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MITOCHONDRIAL DNA MUTATIONS IN HUMAN DISORDERS: MOLECULAR IMPACTS AND CLINICAL IMPLICATIONS

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Abstract

Many human disorders that effect the brain, muscles, heart, and body metabolism are now recognized to be significantly influenced by mitochondrial abnormalities. This overview describes how these mutations arise, how they lead to illness, and how to identify and treat them. (Venditti & Di Meo, 2020). The regular process of energy synthesis in mitochondria is disrupted by alterations in mitochondrial DNA, such as point mutations, deletions, and rearrangements. Less ATP is generated as a result, which causes metabolic complications and progressive cell damage, particularly in tissues with high energy requirements. (De Gaetano and others, 2021).The diagnosis of mtDNA mutations has significantly improved thanks to modern diagnostic methods including next-generation sequencing, digital PCR, and computer-based heteroplasmy analysis. These methods have also helped medical professionals better comprehend the connection between genetic alterations and clinical symptoms. (Silvestri et al., 1992). Future research should aim to improve diagnostic standards, develop safer gene-based treatments, and create preventive strategies to effectively use mitochondrial genetic knowledge in clinical medicine. (Silvestri et al., 1992).

INTRODUCTION

A distinctive feature of mitochondria is their compact, circular genome (16.6 kb) that encodes 13 essential subunits of the respiratory chain, 22 tRNAs and 2 rRNAs, with the remaining mitochondrial proteins encoded in the nucleus and imported post-translationally (Biro, 2022). This streamlined architecture, the absence of protective histones and limited DNA-repair pathways help explain why mitochondrial DNA (mtDNA) accumulates mutations more readily than nuclear DNA, with functional consequences that are most evident in high-energy tissues such as brain, heart and skeletal muscle (Akhmedov & Marín García, 2015; Gaziev et al., 2014).

MtDNA variants arise through endogenous processes especially replication errors and damage from reactive oxygen species (ROS) produced as by-products of respiration, as well as from exogenous exposures (Venditti & Di Meo, 2020). The resulting spectrum includes point mutations, deletions and rearrangements that can impair OXPHOS, disrupt metabolic homeostasis and alter apoptotic signaling (Mayr et al., 2015; Smeitink et al., 2006). Recent work refines our understanding of how ROS injures mtDNA and how such damage feeds back to reinforce mitochondrial dysfunction, contributing to degenerative phenotypes.

A defining principle of mitochondrial genetics is heteroplasmy, the coexistence of wild-type and mutant mtDNA within a cell or tissue. Disease risk and severity usually follow a threshold effect: clinical expression emerges once the proportion of

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deleterious genomes exceeds a tissue-specific level (Lage et al., 2008). Advances in population-scale and single-cell analyses now quantify heteroplasmy dynamics, estimate human mtDNA mutation rates and reveal how selection constrains the expansion of truncating variants over the life course (Kim, 2023; Lage et al., 2008). These insights clarify why phenotypes vary widely among carriers and even between tissues of the same individual. (Venditti & Di Meo, 2020).

Clinically, mtDNA mutations underlie a spectrum of disorders, from classic neuromuscular syndromes such as MELAS, MERRF and LHON to cardiomyopathies, endocrine disease and contributions to neurodegeneration and aging, reflecting both the centrality of mitochondrial bioenergetics and the mosaic distribution of mutant load (Cohen, 2013; Martins, 2024). While robust associations are established for many primary mitochondrial diseases, emerging evidence continues to map how somatic and germline mtDNA variation modifies disease trajectories across common conditions, including cancer and age-related decline (Kopinski et al., 2021; Li et al., 2019; Smith et al., 2022).Together, these developments motivate a timely synthesis of the molecular impacts of mtDNA mutations and their clinical implications, with an eye toward precision approaches in mitochondrial medicine (Bottani et al., 2020; Macken et al., 2021; Rahman & Rahman, 2018).

Structure and Genetic Characteristics of Mitochondrial DNA

The human mitochondrial genome (mtDNA) is a compact, double-stranded, circular molecule of approximately 16.5 to 16.6 kilobases (kb) in length. Unlike the large and highly structured nuclear genome, mtDNA remains relatively small and efficient: it encodes 13 essential polypeptides that are integral subunits of the oxidative phosphorylation (OXPHOS) system, along with 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs) needed for mitochondrial translation (Dawod, 2021; Mingroni Netto, 2021; Schon, 2025).

Core Genome Features

The overall architecture of mtDNA is streamlined: the genes are arranged without introns, and two pairs of genes overlap in reading frame, reflecting the evolutionary pressure to minimize genome size within the mitochondrial matrix. Much of the genome is transcribed as long polycistronic transcripts from both the heavy (H) strand and the light (L) strand; the non-coding control region (also called the D-loop region) serves as the major regulatory hub for replication and transcription initiation (Adams et al., 1986; MW et al., 2013). Because of the compact gene arrangement, the heavy-strand encodes the majority of polypeptides, rRNAs and a subset of tRNAs; the light strand additionally encodes a smaller set of tRNAs and one of the polypeptides (Adams et al., 1986).

Mutation Rate and Unique Genome Vulnerabilities

Several characteristics set mtDNA apart from nuclear DNA in terms of mutational vulnerability: The absence of introns and the high density of coding sequence means that many nucleotide changes affect gene function directly. Its proximity to the inner mitochondrial membrane and the OXPHOS complexes increases exposure to reactive oxygen species (ROS), contributing to DNA damage (Shokolenko & Alexeyev, 2022). Copy number is high but variable across cell types, and the repair and replication machinery are less redundant than those for nuclear DNA. Altogether, estimates place the human mtDNA mutation rate at perhaps 10- to 100-fold higher than that of nuclear DNA per site per generation in some contexts (Otten & Smeets, 2015).

Coordination between Nuclear and Mitochondrial Genomes

Although mtDNA encodes only 13 protein subunits of the respiratory chain, the complete OXPHOS machinery requires over a thousand proteins, the vast majority of which are encoded in the nuclear genome. This dual-genome architecture creates a finely tuned system of cross-compartment coordination: nuclear-encoded mitochondrial proteins (imported into mitochondria) must interact precisely with mtDNA-encoded subunits to assemble

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functional respiratory complexes (Sloan & Taylor, 2011). Disruption of this coordination for instance, through mtDNA mutations that alter a subunit, can destabilize the entire complex, triggering compensatory responses from nuclear-encoded elements or leading to mitochondrial dysfunction (Rahman, 2020).

Replication and Repair Mechanisms

Replication of mtDNA is carried out by a dedicated replisome that is largely composed of nuclear-encoded factors: DNA polymerase γ, the mitochondrial helicase Twinkle, the mitochondrial single-strand binding protein, and accessory proteins. The canonical model involves initiation at the heavy-strand origin followed by light-strand origin initiation, although recent data suggest additional flexibility (e.g., strand-coupled replication) in mammalian mitochondria (Lavrov & Pett, 2016). Repair of mtDNA damage uses a subset of nuclear DNA repair pathways (for example base-excision repair) but lacks many of the complex repair systems found in the nucleus (such as nucleotide excision repair). Because mtDNA exists in multiple copies per mitochondrion, cells can tolerate a certain proportion of mutated genomes (heteroplasmy) while still maintaining function, but the cumulative burden of mutations plus imperfect repair eventually contributes to disease or aging phenotypes (Freitas Jr, 2007).

Mechanisms of Mitochondrial DNA Mutations

Mitochondrial DNA (mtDNA) is subject to multiple mutational mechanisms—both endogenous and exogenous- that underlie the broad phenotypic spectrum of mitochondrial disorders (Taylor & Turnbull, 2005).

Endogenous mechanisms

One major source of mtDNA damage is oxidative stress arising from reactive oxygen species (ROS), which are generated as natural by-products of the mitochondrial respiratory chain. Because mtDNA lies in close proximity to the inner mitochondrial membrane and lacks histones and other protective chromatin structures, it is particularly prone to oxidative lesions (Beckman & Ames, 1999).

Exogenous Factors

Mutations in mitochondrial DNA can be increased not just by internal damage but also by external influences. mtDNA can be harmed by exposure to ultraviolet (UV) light, toxins in the environment, and some drugs, particularly those that disrupt mitochondrial enzymes or raise the generation of free radicals. According to research, harmful chemicals can cause deletions and structural alterations in the mitochondrial genome by disrupting the proper replication of mitochondrial DNA. (Venditti & Di Meo, 2020).

Types of mutation:

Point mutations involve a change in a single nucleotide in the mtDNA sequence. These are the most common type of mtDNA mutations. They are often linked with mitochondrial diseases and are also seen during the aging process. Even a small change like this can disturb energy production in cells. Chinnery, P. F., & Hudson, G. (2013). Deletions occur when large sections of mtDNA are lost. These deletions may remove several thousand base pairs. Such mutations are commonly associated with disorders like chronic progressive external ophthalmoplegia (CPEO), which mainly affects eye and muscle function. (Aw et al., 2018). Insertions happen when extra DNA segments are added, while rearrangements involve changes in the normal order of genes. These types of mutations are less common than point mutations or deletions. Stewart & Chinnery, 2015; Gorman et al., 2016).

Heteroplasmy and the Threshold Effect

Heteroplasmy in mitochondrial genetics refers to the presence of both normal and mutant mitochondrial DNA in similar tissues. The quantity of altered mitochondrial DNA varies depending on the cell, tissue, and individual. This polymorphism is crucial to the development of mitochondrial disorders. Chinnery, P. F., & Hudson, G. (2013).

Heteroplasmy and the threshold effect are intimately related. Typically, mitochondrial malfunction only manifests when the amount of altered mitochondrial DNA exceeds a threshold. Each tissue has a varied threshold based on how much energy it requires. Normal mitochondrial DNA can compensate when the percentage of mutant

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mitochondrial DNA is less than this, allowing the cell to continue operating normally. (Aw et al., 2018). However, energy production stops and illness symptoms start to manifest if the mutation level is over the threshold (Stewart & Chinnery, 2015; Gorman et al., 2016).

Pathogenic Consequences of mtDNA Mutations

Mutations in mitochondrial DNA (mtDNA) precipitate a cascade of molecular and cellular dysfunctions, ultimately manifesting as diverse human disorders (Chinnery & Turnbull, 2000). The primary linkage begins with disruption of oxidative phosphorylation (OXPHOS), but extends to effects on metabolism, apoptosis regulation, nuclear gene expression and tissue- specific vulnerabilities (Zhao & Sumberaz, 2020).

Impact on Oxidative Phosphorylation (OXPHOS)

Reduced ATP Production

Since the mitochondrial genome encodes 13 essential subunits of the respiratory chain, mtDNA-encoded mutations frequently impair assembly or function of OXPHOS complexes. For instance, the well characterised T8993G mutation in the MT-ATP6 gene leads to defective ATP synthase function, impaired proton translocation and markedly reduced ATP production. More broadly, reviews of mitochondrial-disease cases note that OXPHOS impairment is the hallmark of mtDNA-linked disorders, with bioenergetic failure seen in brain, muscle or heart. When ATP synthesis falls below demand, cells shift toward less efficient energy pathways (e.g., glycolysis) or become unable to maintain ion gradients, biosynthetic reactions or repair mechanisms. This energy shortfall is a root cause of many clinical manifestations of mitochondrial disease (Solaini et al., 2011).

Disturbances in Metabolic Homeostasis and Apoptosis Regulation

Beyond energy failure, mtDNA mutations upset broader metabolic homeostasis. Impaired Mitochondria are central regulators of the intrinsic apoptosis pathway. (Aw et al., 2018). mtDNA mutations that compromise mitochondrial function can prompt release of pro-apoptotic factors (e.g., cytochrome c) and activate caspase-dependent or -independent cell death pathways. For example, fibroblasts with the T8993G mutation show increased apoptotic cell death and elevated free radical production. As a result, tissues with high bioenergetic demands may undergo progressive cell loss or fail to regenerate, contributing to organ dysfunction (Solaini et al., 2011).

Secondary Effects on Nuclear Gene Expression

Although mtDNA-encoded subunits are relatively few, their malfunction disrupts the interplay between mitochondrial and nuclear genomes (mito-nuclear cross-talk). Dysfunctional mitochondria trigger signaling to the nucleus that leads to changes in gene expression aimed at compensating for the bioenergetic defect or managing stress (upregulation of antioxidant genes, mitophagy related genes, and mitochondrial biogenesis factors). In some cases, this mitochondrial signaling becomes maladaptive, promoting altered metabolic states, stress responses or inflammation which further contribute to disease phenotypes (DeLong, 1998).

Tissue-Specific Vulnerability (Brain, Muscle, Heart)

Though mtDNA mutations are present systemically, manifestations are often tissue-selective. Organs such as the brain, skeletal muscle and heart are particularly vulnerable because of their high energy consumption, reliance on mitochondrial ATP production, and limited regenerative capacity. For example, in the brain, severe mtDNA-linked OXPHOS deficiencies (e.g., in Leigh syndrome) produce marked necrotic lesions in basal ganglia and brainstem nuclei. Additionally, recent evidence suggests that even within tissues, differences in mitochondrial biogenesis, mtDNA copy number and mitophagy efficiency contribute to variable vulnerability (Cheng & Ristow, 2013; Ryter et al., 2013).

mtDNA Mutations and Associated Human Disorders

Mitochondrial DNA mutations give rise to a broad clinical spectrum. The phenotypes reflect

(i) Which respiratory-chain complex is affected, (ii) the mutant load (heteroplasmy), and (iii) tissue energy demand (Ryter et al., 2013). A structured

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overview of mtDNA mutation classes, their effects on OXPHOS biogenesis, and representative disease phenotypes is provided in Table 01.

Neuromuscular Disorders

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) Most MELAS cases are caused by the m.3243A>G variant in MT-TL1 which impairs mitochondrial translation and OXPHOS, producing multisystem disease with stroke-like episodes, lactic acidosis and myopathy. Mechanistically, defective tRNA modification and codon-specific translation errors contribute to respiratory-chain insufficiency (DiMauro & Hirano, 1993; Murakami & Ono, 2017).

MERRF (Myoclonic Epilepsy with Ragged-Red Fibers)

The classic pathogenic variant is m.8344A>G in MT-TK It reduces levels and amino acylation, compromising synthesis of mtDNA-encoded subunits and leading to myoclonus, epilepsy, ataxia, and RRF pathology in muscle (Shoffner et al., 1990).

LHON (Leber Hereditary Optic Neuropathy)

LHON is most often due to complex I gene mutations, especially m.11778G>A in MT-ND4, causing selective retinal ganglion cell vulnerability and subacute optic neuropathy. The ND4 variant is the most common primary LHON mutation worldwide; synergistic variants can worsen mitochondrial dysfunction (Silvestri et al., 1992).

Mechanistic note (complex defects)

Across these syndromes, the proximate mechanism is impaired electron transfer and ATP synthesis via defects in respiratory-chain complexes I, III, IV, or V (e.g., LHON complex I; MELAS, generalized translation failure affecting multiple complexes; ATP6 mutations, complex V) (Silvestri et al., 1992).

Metabolic Disorders

Mitochondrial diabetes and myopathy

The m.3243A>G variant in MT-TL1 is also a canonical cause of Maternally Inherited Diabetes and Deafness (MIDD), illustrating how mtDNA defects disrupt pancreatic β-cell energetics and cochlear function; variable heteroplasmy explains phenotypic range from isolated diabetes to diabetes-with-myopathy. Contemporary cohorts and reviews consistently identify m.3243A>G as the predominant MIDD allele (Monaco et al., 2017).

Mitochondrial myopathies

Primary mtDNA mutations that diminish respiratory capacity produce exercise intolerance, elevated lactate, and histological hallmarks (ragged-red/COX-negative fibers), with severity tracking mutant load in muscle (Bhattacharjee et al., 2006).

Cardiac and Systemic Diseases

Cardiomyopathies

Mitochondrial cardiomyopathy arises from pathogenic mtDNA (or nuclear mitochondrial) variants that compromise ATP supply, remodel mitochondrial networks, and provoke oxidative stress in myocardium; clinical presentations span conduction disease to dilated or hypertrophic cardiomyopathy (Knockaert, 2007).

Chronic fatigue syndromes (systemic)

Multiple studies suggest mitochondrial bioenergetic abnormalities in subsets of ME/CFS patients (e.g., altered ATP dynamics, redox imbalance), though findings are heterogeneous and not specific to mtDNA disease. These observations indicate systemic consequences of mitochondrial dysfunction but require cautious interpretation (Kuo et al., 2008).

Role of heteroplasmy in disease severity

Across systems, the proportion of mutant to wild-type genomes (heteroplasmy) is a principal determinant of biochemical failure and clinical penetrance, with thresholds that are mutation and tissue-specific (Sarzi Puttini et al., 2010).

Neurodegenerative and Aging-Related Disorders

Mitochondrial dysfunction, often involving complex I defects, oxidative stress, and impaired mitophagy, modulates neuronal vulnerability in common neurodegenerative diseases; accumulating somatic mtDNA mutations further burden high-energy neural tissues (Johnson, 2015). Somatic mtDNA point mutations and large-scale deletions increase with age across human tissues (e.g., brain, skeletal

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muscle), correlating with OXPHOS defects and clonal expansion within fibers or cell populations. Recent multi-tissue and muscle studies demonstrate exponential age-related increases in deletion burden and diverse mutational spectra (Soraci et al., 2024). The relationship between specific mtDNA mutation classes and canonical mitochondrial syndromes such as MELAS, MERRF, and LHON is outlined in **Table 01.**

Table 01. Molecular Mechanisms Connecting mtDNA Perturbations to OXPHOS Failure and Disease

Mutation Class	Typical Molecular Impact (OXPHOS / Biogenesis)	Hallmark Examples (Gene / Variant)	Canonical Syndromes / Phenotypes	Key References
Point mutations (protein-coding genes)	Defective electron transport chain subunits cause reduced electron transfer efficiency, increased reactive oxygen species production, and cellular ATP deficiency	*MT-ND4* m.11778G>A (Complex I)	LHON: subacute optic neuropathy with retinal ganglion cell loss	Silvestri et al. (1992); Taylor & Turnbull (2005); Johnson (2015)
Point mutations (tRNA genes)	Impaired mitochondrial protein translation resulting in combined OXPHOS deficiency across multiple respiratory complexes	*MT-TL1* m.3243A>G (tRNALeu(UUR)); *MT-TK* m.8344A>G (tRNALys)	MELAS: stroke-like episodes with lactic acidosis; MERRF: myoclonus with ragged-red fibers	Shoffner et al. (1990); DiMauro & Hirano (1993); Murakami & Ono (2017)
Large-scale deletions	Loss of multiple mitochondrial genes and open reading frames leading to defective assembly of respiratory complexes I, III, IV, and V	Common deletion (approximately 4.9–5 kb)	CPEO / KSS spectrum with progressive external ophthalmoplegia and multisystem involvement	Chomyn & Attardi (2003); Taylor & Turnbull (2005)
Insertions and rearrangements	Aberrant mitochondrial transcripts or altered replication origins causing transcriptional and replication defects	Chimeric or rearranged mtDNA species	Variable-onset multisystem mitochondrial cytopathies	Lavrov & Pett (2016); Ryzhkova et al. (2018)
Somatic mosaic variants (aging-related)	Clonal expansion of mtDNA variants in post-mitotic tissues leading to localized OXPHOS dysfunction	Tissue-specific single-nucleotide variants and deletions	Sarcopenia, modifiers of neurodegeneration, and links to neuro-inflammaging	Nissanka & Moraes (2018); Smith et al. (2022); Soraci et al. (2024)

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Table 02. Mechanistic Pathways from mtDNA Mutation to Mitochondrial and Clinical Dysfunction

Mechanistic Node	What Changes	Representative Readouts	Clinical Consequence (Tissue Bias)	Citations
OXPHOS failure	Dysfunction of respiratory chain complexes I, III, IV, and V with loss of mitochondrial membrane potential and reduced ATP production	Enzymatic activity assays, blue-native PAGE, and high-resolution respirometry	Cellular energy crisis predominantly affects neurons, skeletal myofibers, and cardiomyocytes	Solaini et al. (2011); Mayr et al. (2015)
ROS and mtDNA damage cycle	Increased mitochondrial superoxide production leading to oxidative base lesions and strand breaks, which further exacerbate respiratory chain defects	8-oxoG quantification, γH2AX staining, oxidative lesion assays targeting mtDNA	Self-amplifying damage cycle that promotes clonal expansion and heteroplasmic drift	Beckman & Ames (1999); Huang et al. (2020); Nissanka & Moraes (2018)
Heteroplasmy threshold effects	Mutant mtDNA load exceeds tissue-specific functional tolerance limits	Droplet digital PCR, next-generation sequencing–based heteroplasmy quantification, single-cell assays	Variable disease penetrance and severity across tissues and individuals	Aryaman et al. (2017); Parakatselaki & Ladoukakis (2021)
Mitonuclear signaling	Activation of mitochondrial stress responses including the	Transcriptomics, PGC-1α–regulated metabolic axes, NRF1/NRF2	Adaptive compensation or maladaptive inflammation	DeLong (1998); Sloan & Taylor

Conclusion

Mitochondrial DNA mutations are an important cause of many human diseases. These mutations are involved in a wide range of conditions, including neuromuscular disorders, metabolic problems, heart diseases, and disorders of the nervous system. Their harmful effects mainly occur because damaged mitochondria cannot produce enough energy. Reduced ATP production disturbs normal cellular activities, especially in organs that need a high amount of energy, such as the brain, muscles, and heart. Recent progress in DNA sequencing technologies and data analysis has made it easier to identify and measure mitochondrial DNA mutations. However, difficulties still exist in understanding the significance of different

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mutations, accurately measuring heteroplasmy, and using genetic findings effectively in patient care. Treatment options are gradually improving and include preventive methods such as mitochondrial replacement therapy, drug-based treatments, and early-stage gene-editing approaches.

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