Mitochondrial Mutations and Athletic Endurance: A Review of Genetics, Energy, and Training

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Abstract

Endurance performance relies on the sustained generation of adenosine triphosphate (ATP) through mitochondrial oxidative phosphorylation in skeletal muscle. Mitochondrial DNA (mtDNA), which encodes essential components of the electron transport chain, plays a critical role in determining mitochondrial efficiency and aerobic capacity. Mutations in mtDNA—ranging from point substitutions to large deletions—can impair ATP production, leading to exercise intolerance in severe cases and more subtle reductions in endurance performance in otherwise healthy individuals. In addition, naturally occurring mtDNA variation, including mitochondrial haplogroups and heteroplasmy, has been associated with interindividual differences in endurance capacity and training responsiveness. This review synthesizes current evidence on the genetic, molecular, and physiological mechanisms linking mtDNA mutations to endurance performance. It further examines how endurance training and environmental factors modulate mitochondrial function through mitochondrial biogenesis, nuclear–mitochondrial signaling, and epigenetic regulation of genes involved in energy metabolism. Advances in sequencing technologies and mitochondrial imaging have provided new insights into mutation burden, mitochondrial ultrastructure, and their relationship to fatigue resistance. Collectively, the literature indicates that mitochondrial genetics establish biological constraints on endurance performance, while training-induced adaptations and epigenetic mechanisms can partially compensate for these constraints. Understanding this interaction has important implications for athletic training, personalized exercise programs, and the early identification of mitochondrial dysfunction.

Keywords: *Mitochondrial DNA, Endurance performance, Oxidative phosphorylation, Heteroplasmy, Mitochondrial biogenesis, Exercise epigenetics*

Introduction

Mitochondria are essential bioenergetic organelles that generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), supplying the energy required for sustained skeletal muscle contraction and whole-body endurance performance. Unlike nuclear DNA, mitochondrial DNA (mtDNA) is a compact, circular genome that is typically maternally inherited and exists in many copies per cell (MedlinePlus Genetics, 2018). Human mtDNA is about 16.6 kb and encodes 13 polypeptides that are core subunits of OXPHOS complexes, along with ribosomal and transfer RNAs needed for intramitochondrial protein translation (Anderson et al., 1981; MedlinePlus Genetics, 2018). Because endurance performance depends heavily on mitochondrial oxidative capacity, mtDNA variation and mitochondrial integrity have been proposed as biologically plausible contributors to inter-individual differences in aerobic fitness, fatigue resistance, and training responsiveness.

Pathogenic mtDNA variants can arise as point mutations, insertions/deletions, or large-scale rearrangements, potentially impairing electron transport chain (ETC) function, reducing ATP yield, and increasing reliance on less efficient anaerobic metabolism (DiMauro & Schon, 2003; Taylor & Turnbull, 2005). Clinical mitochondrial disorders highlight the direct relationship between mitochondrial bioenergetics and exercise tolerance: individuals with respiratory-chain dysfunction frequently exhibit early fatigue, exercise intolerance, and reduced peak oxygen uptake (VO_2max), reflecting limitations in oxygen utilization and oxidative ATP production (DiMauro & Schon, 2003; Jeppesen, 2020). Population-based work also indicates that adult mitochondrial disease is not rare; pathogenic mutations in mtDNA and nuclear genes affecting mitochondrial biology together contribute meaningfully to adult neurologic disease burden (Gorman et al., 2015). At a mechanistic level, mtDNA-encoded subunits are integral to ETC complexes (notably complexes I, III, IV, and V), and deficits in these systems can diminish proton-motive force, constrain ATP synthase flux, and alter redox balance in working muscle (Wallace, 1999).

Importantly, not all mtDNA variation is deleterious. Much of mtDNA diversity is structured into haplogroups that reflect ancient population history and can be associated (sometimes inconsistently) with physiological traits. Multiple studies have examined whether specific mtDNA haplogroups or mtDNA/nuclear-encoded mitochondrial variants correlate with elite athlete status or endurance phenotypes (Harvey et al., 2020; Maruszak et al., 2014; Stefàno et al., 2019). For example, in a large cohort of Finnish conscripts, mtDNA haplogroups J and K were associated with a lower response in endurance-related training outcomes, suggesting that mitochondrial lineage may influence adaptability to standardized training stimuli (Kiiskilä et al., 2021). However, replication challenges and confounding by ancestry/population stratification remain major concerns in sports genomics, underscoring the need for well-powered designs and careful control of genetic background (Harvey et al., 2020; Stefàno et al., 2019).

A central complexity in mitochondrial genetics is heteroplasmy, the coexistence of more than one mtDNA sequence variant within the same cell or tissue. Because mtDNA molecules replicate and segregate stochastically, heteroplasmy levels can vary across tissues and over time, and the phenotypic impact of a mutation often depends on whether it exceeds a functional threshold in the relevant tissue (Taylor & Turnbull, 2005). As a result, interpreting mtDNA “mutation load” in the context of athletic performance requires attention to tissue specificity (e.g., blood vs. skeletal muscle), measurement approach, and the dynamic nature of mitochondrial turnover.

Beyond genetics, endurance capacity is strongly shaped by training-induced remodeling of skeletal muscle. Endurance and interval training activate energy-sensing and transcriptional pathways (e.g., AMPK–PGC-1α signaling) that promote mitochondrial biogenesis, respiratory efficiency, and substrate oxidation, thereby improving aerobic performance (Egan & Zierath, 2013). Recent human work also suggests that training status is associated with distinct epigenetic signatures in skeletal muscle (e.g., differential DNA methylation patterns in exercise-responsive genes), pointing to plausible mechanisms by which repeated exercise exposures "tune" gene regulation relevant to mitochondrial function and adaptation (Geiger et al., 2024). Collectively, these lines of evidence motivate an integrated review of how mtDNA mutations and mtDNA variation intersect with exercise physiology, training responsiveness, and emerging approaches in sports genomics and precision performance.

Methods

Review design

This article is a narrative review synthesizing evidence on (a) mtDNA structure and mutational mechanisms, (b) mitochondrial genetic variation (including haplogroups and heteroplasmy) in relation to endurance phenotypes, and (c) the extent to which endurance training and related molecular pathways can mitigate or interact with mitochondrial genetic constraints.

Literature search strategy

A structured search was conducted in PubMed and supplemented by citation-chaining from seminal reviews and high-relevance primary studies. Search terms were combined using Boolean operators and included: *mitochondrial DNA OR mtDNA*, *heteroplasmy*, *haplogroup*, *endurance*, *VO2max*, *exercise training*, *mitochondrial myopathy*, *DNA methylation*, *PGC-1alpha*, and *sports genomics*. Seminal foundational sources describing the human mitochondrial genome and core mitochondrial disease mechanisms were also included to provide biological context (Anderson et al., 1981; DiMauro & Schon, 2003; Taylor & Turnbull, 2005; Wallace, 1999).

Inclusion and exclusion criteria

Included records were English-language peer-reviewed articles (primary studies, clinical trials, cohort studies, and major reviews) addressing at least one of the following: (1) mtDNA mutations and functional consequences, (2) mtDNA haplogroups or mitochondrial genetic variants and endurance outcomes, (3) training response or exercise interventions in populations with mitochondrial dysfunction, or (4) epigenetic regulation of exercise-responsive genes relevant to endurance adaptation. Studies focused exclusively on non-exercise phenotypes without mechanistic or translational relevance to skeletal muscle energetics were deprioritized.

Study selection and synthesis

Titles/abstracts were screened for relevance, then full texts were reviewed to extract key concepts, study designs, populations, and main findings. Given the heterogeneity in athlete definitions, endurance outcomes, and genetic methods, findings were synthesized qualitatively rather than via meta-analysis. Particular attention was given to limitations common in sports genetics (e.g., underpowered candidate associations and ancestry confounding) (Harvey et al., 2020; Stefàno et al., 2019) and to clinically grounded evidence demonstrating mitochondrial constraints on exercise capacity (DiMauro & Schon, 2003; Jeppesen, 2020).

Discussion

Mechanistic plausibility: why mtDNA variation can matter for endurance

Endurance performance is fundamentally constrained by the capacity of skeletal muscle to generate ATP aerobically. Because mtDNA encodes essential ETC components, pathogenic mtDNA mutations can compromise proton gradient formation and ATP synthase flux, thereby lowering oxidative ATP yield during sustained exercise (Taylor & Turnbull, 2005; Wallace, 1999). Clinical mitochondrial respiratory-chain diseases illustrate this constraint: impaired OXPHOS is linked to exercise intolerance and reduced aerobic capacity, supporting the notion that mitochondrial genotype can be performance-limiting in severe cases (DiMauro & Schon, 2003; Jeppesen, 2020). At the population level, the measurable prevalence of pathogenic mtDNA and nuclear mitochondrial gene mutations in adults reinforces that functionally significant mitochondrial variation is present in the general population, though typically at lower penetrance or subclinical levels (Gorman et al., 2015).

Haplogroups and athlete phenotypes: promising signals, persistent limitations

A major research question is whether common mitochondrial lineages influence athletic performance or trainability. Empirical work has reported associations between mtDNA haplogroups and elite endurance status in some cohorts (Maruszak et al., 2014), while other studies emphasize that earlier candidate findings often fail replication and are vulnerable to population stratification (Harvey et al., 2020; Stefàno et al., 2019). Evidence from large conscript datasets suggests that haplogroups J and K may be linked to lower response in endurance-related training outcomes (Kiiskilä et al., 2021). Still, such associations should be interpreted cautiously because endurance is polygenic, highly environment-dependent, and sensitive to training exposure, measurement variability, and study design choices (Harvey et al., 2020). In practical terms, mtDNA haplogroup alone is unlikely to provide deterministic prediction of endurance success; its most defensible role may be as one modest contributor within a broader multi-omic and training-context framework.

Heteroplasmy and tissue specificity: the interpretive bottleneck

Heteroplasmy complicates direct translation from genotype to phenotype. The same mtDNA mutation may have minimal functional impact at low heteroplasmy but meaningful impact beyond a threshold, and heteroplasmy levels can vary dramatically by tissue and time (Taylor & Turnbull, 2005). For athlete-focused research, this implies that blood-based mtDNA measures

may not reflect skeletal muscle bioenergetic status, particularly when the trait of interest is endurance capacity. Therefore, future studies that integrate tissue-relevant sampling (when ethical/feasible), rigorous quantification of heteroplasmy, and standardized endurance endpoints may be better positioned to test causal pathways.

Training as a compensatory lever—and its interaction with genotype

Training produces robust mitochondrial remodeling via well-characterized molecular pathways. Exercise-induced energy stress activates regulators such as AMPK and promotes transcriptional programs (notably PGC-1α-linked networks) that increase mitochondrial content and oxidative enzyme capacity, supporting improved endurance performance (Egan & Zierath, 2013). Human mitochondrial physiology studies also show that endurance training can increase maximal muscle oxidative power, though mitochondrial efficiency (e.g., P/O ratio) may not change in parallel, suggesting that “more capacity” is not always equivalent to “more efficiency” (Tonkonogi & Sahlin, 2000).

Crucially, genotype may influence the degree or direction of benefit. In mouse models harboring distinct mitochondrial mutations, endurance exercise responses and underlying determinants can differ by mutation context, implying that “one-size-fits-all” prescriptions may not apply when mitochondrial defects are present (Schaefer et al., 2022). Translationally, this aligns with clinical reviews suggesting supervised aerobic training can be safe and beneficial in mtDNA-related mitochondrial myopathy, while emphasizing individualized monitoring and risk assessment (Jeppesen, 2020).

Epigenetic regulation and endurance: emerging human evidence

An important extension beyond sequence variation is whether epigenetic mechanisms shape endurance phenotypes and training responsiveness. In humans, trained vs. untrained status has been associated with differences in DNA methylation of exercise-responsive genes, potentially influencing baseline transcriptional readiness and the magnitude of acute exercise responses (Geiger et al., 2024). While this does not establish causality, it supports a model in which repeated exercise exposures contribute to stable regulatory states that interact with genetic background to produce endurance-relevant phenotypes.

Oxidative stress and antioxidants: nuance over simple supplementation claims

Exercise increases reactive oxygen species (ROS) production, and mitochondria are a major site of ROS generation during metabolic stress. The role of ROS is dual: excessive ROS can contribute to fatigue and cellular damage, yet ROS signaling can also be required for adaptive responses to training (Ristow et al., 2009). Consistent with this, literature cautions that broad antioxidant supplementation can blunt some beneficial exercise-induced adaptations in certain contexts (Ristow et al., 2009). Rather than treating “antioxidants” as uniformly beneficial, a more defensible framing is that endogenous antioxidant defense systems and redox homeostasis adapt with training and may influence fatigue and recovery (Powers et al., 2022; Tonkonogi & Sahlin, 2000). Mitochondria-targeted antioxidant strategies (e.g., MitoQ) are being explored in controlled settings, including effects on exercise-induced mtDNA damage and performance

outcomes, but these remain an evolving area with mixed evidence and context-dependent effects (Williamson et al., 2020).

Practical implications and future directions

From a performance and sports medicine perspective, the best-supported conclusion is that mitochondrial genetics can meaningfully constrain endurance in pathological contexts, while in healthy populations mtDNA variation is more likely to exert small-to-moderate effects that are strongly modulated by training exposure, environment, and study design (DiMauro & Schon, 2003; Harvey et al., 2020; Jeppesen, 2020). Future research should prioritize: (1) adequately powered, ancestry-aware cohorts; (2) standardized endurance phenotyping; (3) tissue-relevant measures of heteroplasmy and mitochondrial function; and (4) integrated models combining genetics, epigenetics, and longitudinal training data to move from association toward mechanism and actionable personalization (Geiger et al., 2024; Schaefer et al., 2022).

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