifically, this mutation converted a highly conserved arginine to a histidine at codon 340 in the NADH dehydrogenase subunit 4 gene [1].

The discovery of mutations in the mitochondrial DNA (mtDNA) led to an explosive expansion of research on mitochondrial myopathies. Over the past two decades, the rapid pace of identification of these clinically diverse disorders and their associated gene defects has left many physicians bewildered about the variety and complexity of these peculiar syndromes. Mitochondria are complex and fundamental organelles that play a central role in energetic metabolism of the cell. In facts, for many of the cells of our organism, mitochondria represent the powerhouse (i.e., the main source for ATP synthesis). This synthesis originates from an aerobic metabolism (i.e., fatty acids, carbohydrates, and amino acids are broken down to form $CO_2$ and $H_2O$). To realize this energetic process some fundamental steps must be implemented: (1) substrate transport; (2) substrate utilization by the Krebs cycle, beta-oxidation and so on; (3) electron transport chain; and (4) oxidative phosphorylation.

It is important to underline that this is only one of the interconnected functions of mitochondria which also regulate nucleotide and lipid synthesis, protein modification, calcium metabolism, free radical production and related signalling pathways, maintenance of the lipid membrane, fusion and fission activities, participation in immunity and programmed cell death.

Importantly, all organs/tissues which heavily rely on oxidative metabolism can show typical clinical manifestations related to energetic deficit (muscle, heart, nervous system, kidneys, endocrine organs).

On this basis, mitochondrial myopathies are a heterogeneous group of diseases mainly originating by the inability of mitochondria to sustain cellular energy demands due to structural and functional alterations of the whole oxidative metabolism apparatus.

Recently, the International Workshop of Experts in Mitochondrial Diseases defined mitochondrial myopathies as a group of progressive muscle conditions, primarily caused by the impairment of oxidative phosphorylation (OXPHOS). Myopathy is a typical manifestation of mitochondrial disorders because skeletal muscles show a high cellular energy demand. However, patients with mitochondrial myopathy often have dysfunction in different organs/tissues resulting in a high variability in clinical phenotype with significant influences on prognosis and, eventually, therapeutic approaches (**Table 1**) [2].

**Table 1.** Typical mitochondrial myopathies that are generally multisystem disorders.

| Myophathy | Pathogenesis | Inheritance | Age | Mitochondrial Target | Main Symptoms | Prognosis |
|---|---|---|---|---|---|---|
| Kearns-Sayre syndrome (KSS) | single large-scale deletions of mtDNA | generally, not inherited. (sporadic), rare case of mitochondrial, autosomal dominant, or autosomal recessive | before the age of 20 | Mainly cyt C oxidase | progressive external ophthalmoplegia, and pigmentary retinopathy. cardiac conduction block, cerebrospinal fluid protein greater than 100 mg/dL, cerebellar ataxia, short stature, deafness, dementia, and endocrine abnormalities | slowly progressive disorder. Prognosis related to level of organs involvment. arrythmias |
| Chronic progressive external ophthalmoplegia (CPEO) | Deletion/mutation of mtDNA (i.e., tRNA at nucleotide 3243 in which there is an A to G), or nuclear genes: *POLG*, *C10orf2*, *RRM2B*, *SLC25A4*, *POLG2*, *DGUOK*, *SPG7* | sporadic, mitochondrial, autosomal dominant, or autosomal recessive | Aroud 40s years | defective function of oxidative phosphorylation | Ptosis, Limited eye movements, and Hearing loss, Mild muscle weakness, dysphagia, cataracts | prognosis depends on the associated features, |
| Leigh syndrome | Different pathogenic mutations identified in over 85 genes | nuclear or mtDNA mutations. | Generally, infancy and childhhod | Dysfunction of pyruvate dehydrogenase complex and oxidative phosphorylation | Mainly developmental delay or psychomotor regression failure to thrive, weakness/hypertonia, ataxia, oculomotor palsy, seizures, lactic acidosis | generally poor |
| Mitochondrial DNA depletion syndrome (MDS) | Different mutations in the TK2,SUCLA2, SUCLG1, RRM2B, DGUOK, MPV17, POLG, C10orf2; TYMP genes | Maternal and autosomal recessive | newborns, infants, children, or adult | different subunits of mitochondrial respiratory chain complexes | Different clinical pictures: Myopathic; encephalomyopathic; hepatocerebral; neurogastrointestinal | generally poor |
| Mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS) | mtDNA: m.3243A > G, gene *MT-TL* (80% of cases) and m.3271T > C tRNA mutation (10%) | maternally inherited | childhood | tRNA and NADH dehydrogenase | stroke-like episode, hemiparesis, hemianopia, or cortical blindness. focal or generalized seizures, recurrent migraine, vomiting, short stature, hearing loss, and muscle weakness. | poor |
| Myoclonus epilepsy with ragged red fibers (MERRF) | A-to-G transition at nucleotide 8344 (m.8344A > G) of the *MT-TK* genetRNA (Lys) | Spontaneous mutations, maternally inherited | Childhood, adolescence or early adulthood | oxidative phosphorylation | myoclonus, epilepsy, ataxia, myopathy, dementia, optic atrophy, deafness, peripheral neuropathy, spasticity, cardiomyopathy with WPW syndrome. | Generally poor. It can depend on age, severity of symptoms, organs involved. |
| Maternally inherited deafness and diabetes (MIDD) | mutation in mtDNA gene MT-TL1, encoding tRNA for leucine, and in rare cases in MT-TE and MT-TK genes, encoding tRNAs for glutamic acid, and lysine, respectively. | maternally inherited | mean age of onset is 30–40 years | defective function of oxidative phosphorylation | Diabetes, deafness, Chorioretinal abnormality, Dyschezia, Macular dystrophy, Malabsorption, Cerebellar hypoplasia, arrhythmias, heart failure, ophthalmoplegia, Muscular weakness, | prognosis for MIDD is better than that for MELAS |

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|---|---|---|---|---|---|---|
| **Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)** | **Mutations of TYMP gene (nDNA)** | **autosomal recessive** | **range from 5–60 years of age** | **defective function of oxidative phosphorylation** | **gastrointestinal disorders (dysphagia, cramping, vomiting, diarrhea, gastroparesis intestinal pseudo-obstruction) related to abnormal bowel motility. Neurological symptoms includes chronic progressive ophthalmoplegia, sensorimotor peripheral neuropathy** | **progressive degenerative disorder with a poor prognosis** |
| **Neuropathy, ataxia, and retinitis pigmentosa (NARP)** | **More frequent: m.8993T > C/G subunit 6 of mt ATPase gene** | **maternally inherited** | **Childhood** | **defective function of oxidative phosphorylation** | **sensory neuropathy, muscle weakness; ataxia, retinitis pigmentosa, developmental delay, seizures, dementia, deafness, arrhythmias.** | **poor prognosis** |

Last, but not least, clinical manifestations also depend on the number of mitochondria that harbour the alteration. In facts, mitochondria contain their own DNA, and this gives them peculiar genetic characteristics with significant clinical implications.

## 2. Epidemiology

Epidemiological studies on mitochondrial myopathies show the same typical difficulties because of the complexity of mitochondrial genetics with their intriguing genotype/phenotype inter-relationships. In fact, a single-point mutation in the mtDNA may produce isolated chronic progressive external ophthalmoplegia in one patient, and in another, a typical mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. Yet, deletions in mtDNA may lead to either isolated ophthalmoplegia or to a more complex Kearns–Sayre syndrome. Moreover, some mitochondrial disorders, such as Leigh syndrome, may be caused by mutations in either mtDNA or a nuclear genome. In the case of Leigh syndrome, mutations have been identified in more than 30 different genes, and all show an effect on genes encoding proteins with fundamental roles in mitochondrial oxidative metabolism. Such a genetic and clinical heterogeneity causes problems in correct identification and diagnosis.

In spite of these difficulties, epidemiologic data seem to suggest that the mitochondrial diseases caused by all mtDNA mutations are not so rare. For example, studies realized in Northern England [3], Finland, Sweden, and Australia, showed disease prevalence (/100,000) of 6.57, 5.71, 4.7, 5.0, respectively [4][5]. Differently, 1 in 34,000 adults is affected by a mitochondrial disease due to nDNA mutation. Similar rates in children have been observed in Europe and Asia. On this basis, by combined biochemical, histologic, and genetic criteria, the prevalence of mitochondrial diseases in children is estimated to be 4.7–15 per 100,000. In the opinion of some epidemiologists, primary mitochondrial diseases affect 1 in 5000 people. Importantly, the real prevalence is probably underestimated because of the complexity of making a correct diagnosis in patients with multisystemic symptoms and with onset ranging from infancy to adulthood [4][5].

## 3. Genetics

Mitochondrial DNA (mtDNA) is a double-stranded circular molecule, composed of 16,569 base pairs. This DNA contains 37 genes: 13 encode polypeptides; 22 encode transfer ribonucleic acids (tRNA) molecules, and two encode ribosomal RNAs (rRNAs). The 13 polypeptide units are all components of the respiratory chain. Specifically, complex I contains seven subunits by mtDNA and 39 subunits derived from nDNA, complex III contains one mtDNA-derived subunit and 10 nDNA-derived subunits, complex IV consists of three mtDNA-derived subunits and 10 nDNA-derived subunits. Importantly, the four subunits of the complex II are all derived from nDNA.

This peculiar mtDNA shows some characteristics that differentiate it from nuclear DNA. These properties are responsible for the unusual genetic and clinical features of mitochondrial myopathies, specifically:

a Each cell usually contains two copies of each autosome chromosome and a single copy of an X/Y chromosome (nDNA); however, each cell may contain hundreds to thousands copies of mtDNA, hence mitochondrial genoma is polyploid.

b mtDNA is mainly maternally inherited.

c mtDNA molecules are organized into discrete aggregates called nucleoids, which are probably linked to the internal mitochondrial membrane.

d This DNA lacks introns, so genetic information is more packed.

e Due to its intrinsic characteristics and particular location, mtDNA undergoes spontaneous mutations more easily than nDNA

These peculiar aspects should be framed in the whole genetic physiology of mitochondria. In fact, nDNA encodes for almost 1700 mitochondrial genes, including over 200 respiratory chain proteins.

So, it has to be stressed that nDNA encodes the following: (1) most electron transport chain subunits and all ancillary proteins needed for proper subunit assembly; (2) factors needed for mitochondrial protein importation; (3) factors needed for mtDNA replication, transcription, and translation ("mtDNA maintenance"); (4) factors controlling the synthesis and assembly of phospholipids in the OMM and IMM; and (5) factors controlling mitochondrial dynamics, i.e., mitochondrial motility, fusion, fission, and mitophagy; (6) moreover, nDNA mutations, at the level of mitochondria, follow Mendelian genetics (inherited in an autosomal dominant, autosomal recessive, or X-linked pattern); (7) finally, de novo sporadic mutations in nDNA, at the mitochondria level, are also described [6][7].

This complex genetic milieu contributes to some significant functional and pathophysiological properties of mitochondria [8][9][10], such as:

*Mutation rate*. As already noted, mtDNA has a high mutation rate due to the lack of histones, the lack of introns and, above all, the potential presence of high concentrations of oxygen radical species in mitochondria.

*Mitochondrial heteroplasmy*. These organelles contain their own genomes. This causes a typical polyploidy which differently characterize each mitochondria/cell/tissue. Thereby, a mutation cannot affect all mtDNA, while it will hit just some mtDNA copies of a mitochondria/cell/tissue with significant implications for the phenotypic expression of a mutation.

*Maternal inheritance*. This is a typical feature of mtDNA, due to the physiology of oocyte fertilization, in which a sperm contains only a small quantity of mitochondria, with respect to oocyte (approximately 100 times less). In addition, the paternal mitochondria are both diluted by cell divisions and mitotic segregation and destroyed via apoptosis. Thus, mitochondria and the mitochondrial genotype of a fertilized egg are derived almost entirely from the mother. Moreover, the total mitochondria content in the primordial germ cell is randomly assigned into each primary oocyte. A rapid replication (i.e., amplification) occurs in each primary oocyte. In the end, each mature oocyte contains a different proportion of possible mutant mitochondrial DNA compared with the proportion found in the primordial germ cell. Importantly, random mutations of mtDNA can also occur in the germ cells, leading to offspring with different mtDNA genotype with respect to their mothers.

*Threshold effect.* As indicated above, considering mitochondrial heteroplasmy, not all cells in a tissue may have a mutation. Consequently, a minimal number of mutated mtDNAs must be present to allow the occurrence of the mitochondrial dysfunction. Hence, the clinical picture does not become evident until enough cells are affected, which in turn also depends on the importance of oxidative metabolism for the cell/tissue/organ. The threshold effect may vary between different tissues (brain, retina, muscles, heart, and kidney). Importantly, the mutation load in the cell/tissue/organ correlates with the severity of the disease and generally for overt disease, the mutation load is high (≥80 percent). Cells with high oxidative metabolism are heavily affected by mtDNA mutations; therefore, these disorders tend to affect disproportionately the brain and muscle (encephalomyopathies).

*Mitotic segregation*. This is the feature by which mitochondria are randomly distributed during cell division. This may cause variation in the amount of mutant mtDNA in a cell. The consequence is a possible modification of clinical phenotype when the level of mutant mtDNA overcomes the threshold for the specific tissue/organ.

*Postmitotic replication*. mtDNA replicates independently by cell cycle. This mtDNA replication in terminally differentiated cells (i.e., neurons or muscle cells) in response to specific stimuli (exercise, increased metabolic demand) may explain

how the clinical symptoms can occur later in life.

Last but not least, it is also important to consider potential congenital (for example: genes: COQ2-7, PDSS1-2. and so on) or acquired derangements (for example, by drugs such as statins) of factors involved in CoQ synthesis, which may differently impair electron flux [2][4][7].

## References


1. Wallace, D.C.; Singh, G.; Lott, M.T.; Hodge, J.A.; Schurr, T.G.; Lezza, A.M.; Elsas, L.J., 2nd; Nikoskelainen, E.K. Mitochondrial DNA mutation associated with Leber's hereditaryoptic neuropathy. Science 1988, 242, 1427–1430.
2. Arena, I.G.; Pugliese, A.; Volta, S.; Toscano, A.; Musumeci, O. Molecular Genetics Overview of Primary Mitochondrial Myopathies. J. Clin. Med. 2022, 11, 632.
3. Bargiela, D.; Yu-Wai-Man, P.; Keogh, M.; Horvath, R.; Chinnery, P.F. Prevalence of neurogenetic disorders in the North of England. Neurology 2015, 85, 1195–1201.
4. DiMauro, S.; Nishino, I.; Hirano, M. Mitochondrial Myopathies. In Neuromuscular Disorders in Clinical Practice; Katirji, B., Kaminski, H.J., Ruff, R.L., Eds.; Springer Science + Business Media: New York, NY, USA, 2014.
5. Gayathri, N.; Deepha, S.; Sharma, S. Diagnosis of primary mitochondrial disorders—Emphasis on myopathological aspects. Mitochondrion 2021, 61, 69–84.
6. DiMauro, S.; Schon, E.A.; Carelli, V.; Hirano, M. The clinical maze of mitochondrial neurology. Nat. Rev. Neurol. 2013, 9, 429–444.
7. Lightowlers, R.N.; Taylor, R.W.; Turnbull, D.M. Mutations causing mitochondrial disease: What is new and what challenges remain? Science 2015, 349, 1494–1499.
8. Li, D.; Liang, C.; Zhang, T.; Marley, J.L.; Zou, W.; Lian, M.; Ji, D. Pathogenic mitochondrial DNA 3243A>G mutation: From genetics to phenotype. Front. Genet. 2022, 13, 2915.
9. Shoop, W.K.; Gorsuch, C.L.; Bacman, S.R.; Moraes, C.T. Precise and Simultaneous Quantification of Mitochondrial DNA Heteroplasmy and Copy Number by Digital PCR. J. Biol. Chem. 2022, 298.
10. Chiaratti, M.R.; Chinnery, P.F. Modulating mitochondrial DNA mutations: Factors shaping heteroplasmy in the germ line and somatic cells. Pharmacol. Res. 2022, 185, 106466.