Received: 18 December 2020 | Revised: 27 May 2021 | Accepted: 28 May 2021

DOI: 10.1002/ajhb.23629

REVIEW

American Journal of Human Biology WILEY

Mitochondrial genetic variation in human bioenergetics, adaptation, and adult disease

Volney K. Friedrich[1] | **Meagan A. Rubel**[1,2] | **Theodore G. Schurr**[1]

[1]Department of Anthropology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Center for Translational Imaging and Precision Medicine, University of California – San Diego, La Jolla, California, USA

Correspondence
Volney K. Friedrich, Department of Anthropology, 421 Penn Museum, 3260 South Street, Philadelphia, PA 19104-6398, USA.
Email: volney@sas.upenn.edu

Funding information
National Science Foundation, Grant/Award Number: BCS-1751863

[Correction added on 30 June 2021, after first online publication: ORCID ID has been updated for Meagan A. Rubel.]

Abstract

Objectives: Mitochondria are critical for the survival of eukaryotic organisms due to their ability to produce cellular energy, which drives virtually all aspects of host biology. However, the effects of mitochondrial DNA (mtDNA) variation in relation to disease etiology and adaptation within contemporary global human populations remains incompletely understood.

Methods: To develop a more holistic understanding of the role of mtDNA diversity in human adaptation, health, and disease, we investigated mitochondrial biology and bioenergetics. More specifically, we synthesized details from studies of mitochondrial function and variation in the context of haplogroup background, climatic adaptation, and oxidative disease.

Results: The majority of studies show that mtDNA variation arose during modern human dispersal around the world. Some of these variants appear to have been positively selected for their adaptiveness in colder climates, with these sequence changes having implications for tissue-specific function and thermogenic capacity. In addition, many variants modulating energy production are also associated with damaging metabolic byproducts and mitochondrial dysfunction, which, in turn, are implicated in the onset and severity of several different adult mitochondrial diseases. Thus, mtDNA variation that governs bioenergetics, metabolism, and thermoregulation may potentially have adverse consequences for human health, depending on the genetic background and context in which it occurs.

Conclusions: Our review suggests that the mitochondrial research field would benefit from independently replicating mtDNA haplogroup-phenotype associations across global populations, incorporating potentially confounding environmental, demographic, and disease covariates into studies of mtDNA variation, and extending association-based studies to include analyses of complete mitogenomes and assays of mitochondrial function.

1 | INTRODUCTION

Modern humans have been subject to varying selective pressures, such as hypoxia at high altitude, temperature, dietary shifts, and disease exposure since spreading across the globe and adapting to new environments and diets (Burtscher et al., 2018; Carmody et al., 2016; Fan et al., 2016; Gu et al., 2012; Marciniak & Perry, 2017). These selective pressures may have produced mitochondrial DNA (mtDNA) variants that influenced cellular

energetics or bioenergetic phenotypes (Mishmar et al., 2003; Wallace, 2005, 2013, 2015, 2016). This review focuses on the way that human mtDNA variation may have facilitated adaptation to different environmental conditions and played a role in the etiology of complex disease.

Mitochondria are eukaryotic organelles that arose around 2 billion years ago through the incorporation of alphaproteobacteria, including a non-alphabacterial component, into the precursor of modern eukaryotic cells, resulting in a substantive increase in cell complexity (Eme et al., 2017; Friedman & Nunnari, 2014; Gray, 2015; López-García & Moreira, 2020). Importantly, mitochondria provided eukaryotic organelles with a constant source of energy—adenosine triphosphate (ATP), the basic unit of cellular energy (Gray & Archibald, 2012; Margulis, 1970). This symbiotic relationship triggered an enormous proliferation of increasingly complex eukaryotic life forms that continue to evolve today. Besides ATP production for cellular energy, mitochondria play a number of other crucial physiological and metabolic roles in eukaryotic cells. They are involved in integrating signaling pathways, responding to stressors, producing macromolecule precursors, maintaining ion homeostasis, and generating and sequestering damaging metabolic byproducts, including partially reduced forms of oxygens and superoxides, known as reactive oxygen species (ROS) (Duchen, 2004; Vyas et al., 2016).

Mitochondria have their own genome, called the mtDNA. This genome is a double stranded, circular molecule of ~16.6 kb size in humans. While nuclear DNA is present as a single copy within a cell, there can be tens to thousands of mtDNA copies within a single cell (e.g., there are over 2000 mtDNA copies in liver cells) (Duchen, 2004; Miller et al., 2003; Reynier et al., 2001). The mutation rate of mtDNA is ~100-fold higher than that of nuclear DNA (Wallace & Chalkia, 2013). This difference arises in part because of the comparatively higher rate of error introduced during replication and repair by mtDNA's sole replication and repair polymerase, Pol γ (Lee et al., 2009), and, to a lesser extent, as a result of damage caused by ROS negatively interacting with biomolecules (Radzvilavicius et al., 2016).

The high mutation rate and lack of recombination are some characteristics of mtDNA that may influence the rate of adaptation (Gu et al., 2012). For example, the high mutation rate of mtDNA has produced many of the haplogroups (matrilineal clusters of sequences, or haplotypes, sharing a common ancestry) that have arisen in geographically isolated populations (Wallace & Chalkia, 2013). Differences in the mutational composition of haplogroups may further have functional consequences that affect the risk for and protection against disease (Mishmar & Zhidkov, 2010; Wallace, 2015; Wallace & Chalkia, 2013). The lack of recombination in mtDNA also increases "genetic hitchhiking," a process where alleles may accompany nearby genetic variants undergoing a selective sweep (Chou & Leu, 2015).

Furthermore, mtDNA is overwhelmingly maternally inherited (al Rawi et al., 2011; Giles et al., 1980; Luo et al., 2018; Sato & Sato, 2013). Its matrilineal inheritance thus offers a unique evolutionary perspective through which human history can be studied. Extensive research into human evolution has focused on the phylogenetic comparison of mtDNA haplotypes (inherited groups of alleles and single-nucleotide polymorphisms (SNPs)), and haplogroups (collections of similar haplotypes with shared common ancestry). Such studies provide an increasingly clear understanding of the way that modern humans migrated across the globe over many millennia (Achilli et al., 2004; Forster, 2004; Hudjashov et al., 2007; Metspalu et al., 2004).

Although previous studies have focused on mtDNA variants and their role in disease etiology, the effects of these variants in relation to disease susceptibility, resistance, and adaptation remains incompletely understood (Chinnery et al., 2018; Mishmar & Zhidkov, 2010; Wallace, 2005, 2012, 2016, 2015). Therefore, in this review, we elaborate on the role of mitochondria in bioenergetics, human adaptation to climate, and disease risk within the context of modern human evolution.

2 | MITOCHONDRIAL BIOENERGETICS

To understand how mitochondrial bioenergetics can potentially alter human metabolism and the adaptive responses to environmental challenges, it is necessary to elucidate the biological basis of this energy production system. Mitochondrial bioenergetics are regulated by the oxidative phosphorylation (OXPHOS) pathway (Freya & Mannellab, 2000). Complex associations between subunits of the OXPHOS pathway are required for efficient electron transport and ATP production, which is the basis of organismal energy production (Figure 1). The efficiency of OXPHOS subunits function is directly correlated with the ratio of ATP synthesis per unit substrate and O_2 consumed (Lowell & Spiegelman, 2000), a phenomenon known as "mitochondrial coupling respiration."

Among the four main OXPHOS complexes, Complex I (NADH dehydrogenase) is both the main electron input of the mitochondrial respiration chain and the primary producer of cellular ROS. Increased levels of ROS are associated with cellular damage, aging, and cancer

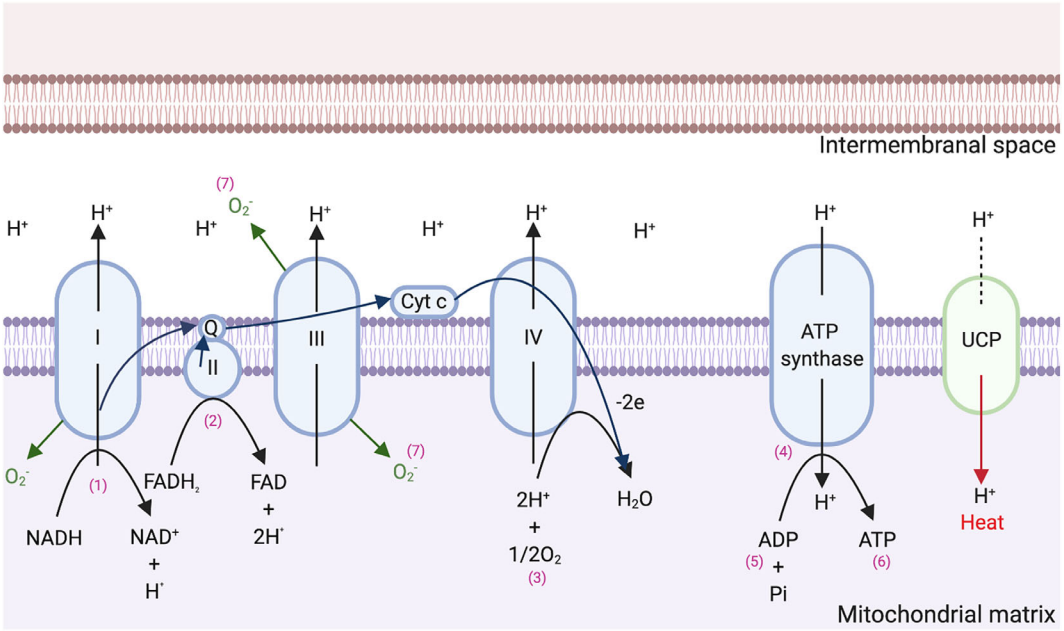

FIGURE 1 Oxidative phosphorylation and uncoupling protein. In humans, electrons derived from consumed nutrients are fed into the electron transport chain (ETC) located in the inner membrane of the mitochondria (Freya & Mannellab, 2000; Friedman & Nunnari, 2014; Mannella, 2006; Ricci et al., 2004). Electrons enter the respiratory chain at a high potential energy through complex I (NADH:ubiquinone oxidoreductase, shown as (1)) or complex II (shown reducing FADH2 (2)) and, via redox reactions, are finally delivered to an oxygen sink via complex IV (3). The energy created by these reactions powers a proton pump which creates a gradient across the inner membrane by pumping protons into the intermembrane space. The resulting gradient force is used by human mitochondrial (mt) ATP synthase, also called complex V (F0F1 ATP synthase, (4)), to phosphorylate adenosine diphosphate (ADP (5)) to ATP (6). ATP can then be used in the cell to generate energy when it is dephosphorylated and returned to its precursor components (ADP + P). Mitochondria also regulate levels of calcium, reactive oxidative species (ROS, labeled as O2- (7)), and apoptosis in the cell and the disruption of these pathways can also be characteristic of disease states (Bell et al., 2011; Chan, 2006; Pelicano et al., 2004; Ralph et al., 2010; Takano et al., 2003)

(Baffy, 2017; Davalli et al., 2016; Hussain et al., 2003; Szatrowski & Nathan, 1991). Changes to the genes encoding the OXPHOS enzyme complexes can produce a range of functional differences, including increased or decreased ATP production seen in tight compared to looser mitochondrial coupling respiration. If these changes significantly modify OXPHOS enzyme function, then they may cause energetic deficiencies such as mitochondrial diseases.

A large number of mitochondrial genes were transferred into the nuclear genome of eukaryotes as part of the process of acquiring new functions during evolution (Friedman & Nunnari, 2014). Most of these nuclear genes play a role in mitochondrial function and bioenergetics. For example, the majority of the subunits for enzyme Complexes I–V in the inner membrane of the mitochondrion, where OXPHOS takes place, are nuclear encoded and imported into the mitochondrion (Ryan & Hoogenraad, 2007). Furthermore, nuclear genes encode for all of the proteins involved in mtDNA replication and transcription, such as Pol ϒ, the mtDNA polymerase (Ryan & Hoogenraad, 2007). As a consequence, the coordinated activity of mitochondrial and nuclear encoded genes is a complex and dynamic process requiring assembly factors, chaperones for protein folding and structural support, and protein translocases to integrate the proteins they produce into the inner and outer membranes of the mitochondria (Larsson, 1995; Lopes, 2020; Ryan & Hoogenraad, 2007).

In addition to these loci, uncoupling proteins (UCPs) are nuclear-encoded mitochondrial transporters that play a role in regulating the relationship between mitochondrial respiration and ATP synthesis (Rousset et al., 2004). UCPs regulate thermogenesis by uncoupling respiration and ATP synthesis, which creates more energy that is given off as body heat (Rousset et al., 2004). This uncoupling process reduces the amount of ATP produced, decreasing levels of ROS byproducts (Figure 2). Accordingly, when mitochondria are tightly coupled, more ATP and ROS are synthesized, resulting in less energy lost as heat (Andrews et al., 2005; Cadenas, 2018; Rousset et al., 2004). Conversely, less tightly coupled mitochondria generate reduced levels of ATP and ROS, and produce greater heat as an energetic byproduct. The expression of UCPs can differ by tissue type and the process of uncoupling can be affected by microenvironments

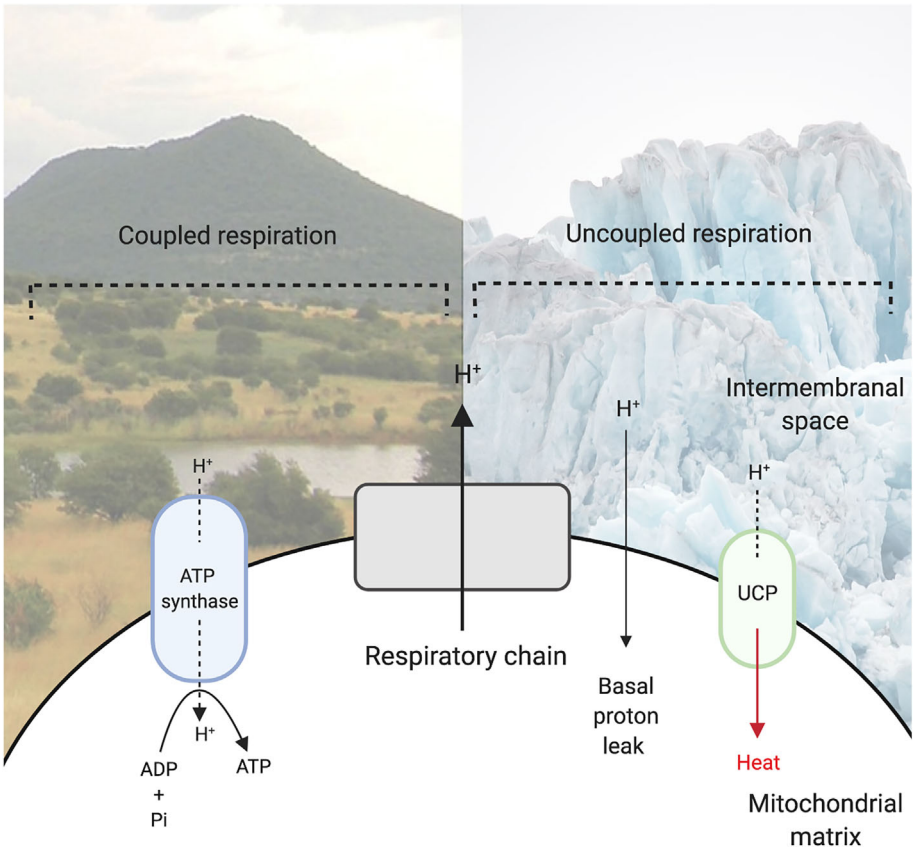

FIGURE 2 Coupled versus uncoupled respiration and climate. ATP synthase drives ATP synthesis using the energy of the proton gradient. In warm conditions, this leads to tightly coupled mitochondrial respiration. However, in cold conditions (right), basal proton leak across the inner mitochondrial membrane and uncouple oxidative phosphorylation. This leak dissipates the energy of the proton gradient as heat, which can serve as an adaptive mechanism for humans to overcome extreme cold temperatures

in the body, such as the physiological conditions created by cancer cell growth with high levels of uncoupling protein 2 (UCP2). These conditions have been reported as contributing to chemoresistance (Baffy, 2017; Cadenas, 2018; Derdak et al., 2008; Woyda-Ploszczyca & Jarmuszkiewicz, 2017).

The bioenergetic characteristics of mitochondrial coupling respiration have been associated with different mitochondrial haplogroups that have evolved over the past 100–200, 000 years. These features have also been linked to the predisposition of populations bearing these mitochondrial haplogroups to certain kinds of diseases (Fetterman et al., 2013; Mishmar & Zhidkov, 2010; Wallace, 2013; Wallace et al., 1999). We discuss this issue in greater detail in the section entitled "Mitochondrial bioenergetics and disease."

3 | MITOCHONDRIAL BIOENERGETICS AND HUMAN ADAPTATION

The root of the modern human mtDNA tree is based in Africa, where it arose some 200–300 thousand years ago (kya) (Behar et al., 2008; Chen et al., 2000; Gonder et al., 2007; Ingman et al., 2000; Torroni et al., 2020). The most ancient mtDNA haplogroups (L0-L7) originated in Africa, and dates to ~70–100 kya (Behar et al., 2008; Chen et al., 2000; Gonder et al., 2007). Three L3-derived macrohaplogroups (M, N, and R) and their sublineages are common in the rest of the world, reflecting their more recent emergence and dispersal with modern human migration out of Africa circa 70 kya (Behar et al., 2008; Kivisild et al., 2006; Quintana-Murci et al., 2004). Humans moved across the Eurasian continent and dispersed into what is now Australasia around 50 kya (Hudjashov et al., 2007; Tobler et al., 2017; Torroni et al., 2020). The Americas were the final continents to be populated by modern humans, who entered these regions from the Bering Strait at least ~16 kya (Perego et al., 2010; Schurr, 2004; Torroni et al., 2020).

During the emergence and later dispersal of anatomically modern humans across the globe, their mtDNA continued to evolve, with novel variants arising and sometimes becoming fixed in a particular maternal lineage, thus giving rise to new haplogroups. MtDNA variants associated with favorable adaptations to local environments (i.e., climate) may have been selected for based on their coupling efficiency (Table 1). This process has been posited as a mechanism for producing haplogroup distinctions (Mishmar et al., 2003; Ruiz-Pesini et al., 2004; Wallace, 2013).

TABLE 1 Temporal and environmental emergence of mtDNA haplogroups

mtDNA Haplogroup	Haplogroup emergence date (ya)	Emergence geographic area	Ave temperature of area at emergence[a]	Source
L0	200 000–130 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Carto et al., 2009; Mishmar et al., 2003
L1	200 000–130 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Carto et al., 2009; Mishmar et al., 2003
L2	130 000–90 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Carto et al., 2009
L5	130 000–90 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Carto et al., 2009
L6	90 000–55 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Willmes et al., 2017
L4	90 000–55 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Willmes et al., 2017
L3	90 000–55 000	Sub-Saharan Africa	Equatorial/Arid/Warm	Mishmar et al., 2003; Willmes et al., 2017
M	90 000–55 000	Asia	Boreal/Polar	Willmes et al., 2017
M7	55 000–30 000	Asia	Boreal/Polar	Willmes et al., 2017
M8	55 000–30 000	Asia	Boreal/Polar	Willmes et al., 2017
M9	55 000–30 000	Asia	Boreal/Polar	Willmes et al., 2017
N2	55 000–30 000	Asia	Boreal/Polar	Willmes et al., 2017
N9	55 000–30 000	Asia	Boreal/Polar	Willmes et al., 2017
A	55 000–30 000	Asia	Boreal/Polar	Mishmar et al., 2003; Ruiz-Pesini et al., 2004; Willmes et al., 2017
D	55 000–30 000	Asia	Boreal/Polar	Mishmar et al., 2003; Ruiz-Pesini et al., 2004; Willmes et al., 2017
G	55 000–30 000	Asia	Boreal/Polar	Mishmar et al., 2003; Willmes et al., 2017
R9	55 000–30 000	Asia	Boreal/Polar	Willmes et al., 2017
B	30 000–10 000	Asia	Boreal/Polar	Mishmar et al., 2003; Willmes et al., 2017
C	30 000–10 000	Asia	Boreal/Polar	Torroni et al., 1993
N	90 000–55 000	Middle East/Asia	Arid/Boreal	Rohling et al., 2013
R	90 000–55 000	Middle East	Arid	Rohling et al., 2013
N1	55 000–30 000	Middle East	Arid	Willmes et al., 2017
R0	55 000–30 000	Middle East	Arid	Willmes et al., 2017
JT	55 000–30 000	Middle East	Arid	Mishmar et al., 2003; Willmes et al., 2017
U	55 000–30 000	Middle East	Arid	Mishmar et al., 2003; Willmes et al., 2017
H	30 000–10 000	Middle East	Arid	Torroni et al., 1998
I	30 000–10 000	Middle East	Arid	Torroni et al., 1998
N1b	30 000–10 000	Middle East	Arid	Behar et al., 2006, 2012
X	30 000–10 000	North America	Polar/Boreal	Mishmar et al., 2003; Ruiz-Pesini et al., 2004; Willmes et al., 2017

Note: van Oven, M., & Kayser, M. (2009). Updated comprehensive phylogenetic tree of global human mitochondrial DNA variation. *Human Mutation*, *30*(2), E386–E394. http://www.phylotree.org.

[a]Using Koppen–Geiger Climate Classification.

These ideas are central to the "mitochondrial climatic adaptation" hypothesis (Camus et al., 2017; Lajbner et al., 2018; Mishmar et al., 2003; Wallace, 2005). According to this hypothesis, mutations that result in excess heat production and less efficiently produced ATP were selected for as humans expanded into more

temperate and colder environments. Various studies have shown that mtDNA lineages in colder climates are associated with uncoupled mitochondria that produce fewer ATP molecules and less energy, but more heat, as a byproduct of OXPHOS (Balloux et al., 2009; Tranah, 2011; Wallace, 2015). It has also been suggested that the greater ratio of mtDNA to nuclear DNA (or the "mt/n ratio") in northern populations may have helped to promote thermogenesis, thus conferring a selective advantage to these populations (Cheng et al., 2013). Overall, higher levels of heat production may have conferred a survival advantage to humans living in colder environments (Mishmar & Zhidkov, 2010; Ruiz-Pesini et al., 2004; Wallace, 2005) (Figure 2).

Conversely, mtDNA haplogroups originating in warmer climates are associated with tightly coupled mitochondria that produce more ATP molecules and less heat as a byproduct of OXPHOS (Camus et al., 2017; Lajbner et al., 2018; Mishmar et al., 2004; Wallace, 2005). An additional consequence of tight mitochondrial coupling respiration is increased production of ROS from OXPHOS activity. High ROS production can lead to cell stress and contribute to pathogenesis in diseases associated with oxidative stress and cellular metabolism (Missanke et al., 2018; Peoples et al., 2019; Trachootham et al., 2009; Wallace, 2005; Wellen & Thompson, 2010). Thus, while reduced heat production in warmer environments was clearly advantageous, the associated thermogenic profile also brought with it somewhat greater oxidative stress due to tighter energetic coupling (Mishmar & Zhidkov, 2010; Ruiz-Pesini et al., 2004; Wallace, 2005) (Figure 2).

To date, research on the relationship between mitochondrial lineages, general measures of bioenergetic function (such as oxygen consumption, coupling, ATP production, and ROS production) and climatic conditions have been limited, as physiological and environmental factors are difficult to parse from genetic factors (Chinnery et al., 2018; Gómez-Durán et al., 2010; Wei & Chinnery, 2020). As a consequence, the relationship between haplogroups (i.e., sequence variation) and the coupling properties of mitochondrial respiration has mostly been based on correlative evidence for mtDNA polymorphisms being present in human populations residing in different and often cold climatic regions (Balloux et al., 2009; Gu et al., 2012; Mishmar et al., 2003; Ruiz-Pesini et al., 2004). For example, Ruiz-Pesini et al. (2004) found evidence of significant positive selection for mutations defining the haplogroups associated with the Americas (haplogroups A, C, D, X2a) and Europe (H, I, N1b, and X), where ancestral populations are believed to have experienced colder climates compared to ancestral African populations bearing haplogroup L mtDNAs. In this regard, two significant SNPs have been associated with American and Eurasian haplogroups in populations living in circum-arctic environments. These include G8701A in the mt *ATP6* gene, thought to be central to proton translocation across the cell membrane, and G10398A in the mt *ND3* gene, which facilitates electron transfer from NADH dehydrogenase to the respiratory chain. These SNPs also seem to be associated with global climatic patterns, leading Balloux et al. (2009) to posit that these genes may have been the site of a selective sweep caused by the lower minimum temperatures found outside of Africa (Balloux et al., 2009).

Other examples of mtDNA variation and climate conditions come from studies of Eurasian populations. One study comparing macrohaplogroup M and N mitogenome sequences from Han Chinese living in a low altitude (∼44 m) warmer climate and Tibetans living in a high altitude (∼4268 m) cold climate found evidence for possible adaptive selection to both cold and high-altitude hypoxia in several mitochondrial genes (Gu et al., 2012). This evidence came from the ratio of nonsynonymous (N) to synonymous (S) substitutions (the "dN/dS ratio") in OXPHOS genes, which indicate whether selection is acting on amino acid variation in encoded proteins. The dN/dS ratios >1 indicated positive selection on Tibetans in the *ATP8*, *CYTB*, and *ATP6* gene, all of which produce protein components in the mitochondrial respiration chain. In similar studies, Mishmar et al. (2003) and Ruiz-Pesini et al. (2004) found that Siberian and Central Asian mtDNA lineages were associated with increased uncoupling phosphorylation and metabolic heat production. They reasoned that this alteration in metabolic function provided adaptations critical to human population expansion into northern climates. Mishmar et al. (2003) further found that the substitution rate for the *ATP6* gene was higher in arctic and subarctic Siberians and Native Americans compared to Africans and Europeans in tropical, subtropical, and temperate environments.

Motivated by similar questions, Leonard et al. (2005) measured basal metabolic rates (BMR) in indigenous Siberians. They concluded that the observed elevated metabolic responses in Siberians were regulated by thyroid hormones levels that increased during cold winter months. Thyroid hormones promote oxidative metabolism in many cells, and are critical to modulating energy expenditure (Hadley et al., 1996; Leonard et al., 2005). Although Leonard et al. (2005) did not explore the association between thyroid levels and mtDNA haplogroup composition in the study populations, they proposed that indigenous Siberians have both short- and long-term mechanisms for adapting to cold stress in which mitochondria play a central role in thyroid hormone

regulation and the uncoupling process in thermogenesis. The ability to modulate OXPHOS for heat production and increase thyroid levels to stimulate BMR would provide short-term acclimatization to climate and activity shifts, while functional changes in the mtDNA sequence governing these responses could provide a long-term method of adaptation (Gnaiger et al., 2015; Gómez-Durán et al., 2010; Nishimura et al., 2012; Ruiz-Pesini et al., 2004). Taken together, the studies suggested that the frequency of these adaptive mtDNA mutations increased via natural selection, driven by climatic conditions as humans migrated into colder, non-equatorial environments.

Research into the relationship between mitochondrial uncoupling respiration, heat production, metabolism and mtDNA variation in the context of climate has frequently focused on adaptation within specific bioenergetically active tissues, such as brown adipose tissue (BAT) and skeletal muscle. White adipose tissue (WAT) and BAT are the main components of human fat reserves (Lo & Sun, 2013; Saely et al., 2011). WAT is used for energy storage and acts as a thermal insulator, whereas BAT is comparatively more vascularized and possesses a high density of cytoplasmic mitochondria (Lee et al., 2009). Mitochondria in BAT can be "activated" during cold exposure to express elevated levels of uncoupling protein 1 (UCP1). UCP1 increases oxidative metabolism and generates heat in a process known as "non-shivering thermogenesis" (NST) that helps to maintain core body temperature (Bertholet & Kirichok, 2017; Chouchani et al., 2019; Nicholls, 2017).

There is some evidence for cold adaptations in populations ancestral to anatomically modern humans. Sazzini et al. (2014) analyzed a panel of 28 genes associated with BAT function in the genomes of modern East Asian and European populations and those of fossil hominins (Neanderthals and Denisovans), and found evidence of positive selection on three SNPs in the leptin receptor (*LEPR*) gene in East Asians. *LEPR* is involved in fat storage and heat dissipation by mitochondria and the regulation of body weight (Cinti et al., 1997). A different variant showing evidence of positive selection was found in the *LEPR* gene in the Neanderthal and Denisovan genomes, suggesting the evolution of independent mechanisms for adaptation to thermal efficiency in these fossil hominin populations. It remains to be seen if variation in cold tolerance response and type of cold acclimatization in modern and ancestral hominins is potentiated by convergent evolution of these traits, the introgression of archaic cold-adapted alleles into modern genomes, or some combination of these and other factors.

Different forms of cold acclimatization have been identified in modern populations with different mtDNA haplotypes. Japanese individuals with haplogroup D, a maternal lineage hypothesized to have arisen in North-East Asia some 30–40 kya (Tanaka et al., 2004), showed strong metabolic tolerance to cold exposure in challenge experiments as compared to those with non-D haplogroups (Nishimura et al., 2012; Ruiz-Pesini et al., 2004). In contrast, non-D participants had an "insulative" cold acclimatization response wherein core body temperature was reduced and heat loss was suppressed at the body's surface.

On the other hand, mitochondrial energy production, climatic variability, and tissue-specific mtDNA sequence variation are not always correlated. A study of Arctic Inuit hunters and Danish participants from more temperate environments did not find any significant differences in the mitochondrial coupling respiration efficiency in their skeletal muscles (Gnaiger et al., 2015). Skeletal muscle is a tissue that constitutes a large portion of body mass, has a higher level of energy turnover capacity compared to other tissues, and was therefore reasoned to have pronounced coupling efficiency (Gnaiger et al., 2015; Rivas et al., 2011; Zierath & Hawley, 2004). After being challenged with exercise in a polar Greenland climate, the Danish participants began oxidizing fat in arm muscles at similarly high levels as Inuit hunters. This similar energy expenditure indicated that mitochondrial coupling efficiency is adaptive and dependent on activity location, and may not have functionality specific to mtDNA haplogroup. Furthermore, the authors noted that active Inuit hunters possessed a higher capacity to oxidize fatty acids than more sedentary Inuit and the Danes. These findings suggested that lower coupling efficiency with a heritable, genetic component may be identified by sampling other tissues, such as adipose tissue.

Studies examining the associations between human mtDNA variation and climate across a wider range of environments and geography beyond northern climates have produced controversial results. Some of these studies suggest that populations from warmer climates may have increased ATP and ROS production due to more tightly coupled mitochondrial respiration, which may be further associated with mtDNA haplogroup. Under this scenario, tighter coupling optimizes energy production over thermogenesis in warmer climates that do not require adaptation to colder environments. This trend has been shown in African and Near Eastern mtDNA lineages from tropical or arid environments (Balloux et al., 2009; Fetterman et al., 2013; Mishmar et al., 2003; Mishmar & Zhidkov, 2010; Ruiz-Pesini et al., 2004; Wallace, 2005; Wallace & Fan, 2010).

Research conducted by Mishmar et al. (2003) found significant variation in the nonsynonymous/synonymous rate ratios (dN/dS ratios) in protein coding genes of

mtDNA lineages from colder geographic origins compared to African lineages. The authors suggested that this pattern is an indication of positive selection and adaptation to colder climates. However, Moilanen et al. (2003) and Elson et al. (2004) were unable to reproduce these results. Instead, they reported gene-specific differences in the dN/dS rate ratio between different European haplogroups (presumably arising in similar climates), suggesting that climatic selection was not the main driver in the observed sequence differences.

Moreover, climate as a source of positive selection in mtDNA lineages continues to be a source of controversy. Several studies found evidence of possible positive selection on specific genes in mtDNAs from different lineages, but not evidence that this selection was linked to climate (Elson et al., 2004; Kivisild et al., 2006; Moilanen et al., 2003). Populations from Oceania, South, and East Asia were also not found to possess extensive or significant differences in dN/dS ratios in mtDNA sequences between regions (Sun et al., 2007), which would be expected if selection was acting on mtDNA variation.

Detailed studies associating particular mtDNA haplogroups or SNPs with tightly coupled mitochondria and physiological function are presently lacking. Such studies could identify associations between mtDNA background and the coupling status of different mitochondria and then use these data to test hypotheses regarding increased risk for diseases associated with high ROS production resulting from tightly coupled mitochondria. The identification of mitochondrial haplogroups associated with high-ROS level diseases could provide an early clinical indicator for the diagnosis and prevention of them.

4 | MITOCHONDRIAL BIOENERGETICS AND DISEASE

MtDNA variants with deep evolutionary histories in human adaptation (i.e., mitochondrial coupling variants and climate) are thought to influence the predisposition to disease in contemporary populations (Fetterman et al., 2013; Mishmar & Zhidkov, 2010; Wallace, 2013). Elucidating the mitochondrial bioenergetic differences between genetic backgrounds is therefore crucial for understanding the etiology of diseases associated with cellular stress. The associations between diseases and mitochondrial bioenergetics described below are garnered primarily from clinical and epidemiological research. Where possible, we have endeavored to contextualize these data within an evolutionary framework, as this approach allows us to assess whether some of the mtDNA variants predisposing contemporary populations to complex diseases may reflect ancestral adaptations. We must note here that inferring selection on the mitochondrial genome from events deep in human evolutionary history remains a contentious and ongoing area of research (Balloux et al., 2009; Kivisild et al., 2006; Mishmar et al., 2003; Mishmar & Zhidkov, 2010; Moilanen et al., 2003; Wallace, 2005; Wallace & Fan, 2010).

4.1 | Diseases of oxidative metabolism

Mitochondrial disorders result in part from genetic mutations that affect the mitochondrial respiratory chain by altering or impairing the assembly and function of the enzyme complexes involved in the OXPHOS pathway (Ghezzi & Zeviani, 2018; Greaves et al., 2012; Larsson, 1995). These disorders can be caused by tissue-specific somatic mtDNA mutations and by germline mtDNA variants that are passed intergenerationally through the maternal lineage and occur within a specific haplogroup background (Table 2).

The heterogeneous presentation of mitochondrial diseases, which have a variable age of onset, severity, symptoms, progression, and outcomes, is explained in part by the complexity of mtDNA replication and cellular distribution. Usually at birth, the many thousands of intracellular mtDNA copies are predominantly identical or "homoplasmic." Healthy individuals may also maintain low levels of "heteroplasmy" (the ratio of mutated mtDNA to wild-type mtDNA). If this ratio changes significantly and begins impairing energy metabolism, then there may be a presentation of a pathogenic phenotype (Holt et al., 1988; Payne et al., 2013; Stewart & Chinnery, 2015). In fact, replicative segregation during embryogenesis and organogenesis leads to the distribution of different ratios of wild-type and mutated mtDNAs in different tissues, depending on the initial ratio in the key progenitor cell types. This phenomenon contributes significantly to the heterogeneous clinical presentations of mitochondrial diseases (Haas et al., 2007; Pfeffer et al., 2013; Rahman, 2020).

The phenomenon of heteroplasmy and its functional consequences have been analyzed in single and cybrid cell studies. Cybrids are eukaryotic cells that retain their own nuclear genome but have had their native mtDNA removed and replaced with mtDNA from another cell. Such studies indicate that the proportion of mutated mtDNA within a cell must reach a critical level before causing biochemical abnormalities in the OXPHOS pathway (the "threshold effect") (DiMauro & Davidzon, 2005; DiMauro & Schon, 2003; Rossignol et al., 2003; Wilkins et al., 2014). When this threshold is exceeded, the resulting biochemical deficiencies in the OXPHOS pathway cause chronic energy failure that affects multiple

TABLE 2 Disease states with associated haplogroups

Phenotype/ disease	Haplogroup	Population	Susceptibility/ resistance	Risk Allele	Citation
Alzheimer's disease		White	No association		Hudson et al., 2012
	U women	Europe	Decreased risk		van der Walt et al., 2004
	H men	Europe	Increased risk		van der Walt et al., 2004
	H5a	Transgenic mice	Increased risk	8336G	Coskun et al., 2012
	H	Meta-analysis across populations	Increased risk		Marom et al., 2017
Parkinson's disease	HV	Meta-analysis across populations	Increased risk		Marom et al., 2017
	JT K	Meta-analysis across populations	Decreased risk		Marom et al., 2017
	H	Meta-analysis across populations	Increased risk		Hudson et al., 2013
	JT J T K	Meta-analysis across populations	Decreased risk		Hudson et al., 2013
Multiple sclerosis	J	Europe	Increased risk	13708A	Yu et al., 2008
		Iran	No association	13708A	Andalib et al., 2017
Amyotrophic lateral sclerosis	H	Italian	Increased risk		Mancuso et al., 2004
		Germany	No association		Ingram et al., 2012
		United Kingdom	No association		Chinnery et al., 2018
Osteoarthritis	T	United Kingdom	Decreased risk		Soto-Hermida et al., 2014
	J	Meta-analysis across populations	Decreased risk		Fernández-Moreno et al., 2017
	J2	Italy	Decreased risk	15257A	Dominguez-Garrido et al., 2009
Type 2 diabetes	JT	Spanish	Increased risk		Diaz-Morales et al., 2018
	JT	Southern Brazil	Increased risk		Crispim et al., 2006
		United Kingdom	No association		Chinnery et al., 2007
	N9a	Japan and Korea	decreased risk		Fuku et al., 2007
	N9a	Southern China	Decreased risk		Fang et al., 2018
Obesity	T	White Australia	Increased risk		Ebner et al., 2015
	IXW	White women North America	Increased risk		Veronese et al., 2018
Cardiovascular disease	HV U	Europe	Increased risk		Rosa et al., 2008
	H K	Europe	Decreased risk		Chinnery et al., 2010
	N9 women	Japan	Decreased risk		Nishigaki et al., 2007
	N9 Men	Japan	No association		Nishigaki et al., 2007
	F1	Taiwan	Increased risk		Tsai et al., 2020
LOHN	J K	Multiple populations	Increased risk	11778G 14484T	Brown et al., 1995, 1997, Hudson et al., 2007, Johns et al., 1992, Torroni et al., 1997
	H	Europe	Decreased risk	17778G	Hudson et al., 2007
Breast cancer	K	European American	Increased risk	9055G 10398A 16 519 T	Bai et al., 2007
	U	European American	Decreased risk		Bai et al., 2007
	X H	Italy	Increased risk		Tommasi et al., 2014
	N	India	Increased risk		Darvishi et al., 2007

(Continues)

TABLE 2 (Continued)

Phenotype/ disease	Haplogroup	Population	Susceptibility/ resistance	Risk Allele	Citation
	M	China	Decreased risk		Fang et al., 2010
Prostate cancer	African Lineages	United States	Increased risk		Petros et al., 2005
Oral cancer	M	India	Increased risk	10398G, 10 400 T	Datta et al., 2007
Thyroid cancer	D5	China	Increased risk		Fang et al., 2010
Gastric cancer	M	China	Increased risk	489C	Wang et al., 2014
Cervical cancer	D	Argentina	Increased risk		Badano et al., 2018
	B2	Mexico	Increased risk		Bayona-Bafaluy et al., 2011
	M	India	Increased risk		Kabekkodu et al., 2014
Sepsis	H	United Kingdom	Decreased risk		Baudouin et al., 2005
	I W X	European Americans	Increased risk		Samuels et al., 2019
	L3	African American	Increased risk		Samuels et al., 2019

systems. In the context of replicative segregation, the ratio of wild-type to mutant mtDNA modulates the threshold effect in a tissue-specific fashion. As a result, tissues with high metabolic demands, such as skeletal muscle, heart muscle, and components of the nervous system, are preferentially involved in mitochondrial disease (McFarland et al., 2010).

4.2 | Mitochondrial bioenergetics and disease

Germ-line mitochondrial mutations are heritable and can affect fertility and longevity, serving as human health indicators (Camus et al., 2015). Significantly, more efficient OXPHOS and increased levels of ROS are associated with mtDNA damage, and high levels of ROS are associated with energetic costs and disease states (Baffy, 2017; Bell et al., 2011; Davalli et al., 2016; Hussain et al., 2003; Pelicano et al., 2004; Ralph et al., 2010; Szatrowski & Nathan, 1991). This feature of mitochondrial metabolism represents a "double-edged sword"—the same variants that may provide a selective advantage to climatic adaptation or other environmental variables may also produce deleterious side-effects and/or disease states, depending on their mutational or genetic context (e.g., haplogroup). Many mitochondrial diseases are pediatric disorders that strike early in life and can lead to complex energetic deficits, heterogeneous phenotypes, and premature death. In the following sections, we review associations between mtDNA genetic variation and specific disease phenotypes in adults, since adult-onset mitochondrial diseases are typically less severe than pediatric cases (Haas et al., 2007; Pfeffer et al., 2013; Rahman, 2020) and are thus less likely to impact adult reproductive fitness.

4.3 | Age-related neurodegenerative disease

Mitochondrial dysfunction and oxidative stress are significant mechanisms in neurodegenerative disease progression in part because neurons are high-energy demanding cells (Kann & Kovács, 2007; Kausar et al., 2018; Son & Han, 2018). Mitochondria are involved in neuronal development, vesicle fusion, and vesicle cycling, and are vital to neurotransmitter secretion (Picard et al., 2011; Son & Han, 2018). As a consequence, diseases linked to the deterioration of neuronal function have been the focus of concerted studies examining the role of mitochondria in their etiology. In what follows, we discuss several kinds of neurological disorders or diseases in which mitochondrial dysfunction is thought to play a key role.

Alzheimer's disease (AD). AD is a degenerative brain disease characterized by dementia. Although its prevalence varies, AD is one of the most common neurodegenerative diseases in the world, with an estimated 46 million people globally being afflicted by it in 2015 (Vos et al., 2016). AD is caused by the formation and accumulation of beta amyloid plaques that clump between neurons, and twisted, insoluble fibers called neurofibrillary tangles that collapse the microtubule structures between neurons (Querfurth & Laferla, 2010). From an epidemiological perspective, a higher incidence

of AD was noted in northwestern European countries compared to southern European countries (Fratiglioni et al., 2000). While it is tempting to speculate about a possible correlation between AD incidence and climate adaptation to colder temperatures in these different countries, the ubiquity of AD globally, irrespective of temperature, and the lack of reproducibility in a study using identical methods (Matthews & Brayne, 2005) indicate that such a correlation is unlikely. Nevertheless, low rates of OXPHOS, high ROS production, and increased reliance on glycolysis precede and exacerbate plaque and neurofibrillary tangle formation, and have been noted in the postmortem brains of AD patients (Coskun et al., 2012; Devi et al., 2006; Swerdlow & Khan, 2004).

Association studies examining whether mtDNA SNPs and haplogroups confer an increased risk of AD have produced contradictory findings. One study of 3250 AD patients and 1221 matched controls from two European and one European descended populations found no significant association between mtDNA background and AD (Hudson et al., 2012). By contrast, other studies have revealed an association between haplogroup U in men with increased risk for AD (van der Walt et al., 2004) and an association of haplogroups H and HV in women with the development of late onset AD (Coskun et al., 2012). Although the association between haplogroup H and an increased risk of AD has been independently corroborated (Marom et al., 2017), most other AD and mtDNA haplogroup association studies have not been replicated or validated experimentally (Ridge & Kauwe, 2018). Thus, further large-scale studies are needed to understand the exact relationship between mtDNA background and AD risk in order to discriminate between the effects of population substructure and heterogeneity.

Parkinson's disease (*PD*). PD is caused by neuron damage and a reduction in dopamine levels that leads to impairment of physical movement, and is a common neurodegenerative disease that affects 3% of the global population over the age of 80 (Davie, 2008; Poewe et al., 2017). Mitochondrial dysfunction is thought to play a role in the onset and development of PD (Di Maio et al., 2016; Kitada et al., 1998; Valente et al., 2001). For example, neurotoxins that inhibit complex I OXPHOS activity are associated with the induction of PD (Hu & Wang, 2016). Complex I deficiencies were also found in the brains of PD patients and in cybrid cell lines created from them (Schapira et al., 1990; Swerdlow et al., 1996). It is yet unknown if inhibited OXPHOS activity and consequent decreased ATP production are linked in global populations with uncoupled mitochondrial respiration and warmer climates. A recent review of the global burden of PD found lower incidence rates of the disease around equatorial regions (which trend toward warmer climates) and sub-Saharan Africa, but linked this pattern to lower socioeconomic status and comparatively less industrialization in these regions (Dorsey et al., 2018).

Among cases with familial PD, most of the genes with SNPs associated with these cases (*SNCA/PARK1*, *LRRK2/PARK8*, *CHCHD2/PARK22*) also play a role in mitochondrial homeostasis (Hu & Wang, 2016; Pickrell & Youle, 2015; Stoker & Greenland, 2018). Of these nuclear genes, *SNCA/PARK1* is associated with oxidative stress-related cell death and mitochondrial fragmentation; *LRRK2/PARK8* is involved in mitochondrial regulation and mutations in this gene result in oxidative stress; and a missense mutation in *CHCHD2/PARK22* was found to increase ROS production and mitochondrial fragmentation (Hu & Wang, 2016; Pickrell & Youle, 2015; Stoker & Greenland, 2018). At the haplogroup level, individuals with haplogroup HV were found to have an increased risk of PD, while those within haplogroup JT and haplogroup K were associated with a reduced risk of developing PD (Marom et al., 2017). The similar results replicated in these studies supports mtDNA background involvement in PD risk and development.

Multiple sclerosis (*MS*). MS is a chronic progressive disorder of the spinal cord and brain which can be potentially disabling. Mitochondrial dysfunction has been reported among patients with MS (Mao & Reddy, 2010) and implicated in disease progression. Haplogroup J has been suggested as a potential risk factor for MS in European cohorts (Tranah et al., 2015; Yu et al., 2008). Within haplogroup J, the nt13708A variant has alternately found to be associated with MS risk in case–control study of Europeans (Tranah et al., 2015), and to have no association with MS risk in a case–control study of Iranians (Andalib et al., 2017). Although mitochondrial involvement in the etiology of MS is generally agreed upon, the specific role of mtDNA background in disease manifestation still remains unresolved.

Amyotrophic lateral sclerosis (*ALS*). ALS causes motor neuron death, producing progressive weakness and the inability to move, speak, swallow, and breathe (Chiò et al., 2013; Zarei et al., 2015). ALS has shown a similar pattern of conflicting associations with mtDNA variation as MS. One study found an increased risk of disease among Italian ALS patients with haplogroup H (Mancuso et al., 2004). However, no such haplogroup association was found in ALS patients from Germany (Ingram et al., 2012) or the United Kingdom (Chinnery et al., 2007). Larger studies involving a variety of haplogroups and global populations need to be conducted to corroborate mtDNA background involvement in risk of ALS to account for population stratification and other possible confounding factors.

4.4 | Mitochondria and complex diseases

Complex or multifactorial diseases are caused by the interactions of lived experiences, environments, and genetics (Veronese et al., 2018). The interplay of these components presents a challenge to researchers looking to pinpoint the significance of any one of them to the etiology of complex disease. Here, we examine how mitochondrial background and the accumulation of mtDNA mutations throughout life can affect the risk and severity of complex diseases (Wallace, 2016; Wei & Chinnery, 2020).

Leber's hereditary optic neuropathy (*LHON*). LHON was the first disease shown to be caused by an mtDNA mutation (Wallace et al., 1988). LHON is a maternally inherited disease that leads to the degeneration of retinal ganglion cells and eventual bilateral vision loss in primarily male individuals between the ages of 30–60 years old (Meyerson et al., 2015; Pilz et al., 2017). Although LHON is primarily attributed to function-altering point mutations within Complex I subunits, there is growing evidence that these mutations are associated with specific mtDNA haplogroups. Multiple studies have confirmed that haplogroup J is associated with pathogenic mutations G11778A and T14484C, which increase LHON penetrance and risk (Brown et al., 1995, 1997; Johns et al., 1992; Torroni et al., 1997). In a pedigree analysis of thousands of individuals with LHON, the manifestation of the disease in individuals with haplogroups J and K sublineages was dependent on the presence of pathogenic mutations G11778A in sub-haplogroup J2, T14484C in subgroup J1, and G3460A in haplogroup K (Hudson et al., 2007). Conversely, the G11778A mutation in haplogroup H was associated with significantly decreased risk of vision failure, indicating that there could be other, as-yet undiscovered epistatic genetic mechanisms governing disease penetrance.

Osteoarthritis (*OA*). OA is a condition characterized by the progressive degradation of joint cartilage (Pereira et al., 2011). Mitochondrial dysfunction in OA chondrocytes, specifically that occurring in Complexes I, II, and III of the electron transport chain (ETC), may play a role in the etiology of OA (Blanco et al., 2011; Maneiro et al., 2003), and could be associated with mtDNA background. Specifically, haplogroups J and T have been associated with a reduced risk of OA in a case–control study of Spanish and United Kingdom patients, respectively (Soto-Hermida et al., 2014). A meta-analysis performed by Fernández-Moreno et al. (2017) validated that haplogroup J conferred a reduced incidence of knee OA among 3214 cases from participants in the Osteoarthritis Initiative (OAI) and the cohort hip and cohort knee (the "CHECK" cohort) multi-center studies (Fernández-Moreno et al., 2017). Fernández-Moreno et al. (2017) also compared mitochondrial cybrids carrying H and J haplogroups to identify differences in metabolic function. The researchers found that J cybrids showed decreased ATP production, reduced ROS levels, and lower grade apoptosis than H cybrids, suggesting the mitochondrial behavior of haplogroup J is protective against the development of OA.

Type 2 diabetes (*T2D*). T2D is a member of a group of metabolic disorders associated with high blood sugar over a prolonged time interval, and is caused by resistance to or a lack of insulin (Dandona et al., 2004; Hurrle & Hsu, 2017). Mitochondrial dysfunction has been linked to deleterious changes in insulin secretion by pancreatic beta-cells and insulin resistance in insulin-sensitive tissues, such as adipose tissue and muscle (Kim et al., 2008), which can increase cell destruction and ROS production (Fridlyand & Philipson, 2004). An imbalance in ROS production plays a role in the early etiology of T2D, and is associated with insulin resistance (Patti et al., 2003).

T2D has been on the rise in many industrialized populations, including populations of African, Pacific Islander, and South Asian descent, although this increased incidence has been comparatively absent in populations from Western Europe (Chatterjee et al., 2017; Diabetes UK, 2019; Diamond, 2003; WHO, 2016). T2D prevalence may be influenced in part by climate. Western European populations that occupy cold climates have associations with increased thermogenesis, uncoupled mitochondrial respiration, and mitochondrial content (discussed previously in the section "Mitochondrial Bioenergetics and Human Adaptation"). Increased mitochondrial uncoupling can decrease ROS production (Fridlyand & Philipson, 2004; Turrens, 2003), which could, in turn, decrease insulin secretion and T2D risk (Fridlyand & Philipson, 2004; Fridlyand & Philipson, 2006). MtDNA variants that allow Western European populations to better adapt to cold climates may also confer pleiotropic and/or polygenic effects that mitigate susceptibility to T2D, partially explaining the ethnic variation in T2D prevalence.

As with other studies of mitochondrial involvement in disease, diabetes researchers have sought to find associations between disease state and specific mtDNA haplogroups and variants. As an example, haplogroup JT has been associated with increased risk of T2D development in a case–controlled Spanish population due to decreased glycemic control and renal function (Diaz-Morales et al., 2018), and in White-Brazilian patients in Southern Brazil due to increased insulin resistance (Crispim et al., 2006). However, a large UK case–control study (Chinnery et al., 2007) found no association between European haplogroups and increased risk of

T2D. In other studies, T2D has been variably associated with mitochondrial haplogroup N9a. While one study indicated that there was a decreased risk of disease with the N9a lineage in populations from Japan and Korea (Fuku et al., 2007), another study reported an increased risk of T2D among people with N9a mtDNAs in Southern China (Fang et al., 2018). The latter study also found that cybrid cells carrying N9a mtDNAs had impaired mitochondrial function, increased ROS levels, and a less active insulin pathway than non-N9a cells. This cybrid study, which included oxidative stress results, represents a more direct examination of metabolic and mitochondrial influences on the development of T2D. Additional studies including the use of the same oxidative stress measurements will be important in understanding the etiology and risk of T2D among haplogroups.

Obesity. Obesity is characterized by the accumulation of surplus body fat and is associated with adverse health outcomes (Eaaswarkhanth et al., 2019). Mitochondria are an integral part of the conversion of calories into energy, where dietary glucose sugar is chemically converted into ATP in a process known as "glycolysis." Mitochondrial dysfunction can affect glycolytic processes and potentially result in obesity (Bournat & Brown, 2010; Veronese et al., 2018; Wortmann et al., 2009). An increase in dietary fructose sugar has been shown to decrease ATP levels and ROS production, which can potentiate mitochondrial dysfunction (Softic et al., 2019). In different study of white Austrian juveniles and adults, obese individuals had an increased frequency of haplogroup T compared to their matched controls (Ebner et al., 2015). However, this same study found no association between any haplogroup or mtDNA polymorphisms associated with other characteristics of obesity (including cholesterol, blood pressure, triglycerides, and blood glucose concentration) and thus could not identify any functional pathways connecting haplogroup metabolism and obesity. In a separate large, longitudinal cohort study of white women from North America, researchers found an association between haplogroup IWX and an increased risk for obesity (Veronese et al., 2018). The replicability of studies of mitochondrial background and obesity risk may be obfuscated by other, thus far untested, genetic interactions and environmental variables such as diet and lived experience (Hu, 2008). In general, these findings highlight the complex interplay of diet, mitochondrial function, and disease development.

Cardiovascular disease (*CVD*). CVD is characterized by inflammation which has been attributed to behavioral, environmental, and genetic factors. Mitochondrial dysfunction and oxidative stress caused by increased levels of ROS can contribute to a pro-inflammatory state that increases CVD susceptibility (Harrison & Gongora, 2009; Krzywanski et al., 2011; Venter et al., 2018). In European populations, haplogroups H and K are reported to have protective effects for CVD risk, while HV and U appear to increase risk of disease development (Chinnery et al., 2010; Rosa et al., 2008). Another study of white individuals from the United States found that haplogroups J and T were associated with reduced CVD risk (Veronese et al., 2019). Haplogroup N9 was found to be protective against CVD in Japanese women, but not men (Nishigaki et al., 2007). In a Taiwanese population, an association was found between haplogroup F1 and increased risk of ischemic stroke (Tsai et al., 2020). This same study also observed a decrease in oxygen consumption, increased ROS production, and lower mitochondrial membrane potential in cybrid cells with haplogroup F1, suggesting that the F1 background is involved in the increased risk of CVD.

Taken together, these studies suggest that the relationship between different mitochondrial haplogroup and CVD risk varies in different populations. However, many of these studies did not incorporate dietary and environmental factors into their analyses, which are known risk factors for CVD. Diets high in polyunsaturated/saturated fats (i.e., nuts, fats from vegetable oils, fish, red meats, and butter) (Hu, 2003; Hu et al., 2003; Iso et al., 2001; Simon et al., 1995) and high-fat, low carbohydrate ketogenic diets (Maalouf et al., 2007) have been shown to modulate ROS production and CVD (Gano et al., 2014; Siri-Tarino et al., 2015). Environmental factors such as family history, age, tobacco smoke exposure, and hypercholesterolemia are also estimated to contribute anywhere from 70% to 80% of CVD risk (Krzywanski et al., 2011; Willett, 2002). Thus, dietary and environmental covariates will need to be incorporated into studies of the influence of mitochondrial function and haplogroup background to fully understand the process of CVD onset and progression in global populations.

4.5 | Mitochondrial bioenergetics and cancer

The "somatic mutation theory" posits that a single somatic cell develops multiple DNA mutations that promulgate cancer, which causes the cell to go through atypical proliferation via mutations in genes controlling cell cycle and cell proliferation (reviewed in Soto & Sonnenschein, 2004). Unlike healthy cells, which primarily use OXPHOS to generate cellular energy, cancerous cells preferentially use glycolytic activity and have reduced mitochondrial respiration, a phenomenon dubbed the "Warburg effect" (Heiden et al., 2009; Vaupel et al., 2019). As mitochondria are central to cellular

metabolism, they have been hypothesized to have a substantial role in carcinogenesis. In this regard, 66% of the cancerous cells across 20 different types of cancer were found to contain mtDNA with at least one somatic point mutation (Hsu et al., 2016; Lee et al., 2014). Thus, mitochondrial dysfunction is essentially involved in the cancer phenotype (Nunnari & Suomalainen, 2012; Rossignol et al., 2004; Wallace, 2005, 2013; Yu et al., 2015), and differences in cancer risk may be associated with mtDNA background.

Several association studies examined the potential heritable links between mitochondrial haplogroups and risk of breast, prostate, oral, thyroid, gastric, and cervical cancer. In different studies, haplogroups M, D5, K, X, H, J, and N have all been associated with breast cancer risk. Macrohaplogroup M, which encompasses a large number of Asian mtDNA lineages, including haplogroup D5, were significantly associated with breast cancer risk in Chinese individuals, although haplogroup M was underrepresented in patients with metastatic breast cancer (Fang et al., 2010). By contrast, the risk of developing breast cancer has been found to increase among individuals with haplogroup K and decrease in women with haplogroup U among European American women (Bai et al., 2007). Haplogroups X and H were also enriched among patients with oncogenic genes *BRCA1* and *BRCA2*, respectively (Tommasi et al., 2014). An analysis of mtDNA variation in Ashkenazi Jewish women, who have a higher incidence of breast cancer than non-Jewish women, revealed that specific sublineages of haplogroups X, H, J, and K were also present at a higher frequency than in non-Jewish women (Behar, Metspalu, et al., 2008; Feder et al., 2007). A re-analysis of around 1000 human mitochondrial genomes found that macrohaplogroup N was associated with increased risk of sporadic breast cancer, and these results were validated in a case–control study of 124 patients and 273 controls (Darvishi et al., 2007). Together, these data suggest that differences in mtDNA sequences and their consequent changes to oxidative function might play a role in breast cancer carcinogenesis.

Petros et al. (2005) reported both germ-line and somatic mutations in the mitochondrial cytochrome oxidase subunit 1 (*CO1*) gene in prostate cancer tumors. They found that African haplogroups harbored more ancient *CO1* variants than other maternal lineages compared to controls. The authors suggested that these ancient variants may predispose African American men to developing prostate cancer in comparison to European American men. Due to the maternal inheritance of *CO1* mutations and the later onset of prostate cancer, though, deleterious *CO1* mutations may not affect male fitness, thereby remaining in the genome and being common in the general population.

Similar comparisons have been made for other types of cancer. Indian patients with oral cancer were enriched for macrohaplogroup M variants 10398G and 10400T as compared to healthy controls and patients with precancerous lesions known as leukoplakia (Datta et al., 2007). Haplogroup M males who smoked showed the most significant increases in cancer risk, hinting that lived experience or sex-specific factors with certain mitochondrial backgrounds may increase cancer risk. Since the 10398G and 10400T variants are central to the differentiation between macrohaplogroups M, N and R (e.g., Quintana-Murci et al., 2004), these results also indicate that further investigation of oral cancer prevalence within lineages deriving from these macrohaplogroups is warranted.

Several studies have been conducted on the association between different cancers and mitochondrial haplogroups in Chinese populations. In one study, haplogroup D4a was associated with an increased risk of thyroid cancer in a Southern Chinese population (Fang et al., 2010). In a separate study, macrohaplogroup M was associated with poorer postoperative survival outcomes in gastric cancer patients as compared to macrohaplogroup N gastric cancer patients (Wang et al., 2014). The authors suggested that the macrohaplogroup M-specific 489C SNP in the D-loop, the control region of the mitochondrion, was involved in the development and progression of gastric cancer. As the D-loop encodes elements critical to mitochondrial transcription and replication, SNPs in this region could potentially alter ROS levels leading to DNA damage (Wallace, 2005).

Finally, studies in cervical cancer have shown a link between cancer development and mtDNA haplogroup background. Argentinian women with African haplogroups were at an increased risk for human papilloma virus (HPV) infection and high grade lesions indicative of cervical cancer compared to those with European or Amerindian mitochondrial backgrounds (Badano et al., 2018). Similar studies conducted in Mexico and India have reported an overrepresentation of mtDNA haplogroups B2 and M, respectively, among cervical cancer patients, suggesting these haplogroups might confer an increased risk for the disease (Bayona-Bafaluy et al., 2011; Guardado-Estrada et al., 2012; Kabekkodu et al., 2014). Overall, it appears that mtDNA variation may play some role in carcinogenesis among HPV positive women.

Several studies have shown that, beyond the somatic point mutation hypothesis, environmental factors, modifiable habits and ways of life as well as comorbidities contribute to cancer risk, including chronic conditions

such as obesity, T2D, and CVD (Sartorius et al., 2016). Industrialized societies have the highest rates of cancer, obesity, T2D, and CVD in the world, even when controlling for variables such as age (Gurven & Kaplan, 2007). These data indicate that cancer also has a metabolic component (Coller, 2014), and the backdrop of human adaptation to a particular nutritive environment, and disturbances to that environment (e.g., through change in subsistence practice, diet, activity pattern, etc.) (Carrera-Bastos et al., 2011; Crittenden & Schnorr, 2017; Lindgärde et al., 2004; Young et al., 2016) may promote cancer risk. Accordingly, high carbohydrate/high insulinemic diets characteristic of industrialized societies can generate oxidative stress, which, in turn, could cause genomic instability and mtDNA damage (Kopp, 2017). This association could partly explain the higher rates of cancer in industrialized societies. Overall, more thorough investigations of cancer risk associations with mitochondrial haplogroup in the context of metabolic adaptations in response to increased industrialization are needed.

4.6 | Infection and sepsis

Researchers have suggested that there is a relationship between recovery from sepsis (microorganism infection in the bloodstream), mitochondrial function, and mtDNA variants that affect the physiological process of infection after a physical trauma. Some studies have indicated that mitochondrial involvement may explain inherited patterns of premature death from infection (Jepson et al., 1995; Lin & Albertson, 2004; Sørensen et al., 1988). As an example, in the United Kingdom, haplogroup H was associated with an increase in survival after admission to the hospital following a 180-day period as compared to individuals with a non-H background (Baudouin et al., 2005). Similarly, European Americans with haplogroups I, W, and X had an increased risk of sepsis-associated delirium compared to those with haplogroup H. Along the same lines, hospitalized patients with haplogroup L3 showed an increased risk for sepsis-associated delirium compared to patients with haplogroup L2 (Samuels et al., 2019). This same study found that L3 patients had decreased cerebral metabolic performance compared to L2 individuals, suggesting the L2 background may reduce the risk of delirium episodes (Samuels et al., 2019). Further research is needed to identify the biological pathways leading to these different disease phenotypes, and determine whether there are any associated adaptive interpretations for why certain haplogroups may confer a protective benefit against sepsis and sepsis-associated delirium.

5 | LIMITATIONS AND FUTURE DIRECTIONS

While not exhaustive, this review has broadly explored the associations between mtDNA genetic variation with bioenergetic function, climate adaptation, and adult mitochondrial disease. Adding to the complexity of this research area, all three of these topics are correlated with one another. Pleiotropy and epistasis make it difficult to parse out the mitochondrial underpinnings of various diseases, particularly in smaller studies, and research efforts must be specifically constructed to investigate mito-nuclear genomic interactions, a key part of mitochondrial evolution and function (Ballinger, 2013; Burton et al., 2013; Chou & Leu, 2015; Marom et al., 2017). Thus, large scale studies and meta-analyses are needed to identify mtDNA haplogroup associations that independently replicate findings across global populations. Furthermore, care must be taken to control for a wide range of potentially confounding effects including differences in demography, environment, and comorbidities.

Most mitochondrial bioenergetics and adaptation studies rely on haplogroups from predominantly European and Asian origins, with very few studies incorporating African and indigenous haplogroups (Bentley et al., 2017; Kelly et al., 2017; Popejoy & Fullerton, 2016; Sirugo et al., 2019). MtDNA haplogroups are correlated with somewhat different phenotypes, creating a more complicated picture of population stratification. The comparative exclusion of non-European and non-Asian populations has resulted in the association of only a small fraction of total mitochondrial genetic diversity with potential adaptive and disease phenotypes. To date, haplogroups associated with European populations H, J, and T are overrepresented in mitochondrial disease studies (Torroni et al., 1997). Thus, the increased inclusion of non-European haplogroups into analyses of the functional effects of mtDNA variation can inform our understanding of the risk for disease development. Shifting focus to underrepresented populations in mtDNA research can improve our understanding of mitochondrial involvement in disease progression in different global populations, and, in turn, provide inclusive clinical targets for disease treatment and prevention.

Mitochondrial association studies suffer from a lack of reproducibility. Many of the sample sizes are small, representing few (primarily European and Asian) populations, and often produce results that cannot be replicated in other studies using different populations and methods. Global surveys of the coupling efficiency

and bioenergetics across mitochondrial haplogroups using the same units of measurement would provide baseline information to better explain bioenergetic differences and their implications across populations. Such surveys could also support or repudiate the "mitochondrial climatic adaptation" hypothesis that links adaptation to climate through the mechanism of some haplogroups being more bioenergetically efficient than others.

Expanding partial genome or haplogroup-only mitochondrial analyses to interrogate full nuclear and mitochondrial genomes will certainly enhance our understanding of functional pathways involved with disease risk and adaptive processes. These types of whole genome sequencing strategies are becoming increasingly tenable with decreased costs and expanded access to computational and experimental tools. Finally, it is important to move beyond studies that are wholly associative to those including assays of mitochondrial function (i.e., mitochondrial respiration and ROS function, measures of adaptive response in the host). Such studies are positioned to greatly advance the understanding of mitochondrial variation in human adaptation, and are of significant clinical importance to establishing risk of and treatment for disease.

ACKNOWLEDGMENTS

The authors thank Alexandra Kralick and Raquel Fleskes for their comments on an early version of this manuscript. This research was supported by NSF grant BCS-1751863.

CONFLICT OF INTEREST

All authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Meagan Rubel: Conceptualization; investigation; writing-original draft; writing-review & editing. **Theodore Schurr:** Conceptualization; writing-original draft; writing-review & editing. **Volney Friedrich:** Conceptualization; investigation; writing-original draft; writing-review & editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Volney K. Friedrich https://orcid.org/0000-0001-7982-1853
Meagan A. Rubel https://orcid.org/0000-0002-4246-9531
Theodore G. Schurr https://orcid.org/0000-0001-9323-9237

REFERENCES

Achilli, A., Rengo, C., Magri, C., Battaglia, V., Olivieri, A., Scozzari, R., Cruciani, F., Zeviani, M., Briem, E., Carelli, V., Moral, P., Dugoujon, J. M., Roostalu, U., Loogväli, E. L., Kivisild, T., Bandelt, H. J., Richards, M., Villems, R., Santachiara-Benerecetti, A. S., ... Torroni, A. (2004). The molecular dissection of mtDNA haplogroup H confirms that the Franco-Cantabrian glacial refuge was a major source for the European gene pool. *American Journal of Human Genetics*, *75*(5), 910–918. https://doi.org/10.1086/425590

Andalib, S., Talebi, M., Sakhinia, E., Farhoudi, M., Sadeghi-Bazargani, H., Emamhadi, M. R., Masoodian, N., Balaghi-Inalou, M., Vafaee, M. S., & Gjedde, A. (2017). Mitochondrial DNA G13708A variation and multiple sclerosis: Is there an association? *Revue Neurologique*, *173*(3), 164–168. https://doi.org/10.1016/j.neurol.2017.02.002

Andrews, Z. B., Diano, S., & Horvath, T. L. (2005). Mitochondrial uncoupling proteins in the CNS: In support of function and survival. *Nature Reviews Neuroscience*, *6*(11), 829–840. https://doi.org/10.1038/nrn1767

Badano, I., Sanabria, D. J., Totaro, M. E., Rubinstein, S., Gili, A., Liotta, D. J., Picconi, M. A., Campos, R. H., & Schurr, T. G. (2018). Mitochondrial DNA ancestry, HPV infection and the risk of cervical cancer in a multiethnic population of northeastern Argentina. *PLoS One*, *13*(1), e0190966.

Baffy, G. (2017). Mitochondrial uncoupling in cancer cells: Liabilities and opportunities. *Biochimica et Biophysica Acta - Bioenergetics*, *1858*(8), 655–664. https://doi.org/10.1016/j.bbabio.2017.01.005

Bai, R. K., Leal, S. M., Covarrubias, D., Liu, A., & Wong, L. J. C. (2007). Mitochondrial genetic background modifies breast cancer risk. *Cancer Research*, *67*(10), 4687–4694. https://doi.org/10.1158/0008-5472.CAN-06-3554

Ballinger, S. W. (2013). Beyond retrograde and anterograde signalling: Mitochondrial–nuclear interactions as a means for evolutionary adaptation and contemporary disease susceptibility. *Biochemical Society Transactions*, *41*(1), 111–117.

Balloux, F., Handley, L.-J. L., Jombart, T., Liu, H., & Manica, A. (2009). Climate shaped the worldwide distribution of human mitochondrial DNA sequence variation. *Proceedings of the Royal Society B: Biological Sciences*, *276*(1672), 3447–3455. https://doi.org/10.1098/rspb.2009.0752

Baudouin, S. V., Saunders, D., Tiangyou, W., Elson, J. L., Poynter, J., Pyle, A., Keers, S., Turnbull, D. M., Howell, N., & Chinnery, P. F. (2005). Mitochondrial DNA and survival after sepsis: A prospective study. *The Lancet*, *366*(9503), 2118–2121.

Bayona-Bafaluy, M. P., López-Gallardo, E., Montoya, J., & Ruiz-Pesini, E. (2011). Maternally inherited susceptibility to cancer. *Biochimica et Biophysica Acta - Bioenergetics*, *1807*(6), 643–649. https://doi.org/10.1016/j.bbabio.2010.08.004

Behar, D. M., Metspalu, E., Kivisild, T., Achilli, A., Hadid, Y., Tzur, S., Pereira, L., Amorim, A., Quintana-Murci, L., Majamaa, K., Herrnstadt, C., Howell, N., Balanovsky, O., Kutuev, I., Pshenichnov, A., Gurwitz, D., Bonne-Tamir, B., Torroni, A., Villems, R., & Skorecki, K. (2006). The matrilineal ancestry of Ashkenazi Jewry: portrait of a recent founder event. *The American Journal of Human Genetics*, *78*(3), 487–497.

Behar, D. M., Metspalu, E., Kivisild, T., Rosset, S., Tzur, S., Hadid, Y., Yudkovsky, G., Rosengarten, D., Pereira, L., Amorim, A., Kutuev, I., Gurwitz, D., Bonne-Tamir, B.,

Villems, R., & Skorecki, K. (2008). Counting the founders: The matrilineal genetic ancestry of the Jewish diaspora. *PLoS One*, *3*(4), e2062. https://doi.org/10.1371/journal.pone.0002062

Behar, D. M., Villems, R., Soodyall, H., Blue-Smith, J., Pereira, L., Metspalu, E., Scozzari, R., Makkan, H., Tzur, S., Comas, D., Bertranpetit, J., Quintana-Murci, L., Tyler-Smith, C., Wells, R. S., Rosset, S., & Genographic Consortium. (2008). The dawn of human matrilineal diversity. *American Journal of Human Genetics*, *82*(5), 1130–1140. https://doi.org/10.1016/j.ajhg.2008.04.002

Behar, D. M., Van Oven, M., Rosset, S., Metspalu, M., Loogväli, E. L., Silva, N. M., Kivisild, T., Torroni, A., & Villems, R. (2012). A "Copernican" reassessment of the human mitochondrial DNA tree from its root. *The American Journal of Human Genetics*, *90*(4), 675–684.

Bell, E. L., Emerling, B. M., Ricoult, S. J. H., & Guarente, L. (2011). SirT3 suppresses hypoxia inducible factor 1α and tumor growth by inhibiting mitochondrial ROS production. *Oncogene*, *30*(26), 2986–2996. https://doi.org/10.1038/onc.2011.37

Bentley, A. R., Callier, S., & Rotimi, C. N. (2017). Diversity and inclusion in genomic research: Why the uneven progress? *Journal of Community Genetics*, *8*(4), 255–266. https://doi.org/10.1007/s12687-017-0316-6

Bertholet, A. M., & Kirichok, Y. (2017). UCP1: A transporter for H + and fatty acid anions. *Biochimie*, *134*, 28–34. https://doi.org/10.1016/j.biochi.2016.10.013

Blanco, F. J., Rego, I., & Ruiz-Romero, C. (2011). The role of mitochondria in osteoarthritis. *Nature Reviews Rheumatology*, *7*(3), 161–169. https://doi.org/10.1038/nrrheum.2010.213

Bournat, J. C., & Brown, C. W. (2010). Mitochondrial dysfunction in obesity. *Current Opinion in Endocrinology, Diabetes and Obesity*, *17*(5), 446–452. https://doi.org/10.1097/MED.0b013e32833c3026

Brown, M. D., Sun, F., & Wallace, D. C. (1997). Clustering of Caucasian Leber hereditary optic neuropathy patients containing the 11778 or 14484 mutations on an mtDNA lineage. *American Journal of Human Genetics*, *60*(2), 381–387.

Brown, M. D., Torroni, A., Calvin, L., & Wallace, D. C. (1995). Phylogenetic analysis of Leber's hereditary optic neuropathy mitochondrial DNAs indicates multiple independent occurrences of the common mutations. *Human Mutation*, *6*(4), 311–325.

Burton, R. S., Pereira, R. J., & Barreto, F. S. (2013). Cytonuclear genomic interactions and hybrid breakdown. *Annual Review of Ecology, Evolution, and Systematics*, *44*, 281–302.

Burtscher, M., Gatterer, H., Burtscher, J., & Mairbäurl, H. (2018). Extreme terrestrial environments: life in thermal stress and hypoxia. A narrative review. *Frontiers in Physiology*, *9*, 572.

Cadenas, S. (2018). Mitochondrial uncoupling, ROS generation and cardioprotection. *Biochimica et Biophysica Acta - Bioenergetics*, *1859*(9), 940–950. https://doi.org/10.1016/j.bbabio.2018.05.019

Camus, M. F., Wolf, J. B. W., Morrow, E. H., & Dowling, D. K. (2015). Single nucleotides in the mtDNA sequence modify mitochondrial molecular function and are associated with sex-specific effects on fertility and aging. *Current Biology*, *25*(20), 2717–2722. https://doi.org/10.1016/j.cub.2015.09.012

Camus, M. F., Wolff, J. N., Sgr, C. M., & Dowling, D. K. (2017). Experimental support that natural selection has shaped the latitudinal distribution of mitochondrial haplotypes in Australian *Drosophila melanogaster*. *Molecular Biology and Evolution*, *34*(10), 2600–2612. https://doi.org/10.1093/molbev/msx184

Carmody, R. N., Dannemann, M., Briggs, A. W., Nickel, B., Groopman, E. E., Wrangham, R. W., & Kelso, J. (2016). Genetic evidence of human adaptation to a cooked diet. *Genome Biology and Evolution*, *8*(4), 1091–1103.

Carrera-Bastos, P., Fontes-Villalba, M., O'Keefe, J. H., Lindeberg, S., & Cordain, L. (2011). The western diet and lifestyle and diseases of civilization. *Research Reports in Clinical Cardiology*, *2*, 15–35.

Carto, S. L., Weaver, A. J., Hetherington, R., Lam, Y., & Wiebe, E. C. (2009). Out of Africa and into an ice age: On the role of global climate change in the late Pleistocene migration of early modern humans out of Africa. *Journal of Human Evolution*, *56*(2), 139–151. https://doi.org/10.1016/j.jhevol.2008.09.004

Chan, D. C. (2006). Mitochondria: Dynamic organelles in disease, aging, and development. *Cell*, *125*(7), 1241–1252. https://doi.org/10.1016/j.cell.2006.06.01

Chatterjee, S., Khunti, K., & Davies, M. J. (2017). Type 2 diabetes. *The Lancet*, *389*(10085), 2239–2251.

Chen, Y.-S., Olckers, A., Schurr, T. G., Kogelnik, A., Huoponen, K., & Wallace, D. C. (2000). Mitochondrial DNA variation in the southern African Kung and Khwe, and their genetic relationships to other African populations. *American Journal of Human Genetics*, *66*(4), 1362–1383.

Cheng, Y. T., Liu, J., Yang, L. Q., Sun, C., & Kong, Q. P. (2013). Mitochondrial DNA content contributes to climate adaptation using chinese populations as a model. *PLoS One*, *8*(11), e79536. https://doi.org/10.1371/journal.pone.0079536

Chinnery, P. F., Elliott, H. R., Syed, A., & Rothwell, P. M. (2010). Mitochondrial DNA haplogroups and risk of transient ischaemic attack and ischaemic stroke: A genetic association study. *The Lancet Neurology*, *9*(5), 498–503. https://doi.org/10.1016/S1474-4422(10)70083-1

Chinnery, P. F., Gomez-duran, A., & Boles, R. G. (2018). Oldies but goldies mtDNA population variants and neurodegenerative diseases. *Frontiers in Neuroscience*, *12*, 682. https://doi.org/10.3389/fnins.2018.00682

Chinnery, P. F., Mowbray, C., Elliot, H., Elson, J. L., Nixon, H., Hartley, J., & Shaw, P. J. (2007). Mitochondrial DNA haplogroups and amyotrophic lateral sclerosis. *Neurogenetics*, *8*(1), 65–67. https://doi.org/10.1007/s10048-006-0066-9

Chiò, A., Logroscino, G., Traynor, B. J., Collins, J., Simeone, J. C., Goldstein, L. A., & White, L. A. (2013). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. *Neuroepidemiology*, *41*(2), 118–130. https://doi.org/10.1159/000351153

Chou, J. Y., & Leu, J. Y. (2015). The Red Queen in mitochondria: Cyto-nuclear co-evolution, hybrid breakdown and human disease. *Frontiers in Genetics*, *6*, 187.

Chouchani, E. T., Kazak, L., & Spiegelman, B. M. (2019). New advances in adaptive thermogenesis: UCP1 and beyond. *Cell Metabolism*, *29*(1), 27–37. https://doi.org/10.1016/j.cmet.2018.11.002

Cinti, S., Frederich, R., Zingaretti, C., De Matteis, R., Flier, J., & Lowell, B. (1997). Immunohistochemical localization of leptin and uncoupling protein in white and brown adipose tissue. *Endocrinology*, *138*(2), 797–804.

Coller, H. A. (2014). Is cancer a metabolic disease? *The American Journal of Pathology*, *184*(1), 4–17.

Coskun, P., Wyrembak, J., Schriner, S. E., Chen, H. W., Marciniack, C., Laferla, F., & Wallace, D. C. (2012). A mitochondrial etiology of Alzheimer and Parkinson disease. *Biochimica et Biophysica Acta*, *1820*(5), 553–564. https://doi.org/10.1016/j.bbagen.2011.08.008

Crispim, D., Canani, L. H., Gross, J. L., Tschiedel, B., Souto, K. E. P., & Roisenberg, I. (2006). The European-specific mitochondrial cluster J/T could confer an increased risk of insulin-resistance and type 2 diabetes: An analysis of the m.4216T>C and m.4917A>G variants. *Annals of Human Genetics*, *70*(4), 488–495. https://doi.org/10.1111/j.1469-1809.2005.00249.x

Crittenden, A. N., & Schnorr, S. L. (2017). Current views on hunter-gatherer nutrition and the evolution of the human diet. *American Journal of Physical Anthropology*, *162*, 84–109.

Dandona, P., Aljada, A., & Bandyopadhyay, A. (2004). Inflammation the link between insulin resistance. *Trends in Immunology*, *25*(1), 4–7. https://doi.org/10.1016/J.IT.2003.10.013

Darvishi, K., Sharma, S., Bhat, A. K., Rai, E., & Bamezai, R. N. K. (2007). Mitochondrial DNA G10398A polymorphism imparts maternal Haplogroup N a risk for breast and esophageal cancer. *Cancer Letters*, *249*(2), 249–255. https://doi.org/10.1016/j.canlet.2006.09.005

Datta, S., Majumder, M., Biswas, N. K., Sikdar, N., & Roy, B. (2007). Increased risk of oral cancer in relation to common Indian mitochondrial polymorphisms and Autosomal GSTP1 locus. *Cancer*, *110*(9), 1991–1999.

Davalli, P., Mitic, T., Caporali, A., Lauriola, A., & D'Arca, D. (2016). ROS, cell senescence, and novel molecular mechanisms in aging and age-related diseases. *Oxidative Medicine and Cellular Longevity*, *2016*, 3565127. https://doi.org/10.1155/2016/3565127

Davie, C. A. (2008). A review of Parkinson's disease. *British Medical Bulletin*, *86*(1), 109–127. https://doi.org/10.1093/bmb/ldn013

Derdak, Z., Mark, N. M., Beldi, G., Robson, S. C., Wands, J. R., & Baffy, G. (2008). The mitochondrial uncoupling protein-2 promotes chemoresistance in cancer cells. *Cancer Research*, *68*(8), 2813–2819. https://doi.org/10.1158/0008-5472.CAN-08-0053

Devi, L., Prabhu, B. M., Galati, D. F., Avadhani, N. G., & Anandatheerthavarada, H. K. (2006). Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. *Journal of Neuroscience*, *26*(35), 9057–9068. https://doi.org/10.1523/JNEUROSCI.1469-06.2006

di Maio, R., Barrett, P. J., Hoffman, E. K., Barrett, C. W., Zharikov, A., Borah, A., Hu, X., McCoy, J., Chu, C. T., Burton, E. A., Hastings, T. G., & Greenamyre, J. T. (2016). α-Synuclein binds to TOM20 and inhibits mitochondrial protein import in Parkinson's disease. *Science Translational Medicine*, *8*(342), 342ra78. https://doi.org/10.1126/scitranslmed.aaf3634

Diabetes, U. K. (2019). Tackling the crisis: transforming diabetes care for a better future. England.

Diamond, J. (2003). The double puzzle of diabetes. *Nature*, *423*(6940), 599–602.

Diaz-Morales, N., Lopez-Domenech, S., Iannantuoni, F., Lopez-Gallardo, E., Sola, E., Morillas, C., Rocha, M., Ruiz-Pesini, E., & Victor, V. (2018). Mitochondrial DNA haplogroup JT is related to impaired glycaemic control and renal function in Type 2 diabetic patients. *Journal of Clinical Medicine*, *7*(8), 220. https://doi.org/10.3390/jcm7080220

DiMauro, S., & Davidzon, G. (2005). Mitochondrial DNA and disease. *Annals of Medicine*, *37*(3), 222–232. https://doi.org/10.1080/07853890510007368

DiMauro, S., & Schon, E. A. (2003). Mitochondrial respiratory-chain diseases. *New England Journal of Medicine*, *348*(26), 2656–2668. https://doi.org/10.1056/NEJMra022567

Dorsey, E. R., Elbaz, A., Nichols, E., Abd-Allah, F., Abdelalim, A., Adsuar, J. C., Ansha, M. G., Brayne, C., Choi, J. Y. J., Collado-Mateo, D., Dahodwala, N., Do, H. P., Edessa, D., Endres, M., Fereshtehnejad, S. M., Foreman, K. J., Gankpe, F. G., Gupta, R., Hankey, G. J., ... Murray, C. J. (2018). Global, regional, and national burden of Parkinson's disease, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *17*(11), 939–953.

Domínguez-Garrido, E., Martínez-Redondo, D., Martín-Ruiz, C., Gómez-Durán, A., Ruiz-Pesini, E., Madero, P., Tamparillas, M., Montoya, J., von Zglinicki, T., Díez-Sánchez, C., & López-Pérez, M. J. (2009). Association of mitochondrial haplogroup J and mtDNA oxidative damage in two different North Spain elderly populations. *Biogerontology*, *10*(4), 435–442.

Duchen, M. R. (2004). Mitochondria in health and disease: Perspectives on a new mitochondrial biology. *Molecular Aspects of Medicine*, *25*(4), 365–451. https://doi.org/10.1016/j.mam.2004.03.001

Eaaswarkhanth, M., Melhem, M., Sharma, P., Nizam, R., al Madhoun, A., Chaubey, G., Alsmadi, O., al-Ozairi, E., & al-Mulla, F. (2019). Mitochondrial DNA D-loop sequencing reveals obesity variants in an Arab population. *The Application of Clinical Genetics*, *12*, 63–70. https://doi.org/10.2147/tacg.s198593

Ebner, S., Mangge, H., Langhof, H., Halle, M., Siegrist, M., Aigner, E., Paulmichl, K., Paulweber, B., Datz, C., Sperl, W., Kofler, B., & Weghuber, D. (2015). Mitochondrial haplogroup T is associated with obesity in Austrian juveniles and adults. *PLoS One*, *10*(8), 1–13. https://doi.org/10.1371/journal.pone.0135622

Elson, J. L., Turnbull, D. M., & Howell, N. (2004). Comparative genomics and the evolution of human mitochondrial DNA: Assessing the effects of selection. *American Journal of Human Genetics*, *74*(2), 229–238.

Eme, L., Spang, A., Lombard, J., Stairs, C. W., & Ettema, T. J. (2017). Archaea and the origin of eukaryotes. *Nature Reviews Microbiology*, *15*(12), 711–723.

Fan, S., Hansen, M. E., Lo, Y., & Tishkoff, S. A. (2016). Going global by adapting local: A review of recent human adaptation. *Science*, *354*(6308), 54–59.

Fang, H., Shen, L., Chen, T., He, J., Ding, Z., Wei, J., Qu, J., Chen, G., Lu, J., & Bai, Y. (2010). Cancer type-specific modulation of mitochondrial haplogroups in breast, colorectal and thyroid cancer. *BMC cancer*, *10*(1), 1–10.

Fang, H., Shen, L., Chen, T., He, J., Ding, Z., Wei, J., Qu, J., Chen, G., Lu, J., & Bai, Y. (2010). Cancer type-specific modulation of mitochondrial haplogroups in breast, colorectal and thyroid cancer. *BMC Cancer*, *10*(1), 421.

Feder, J., Ovadia, O., Glaser, B., & Mishmar, D. (2007). Ashkenazi Jewish mtDNA haplogroup distribution varies among distinct subpopulations: Lessons of population substructure in a closed

group. *European Journal of Human Genetics*, *15*(4), 498–500. https://doi.org/10.1038/sj.ejhg.5201764

Fernández-Moreno, M., Soto-Hermida, A., Vázquez-Mosquera, M. E., Cortés-Pereira, E., Relaño, S., Hermida-Gómez, T., Pértega, S., Oreiro-Villar, N., Fernández-López, C., Garesse, R., Blanco, F. J., & Rego-Pérez, I. (2017). Mitochondrial DNA haplogroups influence the risk of incident knee osteoarthritis in OAI and CHECK cohorts. A meta-analysis and functional study. *Annals of the Rheumatic Diseases*, *76*(6), 1114–1122. https://doi.org/10.1136/annrheumdis-2016-210131

Fetterman, J. L., Zelickson, B. R., Johnson, L. W., Moellering, D. R., Westbrook, D. G., Pompilius, M., Sammy, M. J., Johnson, M., Dunham-Snary, K. J., Cao, X., Bradley, W. E., Zhang, J., Wei, C. C., Chacko, B., Schurr, T. G., Kesterson, R. A., Dell'italia, L. J., Darley-Usmar, V. M., Welch, D. R., & Ballinger, S. W. (2013). Mitochondrial genetic background modulates bioenergetics and susceptibility to acute cardiac volume overload. *Biochemical Journal*, *455*, 157–167. https://doi.org/10.1042/BJ20130029

Forster, P. (2004). Ice ages and the mitochondrial DNA chronology of human dispersals: A review. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *359*(1442), 255–264. https://doi.org/10.1098/rstb.2003.139

Fratiglioni, L., Launer, L. J., Andersen, K., Breteler, M. M., Copeland, J. R., Dartigues, J. F., Lobo, A., Martinez-Lage, J., Soininen, H., & Hofman, A. (2000). Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology*, *54*(11 Suppl 5), S10–S15.

Fridlyand, L. E., & Philipson, L. H. (2004). Does the glucose-dependent insulin secretion mechanism itself cause oxidative stress in pancreatic β-cells? *Diabetes*, *53*(8), 1942–1948.

Freya, T. G., & Mannellab, C. A. (2000). The internal structure of mitochondria. *Trends in Biochemical Sciences*, *25*(7), 319–324. https://doi.org/10.1016/S0968-0004(00)01609-1

Friedman, J. R., & Nunnari, J. (2014). Mitochondrial form and function. *Nature*, *505*(7483), 335–343. https://doi.org/10.1038/nature12985

Fuku, N., Park, K. S., Yamada, Y., Nishigaki, Y., Cho, Y. M., Matsuo, H., Segawa, T., Watanabe, S., Kato, K., Yokoi, K., Nozawa, Y., Lee, H. K., & Tanaka, M. (2007). Mitochondrialhaplogroup N9a confers resistance against Type 2 diabetes in Asians. *American Journal of Human Genetics*, *80*(3), 407–415. https://doi.org/10.1086/512202

Gano, L. B., Patel, M., & Rho, J. M. (2014). Ketogenic diets, mitochondria, and neurological diseases. *Journal of Lipid Research*, *55*(11), 2211–2228.

Ghezzi, D., & Zeviani, M. (2018). Human diseases associated with defects in assembly of OXPHOS complexes. *Essays in Biochemistry*, *62*(3), 271–286. https://doi.org/10.1042/EBC20170099

Giles, R. E., Blanc, H., Cann, H. M., & Wallace, D. C. (1980). Maternal inheritance of human mitochondrial DNA. *Proceedings of the National Academy of Sciences of the United States of America*, *77*(11), 6715–6719. https://doi.org/10.1073/pnas.77.11.6715

Gnaiger, E., Boushel, R., Søndergaard, H., Munch-Andersen, T., Damsgaard, R., Hagen, C., Díez-Sánchez, C., Ara, I., Wright-Paradis, C., Schrauwen, P., Hesselink, M., Calbet, J. A. L., Christiansen, M., Helge, J. W., & Saltin, B. (2015). Mitochondrial coupling and capacity of oxidative phosphorylation in skeletal muscle of Inuit and Caucasians in the arctic winter. *Scandinavian Journal of Medicine and Science in Sports*, *25*, 126–134. https://doi.org/10.1111/sms.12612

Gómez-Durán, A., Pacheu-Grau, D., López-Gallardo, E., Díez-Sánchez, C., Montoya, J., López-Pérez, M. J., & Ruiz-Pesini, E. (2010). Unmasking the causes of multifactorial disorders: OXPHOS differences between mitochondrial haplogroups. *Human Molecular Genetics*, *19*(17), 3343–3353.

Gonder, M. K., Mortensen, H. M., Reed, F. A., De Sousa, A., & Tishkoff, S. A. (2007). Whole-mtDNA genome sequence analysis of ancient African lineages. *Molecular Biology and Evolution*, *24*(3), 757–768. https://doi.org/10.1093/molbev/msl209

Gray, M. W., & Archibald, J. M. (2012). Origins of mitochondria and plastids. In R. Bock & V. Knopp (Eds.), *Genomics of chloroplasts and mitochondria* (pp. 1–30). Springer. https://doi.org/10.1007/978-94-007-2920-9_1

Gray, M. W. (2015). Mosaic nature of the mitochondrial proteome: Implications for the origin and evolution of mitochondria. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(33), 10133–10138.

Greaves, L. C., Reeve, A. K., Taylor, R. W., & Turnbull, D. M. (2012). Mitochondrial DNA and disease. *Journal of Pathology*, *226*(2), 274–286. https://doi.org/10.1002/path.3028

Gu, M., Dong, X., Shi, L., Shi, L., Lin, K., Huang, X., & Chu, J. (2012). Differences in mtDNA whole sequence between Tibetan and Han populations suggesting adaptive selection to high altitude. *Gene*, *496*(1), 37–44. https://doi.org/10.1016/j.gene.2011.12.016

Guardado-Estrada, M., Medina-Martínez, I., Juárez-Torres, E., Roman-Bassaure, E., Macías, L., Alfaro, A., Alcántara-Vázquez, A., Alonso, P., Gomez, G., Cruz-Talonia, F., Serna, L., Muñoz-Cortez, S., Borges-Ibañez, M., Espinosa, A., Kofman, S., & Berumen, J. (2012). The Amerindian mtDNA haplogroup B2 enhances the risk of HPV for cervical cancer: de-regulation of mitochondrial genes may be involved. *Journal of Human Genetics*, *57*(4), 269–276. https://doi.org/10.1038/jhg.2012.17

Gurven, M., & Kaplan, H. (2007). Longevity among hunter-gatherers: A cross-cultural examination. *Population and Development Review*, *33*(2), 321–365.

Haas, R. H., Parikh, S., Falk, M. J., Saneto, R. P., Wolf, N. I., Darin, N., & Cohen, B. H. (2007). Mitochondrial disease: A practical approach for primary care physicians. *Pediatrics*, *120*(6), 1326–1333. https://doi.org/10.1542/peds.2007-0391

Hadley, M. E. (1996). The endocrine hypothalamus. In *Endocrinology* 4th Ed., Upper Saddle River (pp. 102–126) NJ: Prentice-Hall, Inc.

Harrison, D. G., & Gongora, M. C. (2009). Oxidative stress and hypertension. *Medical Clinics of North America*, *93*(3), 621–635. https://doi.org/10.1016/j.mcna.2009.02.015

Heiden, M. G. V., Cantley, L. C., & Thompson, C. B. (2009). Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science*, *324*(5930), 1029–1033. https://doi.org/10.1126/science.1160809

Holt, I. J., Harding, A. E., & Morgan-Hughes, J. A. (1988). Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. *Nature*, *331*(6158), 717–719. https://doi.org/10.1038/331717a0

Hsu, C. C., Tseng, L. M., & Lee, H. C. (2016). Role of mitochondrial dysfunction in cancer progression. *Experimental Biology and*

Medicine, *241*(12), 1281–1295. https://doi.org/10.1177/1535370216641787

Hu, F. (2008). *Obesity epidemiology*. Oxford University Press.

Hu, F. B. (2003). Plant-based foods and prevention of cardiovascular disease: An overview. *American Journal of Clinical Nutrition*, *78*(3 Suppl), 544–551. https://doi.org/10.1093/ajcn/78.3.544s

Hu, F. B., Cho, E., Rexrode, K. M., Albert, C. M., & Manson, J. A. E. (2003). Fish and long-chain ω-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*, *107*(14), 1852–1857. https://doi.org/10.1161/01.CIR.0000062644.42133.5F

Hu, Q., & Wang, G. (2016). Mitochondrial dysfunction in Parkinson's disease. *Translational Neurodegeneration*, *5*(1), 1–8. https://doi.org/10.1186/s40035-016-0060-6

Hudjashov, G., Kivisild, T., Underhill, P. A., Endicott, P., Sanchez, J. J., Lin, A. A., Shen, P., Oefner, P., Renfrew, C., Villems, R., & Forster, P. (2007). Revealing the prehistoric settlement of Australia by Y chromosome and mtDNA analysis. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(21), 8726–8730. https://doi.org/10.1073/pnas.0702928104

Hudson, G., Sims, R., Harold, D., Chapman, J., Hollingworth, P., Gerrish, A., Russo, G., Hamshere, M., Moskvina, V., Jones, N., Thomas, C., Stretton, A., Holmans, P. A., O'Donovan, M. C., Owen, M. J., Williams, J., Chinnery, P. F., GERAD1 Consortium, & Chinnery, P. F. (2012). No consistent evidence for association between mtDNA variants and Alzheimer disease. *Neurology*, *78*(14), 1038–1042. https://doi.org/10.1212/WNL.0b013e31824e8f1d

Hudson, G., Nalls, M., Evans, J. R., Breen, D. P., Winder-Rhodes, S., Morrison, K. E., Morris, H. R., Williams-Gray, C. H., Barker, R. A., Singleton, A. B., Hardy, J., Wood, N. E., Burn, D. J., & Chinnery, P. F. (2013). Two-stage association study and meta-analysis of mitochondrial DNA variants in Parkinson disease. *Neurology*, *80*(22), 2042–2048.

Hudson, G., Carelli, V., Spruijt, L., Gerards, M., Mowbray, C., Achilli, A., Pyle, A., Elson, J., Howell, N., la Morgia, C., Valentino, M. L., Huoponen, K., Savontaus, M. L., Nikoskelainen, E., Sadun, A. A., Salomao, S. R., Belfort, R., Jr., Griffiths, P., Man, P. Y. W., ... Chinnery, P. F. (2007). Clinical expression of Leber hereditary optic neuropathy is affected by the mitochondrial DNA-haplogroup background. *American Journal of Human Genetics*, *81*(2), 228–233. https://doi.org/10.1086/519394

Hurrle, S., & Hsu, W. H. (2017). The etiology of oxidative stress in insulin resistance. *Biomedical Journal*, *40*(5), 257–262. https://doi.org/10.1016/j.bj.2017.06.007

Hussain, S. P., Hofseth, L. J., & Harris, C. C. (2003). Radical causes of cancer. *Nature Reviews Cancer*, *3*(4), 276–285. https://doi.org/10.1038/nrc1046

Ingman, M., Kaessmann, H., Pääbo, S., & Gyllensten, U. (2000). Mitochondrial genome variation and the origin of modern humans. *Nature*, *408*(6813), 708–713.

Ingram, C. J. E., Weale, M. E., Plaster, C. A., Morrison, K. E., Goodall, E. F., Pall, H. S., Beck, M., Jablonka, S., Sendtner, M., Fisher, E. M. C., Bradman, N., & Kasperavičiūtė, D. (2012). Analysis of European case-control studies suggests that common inherited variation in mitochondrial DNA is not involved in susceptibility to amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*, *13*(4), 341–346. https://doi.org/10.3109/17482968.2012.654394

Iso, H., Rexrode, K. M., Stampfer, M. J., Manson, J. A. E., Colditz, G. A., Speizer, F. E., Hennekens, C. H., & Willett, W. C. (2001). Intake of fish and omega-3 fatty acids and risk of stroke in women. *Journal of the American Medical Association*, *285*(3), 304–312. https://doi.org/10.1001/jama.285.3.304

Jepson, A. P., Banya, W. A. S., Sisay-Joof, F., Hassan-King, M., Bennett, S., & Whittle, H. C. (1995). Genetic regulation of fever in *Plasmodium falciparum* malaria in gambian twin children. *Journal of Infectious Diseases*, *172*(1), 316–319. https://doi.org/10.1093/infdis/172.1.316

Johns, D. R., Neufeld, M. J., & Park, R. D. (1992). An ND-6 mitochondrial DNA mutation associated with Leber hereditary optic neuropathy. *Biochemical and Biophysical Research Communications*, *187*(30), 1551–1557.

Kabekkodu, S. P., Bhat, S., Mascarenhas, R., Mallya, S., Bhat, M., Pandey, D., Kushtagi, P., Thangaraj, K., Gopinath, P. M., & Satyamoorthy, K. (2014). Mitochondrial DNA variation analysis in cervical cancer. *Mitochondrion*, *16*, 73–82. https://doi.org/10.1016/j.mito.2013.07.001

Kann, O., & Kovács, R. (2007). Mitochondria and neuronal activity. *American Journal of Physiology Cell Physiology*, *292*(2), C641–C657. https://doi.org/10.1152/ajpcell.00222.2006

Kausar, S., Wang, F., & Cui, H. (2018). The role of mitochondria in reactive oxygen species generation and its implications for neurodegenerative diseases. *Cell*, *7*(12), 274. https://doi.org/10.3390/cells7120274

Kelly, D. E., Hansen, M. E. B., & Tishkoff, S. A. (2017). Global variation in gene expression and the value of diverse sampling. *Current Opinion in Systems Biology*, *1*, 102–108. https://doi.org/10.1016/j.coisb.2016.12.018

Kim, J. A., Wei, Y., & Sowers, J. R. (2008). Role of mitochondrial dysfunction in insulin resistance. *Circulation Research*, *102*(4), 401–414. https://doi.org/10.1161/CIRCRESAHA.107.165472

Kitada, T., Aakawa, S., Hattori, N., Matsumine, H., Yokochi, M., Mizuno, Y., & Shimizu, N. (1998). Mutations in the *parkin* gene cause autosomal recessive juvenile parkinsonism. *Nature*, *169* (1993), 166–169.

Kivisild, T., Shen, P., Wall, D. P., Do, B., Sung, R., Davis, K., Passarino, G., Underhill, P. A., Scharfe, C., Torroni, A., Scozzari, R., Modiano, D., Coppa, A., de Knijff, P., Feldman, M., Cavalli-Sforza, L. L., & Oefner, P. J. (2006). The role of selection in the evolution of human mitochondrial genomes. *Genetics*, *172*(1), 373–387. https://doi.org/10.1534/genetics.105.043901

Kopp, W. (2017). Significant dietary changes during human evolution and the development of cancer: From cells in trouble to cells causing trouble. *Journal of Carcinogensis and Mutagenesis*, *8*(04), 303.

Krzywanski, D. M., Moellering, D. R., Fetterman, J. L., Dunham-Snary, K. J., Sammy, M. J., & Ballinger, S. W. (2011). The mitochondrial paradigm for cardiovascular disease susceptibility and cellular function: A complementary concept to Mendelian genetics. *Laboratory Investigation*, *91*(8), 1122–113595. https://doi.org/10.1038/labinvest.2011.95

Lajbner, Z., Pnini, R., Camus, M. F., Miller, J., & Dowling, D. K. (2018). Experimental evidence that thermal selection shapes

mitochondrial genome evolution. *Scientific Reports*, *8*(1), 1–12.

Larsson, N.-G. (1995). Molecular genetic aspects of human mitochondrial disorders. *Annual Review of Genetics*, *29*(1), 151–178. https://doi.org/10.1146/annurev.genet.29.1.151

Lee, H. C., Huang, K. H., Yeh, T. S., & Chi, C. W. (2014). Somatic alterations in mitochondrial DNA and mitochondrial dysfunction in gastric cancer progression. *World Journal of Gastroenterology*, *20*(14), 3950–3959. https://doi.org/10.3748/wjg.v20.i14.3950

Lee, Y. S., Kennedy, W. D., & Yin, Y. W. (2009). Structural insight into processive human mitochondrial DNA synthesis and disease-related polymerase mutations. *Cell*, *139*(2), 312–324. https://doi.org/10.1016/j.cell.2009.07.050

Leonard, W. R., Snodgrass, J. J., & Sorensen, M. V. (2005). Metabolic adaptation in indigenous Siberian populations. *Annual Review of Anthropology*, *34*(1), 451–471. https://doi.org/10.1146/annurev.anthro.34.081804.120558

Lin, M. T., & Albertson, T. E. (2004). Genomic polymorphisms in sepsis. *Critical Care Medicine*, *32*(2), 569–579. https://doi.org/10.1097/01.CCM.0000110878.49476.42

Lindgärde, F., Widén, I., Gebb, M., & Ahrén, B. (2004). Traditional versus agricultural lifestyle among Shuar women of the Ecuadorian Amazon: Effects on leptin levels. *Metabolism*, *53*(10), 1355–1358.

Lo, K. A., & Sun, L. (2013). Turning WAT into BAT: A review on regulators controlling the browning of white adipocytes. *Bioscience Reports*, *33*(5), 711–719. https://doi.org/10.1042/BSR20130046

Lopes, A. F. C. (2020). Mitochondrial metabolism and DNA methylation: A review of the interaction between two genomes. *Clinical Epigenetics*, *12*, 182. https://doi.org/10.1186/s13148-020-00976-5

López-García, P., & Moreira, D. (2020). The Syntrophy hypothesis for the origin of eukaryotes revisited. *Nature Microbiology*, *5*(5), 655–667.

Lowell, B. B., Spiegelman, B. M. (2000). Towards a molecular understanding of adaptive thermogenesis. *Nature*, *404*(6778), 652–660.

Luo, S., Valencia, C. A., Zhang, J., Lee, N. C., Slone, J., Gui, B., Wang, X., Li, Z., Dell, S., Brown, J., Chen, S. M., Chien, Y. H., Hwu, W. L., Fan, P. C., Wong, L. J., Atwal, P. S., & Huang, T. (2018). Biparental inheritance of mitochondrial DNA in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(51), 13039–13044. https://doi.org/10.1073/pnas.1810946115

Maalouf, M., Sullivan, P. G., Davis, L., Kim, D. Y., & Rho, J. M. (2007). Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. *Neuroscience*, *145*(1), 256–264. https://doi.org/10.1016/j.neuroscience.2006.11.065

Mancuso, M., Conforti, F. L., Rocchi, A., Tessitore, A., Muglia, M., Tedeschi, G., Panza, D., Monsurrò, M. R., Sola, P., Mandrioli, J., Choub, A., DelCorona, A., Manca, M. L., Mazzei, R., Sprovieri, T., Filosto, M., Salviati, A., Valentino, P., Bono, F., … Quattrone, A. (2004). Could mitochondrial haplogroups play a role in sporadic amyotrophic lateral sclerosis ? *Neuroscience Letters*, *371*(2–3), 158–162. https://doi.org/10.1016/j.neulet.2004.08.060

Maneiro, E., Martín, M. A., de Andres, M. C., López-Armada, M. J., Fernández-Sueiro, J. L., del Hoyo, P., Galdo, F., Arenas, J., & Blanco, F. J. (2003). Mitochondrial respiratory activity is altered in osteoarthritic human articular chondrocytes. *Arthritis and Rheumatism*, *48*(3), 700–708. https://doi.org/10.1002/art.10837

Mannella, C. A. (2006). The relevance of mitochondrial membrane topology to mitochondrial function. *Biochimica et Biophysica Acta*, *1762*(2), 140–147. https://doi.org/10.1016/j.bbadis.2005.07.001

Mao, P., & Reddy, P. H. (2010). Is multiple sclerosis a mitochondrial disease? *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1802*(1), 66–79. https://doi.org/10.1016/j.bbadis.2009.07.002

Marciniak, S., & Perry, G. H. (2017). Harnessing ancient genomes to study the history of human adaptation. *Nature Reviews Genetics*, *18*(11), 659–674.

Margulis, L. (1970). *Origin of eukaryotic cells: Evidence and research implications for a theory of the origin and evolution of microbial, plant and animal cells on the Precambrian Earth*. Yale University Press.

Marom, S., Friger, M., & Mishmar, D. (2017). MtDNA meta-analysis reveals both phenotype specificity and allele heterogeneity: A model for differential association. *Scientific Reports*, *7*, 43449. https://doi.org/10.1038/srep43449

Matthews, F., & Brayne, C. (2005). The incidence of dementia in England and Wales: Findings from the five identical sites of the MRC CFA Study. *PLoS Medicine*, *2*(8), e193.

McFarland, R., Taylor, R. W., & Turnbull, D. M. (2010). A neurological perspective on mitochondrial disease. *The Lancet Neurology*, *9*(8), 829–840. https://doi.org/10.1016/S1474-4422(10)70116-2

Metspalu, M., Kivisild, T., Metspalu, E., Parik, J., Hudjashov, G., Kaldma, K., Serk, P., Karmin, M., Behar, D. M., Gilbert, M. T. P., Endicott, P., Mastana, S., Papiha, S. S., Skorecki, K., Torroni, A., & Villems, R. (2004). Most of the extant mtDNA boundaries in South and Southwest Asia were likely shaped during the initial settlement of Eurasia by anatomically modern humans. *BMC Genetics*, *5*, 1–25. https://doi.org/10.1186/1471-2156-5-26

Meyerson, C., Van Stavern, G., & McClelland, C. (2015). Leber hereditary optic neuropathy: Current perspectives. *Clinical Ophthalmology*, *9*, 1165–1176. https://doi.org/10.2147/OPTH.S62021

Miller, F. J., Rosenfeldt, F. L., Zhang, C., Linnane, A. W., & Nagley, P. (2003). Precise determination of mitochondrial DNA copy number in human skeletal and cardiac muscle by a PCR-based assay: Lack of change of copy number with age. *Nucleic Acids Research*, *31*(11), e61. https://doi.org/10.1093/nar/gng060

Mishmar, D., & Zhidkov, I. (2010). Evolution and disease converge in the mitochondrion. *Biochimica et Biophysica Acta - Bioenergetics*, *1797*(6–7), 1099–1104. https://doi.org/10.1016/j.bbabio.2010.01.003

Mishmar, D., Ruiz-Pesini, E., Golik, P., Macaulay, V., Clark, A. G., Hosseini, S., Brandon, M., Easley, K., Chen, E., Brown, M. D., Sukernik, R. I., Olckers, A., & Wallace, D. C. (2003). Natural selection shaped regional mtDNA variation in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 171–176. https://doi.org/10.1073/pnas.0136972100

Moilanen, J. S., Finnilä, S., & Majamaa, K. (2003). Lineage-specific selection in human mtDNA: Lack of polymorphisms in a segment of MTND5 gene in haplogroup J. *Molecular Biology and Evolution*, *20*(12), 2132–2142.

Nicholls, D. G. (2017). The hunt for the molecular mechanism of brown fat thermogenesis. *Biochimie*, *134*, 9–18. https://doi.org/10.1016/j.biochi.2016.09.003

Nishigaki, Y., Yamada, Y., Fuku, N., Matsuo, H., Segawa, T., Watanabe, S., Kato, K., Yokoi, K., Yamaguchi, S., Nozawa, Y., & Tanaka, M. (2007). Mitochondrial haplogroup N9b is protective against myocardial infarction in Japanese males. *Human genetics*, *120*(6), 827–836.

Nishimura, T., Motoi, M., Niri, Y., Hoshi, Y., Kondo, R., & Watanuki, S. (2012). Relationship between seasonal cold acclimatization and mtDNA haplogroup in Japanese. *Journal of Physiological Anthropology*, *31*(1), 1–10. https://doi.org/10.1186/1880-6805-31-22

Nunnari, J., & Suomalainen, A. (2012). Mitochondria: In sickness and in health. *Cell*, *148*(6), 1145–1159. https://doi.org/10.1016/j.cell.2012.02.035

Patti, M. E., Butte, A. J., Crunkhorn, S., Cusi, K., Berria, R., Kashyap, S., Miyazaki, Y., Kohane, I., Costello, M., Saccone, R., Landaker, E. J., Goldfine, A. B., Mun, E., DeFronzo, R., Finlayson, J., Kahn, C. R., & Mandarino, L. J. (2003). Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(14), 8466–8471.

Payne, B. A., Wilson, I. J., Yu-Wai-Man, P., Coxhead, J., Deehan, D., Horvath, R., Taylor, R. W., Samuels, D. C., Santibanez-Koref, M., & Chinnery, P. F. (2013). Universal heteroplasmy of human mitochondrial DNA. *Human molecular genetics*, *22*(2), 384–390.

Pelicano, H., Carney, D., & Huang, P. (2004). ROS stress in cancer cells and therapeutic implications. *Drug Resistance Updates*, *7*(2), 97–110. https://doi.org/10.1016/j.drup.2004.01.004

Peoples, J. N., Saraf, A., Ghazal, N., Pham, T. T., & Kwong, J. Q. (2019). Mitochondrial dysfunction and oxidative stress in heart disease. *Experimental and Molecular Medicine*, *51*(12), 1–13.

Perego, U. A., Angerhofer, N., Pala, M., Olivieri, A., Lancioni, H., Kashani, B. H., Carossa, V., Ekins, J. E., Gomez-Carballa, A., Huber, G., Zimmermann, B., Corach, D., Babudri, N., Panara, F., Myres, N. M., Parson, W., Semino, O., Salas, A., Woodward, S. R., … Torroni, A. (2010). The initial peopling of the Americas: A growing number of founding mitochondrial genomes from Beringia. *Genome Research*, *20*(9), 1174–1179. https://doi.org/10.1101/gr.109231.110

Pereira, D., Peleteiro, B., Araújo, J., Branco, J., Santos, R. A., & Ramos, E. (2011). The effect of osteoarthritis definition on prevalence and incidence estimates: A systematic review. *Osteoarthritis and Cartilage*, *19*(11), 1270–1285. https://doi.org/10.1016/j.joca.2011.08.009

Petros, J. A., Baumann, A. K., Ruiz-Pesini, E., Amin, M. B., Sun, C. Q., Hall, J., Lim, S., Issa, M. M., Flanders, W. D., Hosseini, S. H., Marshall, F. F., & Wallace, D. C. (2005). mtDNA mutations increase tumorigenicity in prostate cancer. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(3), 719–724.

Pfeffer, G., Horvath, R., Klopstock, T., Mootha, V. K., Suomalainen, A., Koene, S., Hirano, M., Zeviani, M., Bindoff, L. A., Yu-Wai-Man, P., Hanna, M., Carelli, V., McFarland, R., Majamaa, K., Turnbull, D. M., Smeitink, J., & Chinnery, P. F. (2013). New treatments for mitochondrial disease—No time to drop our standards. *Nature Reviews Neurology*, *9*(8), 474–481. https://doi.org/10.1038/nrneurol.2013.129

Picard, M., Taivassalo, T., Gouspillou, G., & Hepple, R. T. (2011). Mitochondria: Isolation, structure and function. *Journal of Physiology*, *589*(18), 4413–4421. https://doi.org/10.1113/jphysiol.2011.212712

Pickrell, A. M., & Youle, R. J. (2015). The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron*, *85*(2), 257–273. https://doi.org/10.1016/j.neuron.2014.12.007

Pilz, Y. L., Bass, S. J., & Sherman, J. (2017). Revisión de las neuropatías ópticas mitocondriales: de las formas hereditarias a las adquiridas. *Journal of Optometry*, *10*(4), 205–214. https://doi.org/10.1016/j.optom.2016.09.003

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, *3*, 1–21. https://doi.org/10.1038/nrdp.2017.13

Popejoy, A. B., & Fullerton, S. M. (2016). Genomics is failing diversity. *Nature*, *538*(7624), 1–10. https://doi.org/10.1109/EMBC.2016.7590696

Querfurth, H. W., & Laferla, F. M. (2010). Mechanisms of disease. *New England Journal of Medicine*, *362*(4), 329–344.

Quintana-Murci, L., Chaix, R., Wells, R. S., Behar, D. M., Sayar, H., Scozzari, R., Rengo, C., al-Zahery, N., Semino, O., Santachiara-Benerecetti, A. S., Coppa, A., Ayub, Q., Mohyuddin, A., Tyler-Smith, C., Qasim Mehdi, S., Torroni, A., & McElreavey, K. (2004). Where west meets east: The complex mtDNA landscape of the southwest and Central Asian corridor. *The American Journal of Human Genetics*, *74*(5), 827–845.

Radzvilavicius, A. L., Hadjivasiliou, Z., Pomiankowski, A., & Lane, N. (2016). Selection for mitochondrial quality drives evolution of the germline. *PLoS Biology*, *14*(12), 1–26. https://doi.org/10.1371/journal.pbio.2000410

Rahman, S. (2020). Mitochondrial disease in children. *Journal of Internal Medicine*, *287*(6), 609–633. https://doi.org/10.1111/joim.13054

Ralph, S. J., Rodríguez-Enríquez, S., Neuzil, J., Saavedra, E., & Moreno-Sánchez, R. (2010). The causes of cancer revisited: "Mitochondrial malignancy" and ROS-induced oncogenic transformation—Why mitochondria are targets for cancer therapy. *Molecular Aspects of Medicine*, *31*(2), 145–170. https://doi.org/10.1016/j.mam.2010.02.008

al Rawi, S., Louvet-Vallee, S., Djeddi, A., Sachse, M., Culetto, E., Hajjar, C., Boyd, L., Legouis, R., & Galy, V. (2011). Postfertilization autophagy of sperm organelles prevents paternal mitochondrial DNA transmission. *Science*, *334*(6059), 1144–1147. https://doi.org/10.1126/science.1211878

Reynier, P., May-Panloup, P., Chretien, M. F., Morgan, C. J., Jean, M., Savagner, F., Barriere, P., & Malthiery, Y. (2001). Mitochondrial DNA content affects the fertilizability of human oocytes. *Molecular Human Reproduction*, *7*(5), 425–429. https://doi.org/10.1093/molehr/7.5.425

Ricci, J. E., Muñoz-Pinedo, C., Fitzgerald, P., Bailly-Maitre, B., Perkins, G. A., Yadava, N., Scheffler, I. E., Ellisman, M. H., &

Green, D. R. (2004). Disruption of mitochondrial function during apoptosis is mediated by caspase cleavage of the p75 subunit of complex I of the electron transport chain. *Cell*, *117*(6), 773–786. https://doi.org/10.1016/j.cell.2004.05.008

Ridge, P. G., & Kauwe, J. S. K. (2018). Mitochondria and Alzheimer's disease: The role of mitochondrial genetic variation. *Current Genetic Medicine Reports*, *6*(10), 1–10.

Rivas, D. A., Lessard, S. J., Saito, M., Friedhuber, A. M., Koch, L. G., Britton, S. L., Yaspelkis, B. B., III, & Hawley, J. A. (2011). Low intrinsic running capacity is associated with reduced skeletal muscle substrate oxidation and lower mitochondrial content in white skeletal muscle. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*, *300*(4), R835–R843.

Rohling, E. J., Grant, K. M., Roberts, A. P., & Larrasoaña, J. C. (2013). Paleoclimate variability in the Mediterranean and Red Sea regions during the last 500,000 years: Implications for hominin migrations. *Current Anthropology*, *54*(S8), S183–S201. https://doi.org/10.1086/673882

Rosa, A., Fonseca, B. V., Krug, T., Manso, H., Gouveia, L., Albergaria, I., Gaspar, G., Correia, M., Viana-Baptista, M., Simões, R. M., Pinto, A. N., Taipa, R., Ferreira, C., Fontes, J. R., Silva, M. R., Gabriel, J. P., Matos, I., Lopes, G., Ferro, J. M., … Oliveira, S. A. (2008). Mitochondrial haplogroup H1 is protective for ischemic stroke in Portuguese patients. *BMC Medical Genetics*, *9*, 1–10. https://doi.org/10.1186/1471-2350-9-57

Rossignol, R., Gilkerson, R., Aggeler, R., Yamagata, K., Remigton, S. J., & Capaldi, R. A. (2004). Energy substrate modulates mitochondrial structures and oxidative capacityin cancer cells. *Cancer Research*, *64*, 985–993.

Rossignol, R., Faustin, B., Rocher, C., Malgat, M., Mazat, J. P., & Letellier, T. (2003). Mitochondrial threshold effects. *Biochemical Journal*, *370*(3), 751–762. https://doi.org/10.1042/BJ20021594

Rousset, S., Alves-Guerra, M. C., Mozo, J., Miroux, B., Cassard-Doulcier, A. M., Bouillaud, F., & Ricquier, D. (2004). The biology of mitochondrial uncoupling proteins. *Diabetes*, *53*(S1), S130–S135. https://doi.org/10.2337/diabetes.53.2007.s130

Ruiz-Pesini, E., Mishmar, D., Brandon, M., Procaccio, V., & Wallace, D. C. (2004). Effects of purifying and adaptive selection on regional variation in human mtDNA. *Science*, *303* (5655), 223–227.

Ryan, M. T., & Hoogenraad, N. J. (2007). Mitochondrial-nuclear communications. *Annual Review of Biochemistry*, *76*, 701–722. https://doi.org/10.1146/annurev.biochem.76.052305.091720

Saely, C. H., Geiger, K., & Drexel, H. (2011). Brown versus white adipose tissue: A mini-review. *Gerontology*, *58*(1), 15–23. https://doi.org/10.1159/000321319

Samuels, D. C., Hulgan, T., Fessel, J. P., Billings, F. T., IV, Thompson, J. L., Chandrasekhar, R., & Girard, T. D. (2019). Mitochondrial DNA haplogroups and delirium during sepsis. *Critical Care Medicine*, *47*(8), 1065–1071.

Sartorius, B., Sartorius, K., Aldous, C., Madiba, T. E., Stefan, C., & Noakes, T. (2016). Carbohydrate intake, obesity, metabolic syndrome and cancer risk? A two-part systematic review and meta-analysis protocol to estimate attributability. *BMJ Open*, *6*(1), e009301.

Sato, M., & Sato, K. (2013). Maternal inheritance of mitochondrial DNA by diverse mechanisms to eliminate paternal mitochondrial DNA. *Biochimica et Biophysica Acta - Molecular Cell Research*, *1833*(8), 1979–1984. https://doi.org/10.1016/j.bbamcr.2013.03.010

Sazzini, M., Schiavo, G., De Fanti, S., Martelli, P. L., Casadio, R., & Luiselli, D. (2014). Searching for signatures of cold adaptations in modern and archaic humans: Hints from the brown adipose tissue genes. *Heredity*, *113*(3), 259–267. https://doi.org/10.1038/hdy.2014.24

Schapira, A. H., Cooper, J. M., Dexter, D., Clark, J. B., Jenner, P., & Marsden, C. D. (1990). Mitochondrial complex I deficiency in Parkinson's disease. *Journal of Neurochemistry*, *54*(3), 823–827. https://doi.org/10.1111/j.1471-4159.1990.tb02325.x

Schurr, T. G. (2004). The peopling of the New World: Perspectives from molecular anthropology. *Annual Review of Anthropology*, *33*, 551–583.

Simon, J. A., Fong, J., Bernert, J. T., & Browner, W. S. (1995). Serum fatty acids and the risk of fatal cancer. *American Journal of Epidemiology*, *148*(9), 854–858. https://doi.org/10.1093/oxfordjournals.aje.a009710

Siri-Tarino, P. W., Chiu, S., Bergeron, N., & Krauss, R. M. (2015). Saturated fats versus polyunsaturated fats versus carbohydrates for cardiovascular disease prevention and treatment. *Annual Review of Nutrition*, *35*, 517–543.

Sirugo, G., Williams, S. M., & Tishkoff, S. A. (2019). The missing diversity in human genetic studies. *Cell*, *177*(1), 26–31. https://doi.org/10.1016/j.cell.2019.02.048

Softic, S., Meyer, J. G., Wang, G. X., Gupta, M. K., Batista, T. M., Lauritzen, H. P. M. M., Fujisaka, S., Serra, D., Herrero, L., Willoughby, J., Fitzgerald, K., Ilkayeva, O., Newgard, C. B., Gibson, B. W., Schilling, B., Cohen, D. E., & Kahn, C. R. (2019). Dietary sugars alter hepatic fatty acid oxidation via transcriptional and post-translational modifications of mitochondrial proteins. *Cell Metabolism*, *30*(4), 735–753.e4. https://doi.org/10.1016/j.cmet.2019.09.003

Son, G., & Han, J. (2018). Roles of mitochondria in neuronal development. *BMB Reports*, *51*(11), 549–556. https://doi.org/10.5483/BMBRep.2018.51.11.226

Sørensen, T. I. A., Nielsen, G. G., Andersen, P. K., & Teasdale, T. W. (1988). Genetic and environmental influences on premature death in adult adoptees. *New England Journal of Medicine*, *318*(12), 727–732. https://doi.org/10.1056/NEJM198803243181202

Soto, A. M., & Sonnenschein, C. (2004). The somatic mutation theory of cancer: growing problems with the paradigm? *Bioessays*, *26*(10), 1097–1107.

Soto-Hermida, A., Fernández-Moreno, M., Oreiro, N., & Fernández-lópez, C. (2014). Mitochondrion mtDNA haplogroups and osteoarthritis in different geographic populations. *Mitochondrion*, *15*, 18–23. https://doi.org/10.1016/j.mito.2014.03.001

Stewart, J. B., & Chinnery, P. F. (2015). The dynamics of mitochondrial DNA heteroplasmy: implications for human health and disease. *Nature Reviews Genetics*, *16*(9), 530–542.

Stoker, T. B., & Greenland, J. C. (2018). *Parkinson's disease: Pathogenesis and clinical aspects*. Codon Publications. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.pr

Sun, C., Kong, Q. P., & Zhang, Y. P. (2007). The role of climate in human mitochondrial DNA evolution: A reappraisal. *Genomics*, *89*(3), 338–342. https://doi.org/10.1016/j.ygeno.2006.11.005

Swerdlow, R. H., & Khan, S. M. (2004). A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. *Medical*

Hypotheses, *63*(1), 8–20. https://doi.org/10.1016/j.mehy.2003.12.045

Swerdlow, R. H., Parks, J. K., Miller, S. W., Davis, R. E., Tuttle, J. B., Trimmer, P. A., Sheehan, J. P., Bennett, J. P., & Parker, W. D. (1996). Origin and functional consequences of the complex I defect in Parkinson's disease. *Annals of Neurology*, *40*(4), 663–671. https://doi.org/10.1002/ana.410400417

Szatrowski, T. P., & Nathan, C. F. (1991). Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Research*, *51*(3), 794–798.

Takano, H., Zou, Y., Hasegawa, H., Akazawa, H., Nagai, T., & Komuro, I. (2003). Oxidative stress-induced signal transduction pathways in cardiac myocytes: Involvement of ROS in heart diseases. *Antioxidants and Redox Signaling*, *5*(6), 789–794. https://doi.org/10.1089/152308603770380098

Tanaka, M., Takeyasu, T., Fuku, N., Li-Jun, G., & Kurata, M. (2004). Mitochondrial genome single nucleotide polymorphisms and their phenotypes in the Japanese. In *Mitochondrial Pathogenesis* (pp. 7–20). Springer. https://doi.org/10.1007/978-3-662-41088-2_2

Tobler, R., Rohrlach, A., Soubrier, J., Bover, P., Llamas, B., Tuke, J., Bean, N., Abdullah-Highfold, A., Agius, S., O'Donoghue, A., O'Loughlin, I., Sutton, P., Zilio, F., Walshe, K., Williams, A. N., Turney, C. S. M., Williams, M., Richards, S. M., Mitchell, R. J., … Cooper, A. (2017). Aboriginal mitogenomes reveal 50,000 years of regionalism in Australia. *Nature*, *544*(7649), 180–184. https://doi.org/10.1038/nature21416

Tommasi, S., Favia, P., Weigl, S., Bianco, A., Pilato, B., Russo, L., Paradiso, A., & Petruzzella, V. (2014). Mitochondrial DNA variants and risk of familial breast cancer: An exploratory study. *International Journal of Oncology*, *44*(5), 1691–1698. https://doi.org/10.3892/ijo.2014.2324

Torroni, A., Schurr, T. G., Cabell, M. F., Brown, M. D., Neel, J. V., Larsen, M., Smith, D. G., Vullo, C. M., & Wallace, D. C. (1993). Asian affinities and continental radiation of the four founding Native American mtDNAs. *American Journal of Human Genetics*, *53*(3), 563–590.

Torroni, A., Petrozzi, M., Urbano, L. D., Sellitto, D., Zeviani, M., Carrara, F., Carducci, C., Leuzzi, V., Carelli, V., Barboni, P., De Negri, A., & Scozzari, R. (1997). Haplotype and phylogenetic analyses suggest that one European- specific mtDNA background plays a role in the expression of Leber hereditary optic neuropathy by increasing the penetrance of the primary mutations 11778 and 14484, 1107–1121. *American Journal of Human Genetics*, *60*(5), 1107.

Torroni, A., Bandelt, H. J., D'Urbano, L., Lahermo, P., Moral, P., Sellitto, D., Rengo, C., Forster, P., Savontaus, M. L., Bonné-Tamir, B., & Scozzari, R. (1998). mtDNA analysis reveals a major late paleolithic population expansion from southwestern to northeastern Europe. *American Journal of Human Genetics*, *62*(5), 1137–1152. https://doi.org/10.1086/301822

Torroni, A., Achilli, A., Olivieri, A., & Semino, O. (2020). Haplogroups and the history of human evolution through mtDNA. In G. Gasparre & A. M. Porcelli (Eds.), *The human mitochondrial genome* (pp. 111–129). Academic Press. https://doi.org/10.1016/b978-0-12-819656-4.00005-x

Trachootham, D., Alexandre, J., & Huang, P. (2009). Targeting cancer cells by ROS-mediated mechanisms: A radical therapeutic approach? *Nature Reviews Drug Discovery*, *8*(7), 579–591.

Tranah, G. J. (2011). Mitochondrial-nuclear epistasis: Implications for human aging and longevity. *Ageing Research Review*, *10*(2), 238–252. https://doi.org/10.1016/j.arr.2010.06.003

Tranah, G. J., Santaniello, A., Caillier, S. J., Alfonso, S. D., Hauser, S. L., & Oksenberg, J. R. (2015). Mitochondrial DNA sequence variation in multiple sclerosis. *Neurology*, *85*(4), 325–330.

Tsai, M. H., Kuo, C. W., Lin, T. K., Ho, C. J., Wang, P. W., Chuang, J. H., & Liou, C. W. (2020). Ischemic stroke risk associated with mitochondrial haplogroup F in the Asian population. *Cell*, *9*(8), 1885. https://doi.org/10.3390/cells9081885

Turrens, J. F. (2003). Mitochondrial formation of reactive oxygen species. *Journal of Physiology*, *552*(2), 335–344.

Valente, E. M., Bentivoglio, A. R., Dixon, P. H., Ferraris, A., Ialongo, T., Frontali, M., Albanese, A., & Wood, N. W. (2001). Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35-p36. *American Journal of Human Genetics*, *68*(4), 895–900. https://doi.org/10.1086/319522

Vaupel, P., Schmidberger, H., & Mayer, A. (2019). The Warburg effect: Essential part of metabolic reprogramming and central contributor to cancer progression. *International Journal of Radiation Biology*, *95*(7), 912–919. https://doi.org/10.1080/09553002.2019.1589653

Venter, M., Van Der Westhuizen, F. H., & Elson, J. L. (2018). The aetiology of cardiovascular disease: A role for mitochondrial DNA? *Cardiovascular Journal of Africa*, *29*(2), 122–132. https://doi.org/10.5830/CVJA-2017-037

Veronese, N., Stubbs, B., Koyanagi, A., Vaona, A., Demurtas, J., Schofield, P., Thompson, T., & Maggi, S. (2018). Mitochondrial genetic haplogroups and incident obesity: A longitudinal cohort study. *European Journal of Clinical Nutrition*, *72*(4), 587–592. https://doi.org/10.1038/s41430-018-0097-y

Veronese, N., Stubbs, B., Koyanagi, A., Vaona, A., Demurtas, J., Schofield, P., & Maggi, S. (2019). Mitochondrial genetic haplogroups and cardiovascular diseases: Data from the osteoarthritis initiative. *PLoS One*, *14*(3), e0213656.

Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., Carter, A., Casey, D. C., Charlson, F. J., Chen, A. Z., Coggeshall, M., Cornaby, L., Dandona, L., Dicker, D. J., Dilegge, T., Erskine, H. E., Ferrari, A. J., Fitzmaurice, C., Fleming, T., … Zuhlke, L. J. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1545–1602. https://doi.org/10.1016/S0140-6736(16)31678-6

Vyas, S., Zaganjor, E., & Haigis, M. C. (2016). Mitochondria and Cancer. *Cell*, *166*(3), 555–566. https://doi.org/10.1016/j.cell.2016.07.002

Wallace, D. C. (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: A dawn for evolutionary medicine. *Annual Review of Genetics*, *39*, 359–407. https://doi.org/10.1146/annurev.genet.39.110304.095751

Wallace, D. C., Brown, M. D., & Lott, M. T. (1999). Mitochondrial DNA variation in human evolution and disease. *Gene*, *238*(1), 211–230. https://doi.org/10.1016/S0378-1119(99)00295-4

Wallace, D. C. (2012). Mitochondria and cancer. *Nature Reviews*, *12*(10), 685–698. https://doi.org/10.1007/978-0-387-84835-8

Wallace, D. C. (2016). Mitochondrial DNA in evolution and disease. *Nature*, *535*(7613), 498–500. https://doi.org/10.1038/nature18902

Wallace, D. C., & Fan, W. (2010). Energetics, epigenetics, mitochondrial genetics. *Mitochondrion*, *10*(1), 12–31. https://doi.org/10.1016/j.mito.2009.09.006

Wallace, D. C. (2013). Bioenergetics in human evolution and disease: Implications for the origins of biological complexity and the missing genetic variation of common diseases. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *368* (1622), 20120267.

Wallace, D. C. (2015). Perspective mitochondrial DNA variation in human radiation and disease. *Cell*, *163*(1), 33–38. https://doi.org/10.1016/j.cell.2015.08.067

Wallace, D. C., & Chalkia, D. (2013). Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. *Cold Spring Harbor Perspectives in Biology*, *5*(11), a021220.

Wallace, D. C., Singh, G., Lott, M. T., Hodge, J. A., Schurr, T. G., Lezza, A. M., Elsas, L. J., 2nd, & Nikoskelainen, E. K. (1988). Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science*, *242*(4884), 1427–1430.

van der Walt, J. M., Dementieva, Y. A., Martin, E. R., Scott, W. K., Nicodemus, K. K., Kroner, C. C., Welsh-Bohmer, K. A., Saunders, A. M., Roses, A. D., Small, G. W., Schmechel, D. E., Murali Doraiswamy, P., Gilbert, J. R., Haines, J. L., Vance, J. M., & Pericak-Vance, M. A. (2004). Analysis of European mitochondrial haplogroups with Alzheimer disease risk. *Neuroscience Letters*, *365*(1), 28–32. https://doi.org/10.1016/j.neulet.2004.04.051

Wang, C., Wang, Y., Wang, H., Zhang, R., & Guo, Z. (2014). Mitochondrial DNA haplogroup N is associated good outcome of gastric cancer. *Tumor Biology*, *35*(12), 12555–12559.

Wei, W., & Chinnery, P. F. (2020). Inheritance of mitochondrial DNA in humans: Implications for rare and common diseases. *Journal of Internal Medicine*, *287*(6), 634–644. https://doi.org/10.1111/joim.13047

Wellen, K. E., & Thompson, C. B. (2010). Cellular metabolic stress: Considering how cells respond to nutrient excess. *Molecular Cell*, *40*(2), 323–332.

Wilkins, H. M., Carl, S. M., & Swerdlow, R. H. (2014). Cytoplasmic hybrid (cybrid) cell lines as a practical model for mitochondriopathies. *Redox Biology*, *2*(1), 619–631. https://doi.org/10.1016/j.redox.2014.03.006

Willett, W. C. (2002). Balancing life-style and genomics research for disease prevention. *Science*, *296*(5568), 695–698. https://doi.org/10.1126/science.1071055

Willmes, C., Becker, D., Brocks, S., Hütt, C., & Bareth, G. (2017). High resolution Köppen-Geiger classifications of paleoclimate simulations. *Transactions in GIS*, *21*(1), 57–73. https://doi.org/10.1111/tgis.12187

World Health Organization. (2016). Global report on diabetes: executive summary (No. WHO/NMH/NVI/16.3). World Health Organization.

Wortmann, S. B., Zweers-van Essen, H., Rodenburg, R. J. T., van den Heuvel, L. P., de Vries, M. C., Rasmussen-Conrad, E., Smeitink, J. A. M., & Morava, E. (2009). Mitochondrial energy production correlates with the age-related BMI. *Pediatric Research*, *65*(1), 103–108. https://doi.org/10.1203/PDR.0b013e31818d1c8a

Woyda-Ploszczyca, A. M., & Jarmuszkiewicz, W. (2017). The conserved regulation of mitochondrial uncoupling proteins: From unicellular eukaryotes to mammals. *Biochimica et Biophysica Acta - Bioenergetics*, *1858*(1), 21–33. https://doi.org/10.1016/j.bbabio.2016.10.003

Young, T. K., Kelly, J. J., Friborg, J., Soininen, L., & Wong, K. O. (2016). Cancer among circumpolar populations: An emerging public health concern. *International Journal of Circumpolar Health*, *75*(1), 29787.

Yu, X., Koczan, D., Sulonen, A., Akkad, D. A., Kroner, A., Comabella, M., Costa, G., Corongiu, D., Goertsches, R., Camina-Tato, M., Thiesen, H. J., Nyland, H. I., Mørk, S. J., Montalban, X., Rieckmann, P., Marrosu, M. G., Myhr, K. M., Epplen, J. T., Saarela, J., & Ibrahim, S. M. (2008). mtDNA nt13708A variant increases the risk of multiple sclerosis. *PLoS One*, *3*(2), 1–7. https://doi.org/10.1371/journal.pone.0001530

Yu, Y., Lv, F., Lin, H., Qian, G., Jiang, Y. S., Pang, L. X., Wang, Y. P., Wang, X. F., Kang, Y. M., Li, C. B., Liu, Q., Xu, J. Z., & You, W. (2015). Mitochondrial ND3 G10398A mutation: A biomarker for breast cancer. *Genetics and Molecular Research*, *14*(4), 17426–17431. https://doi.org/10.4238/2015.December.21.12

Zarei, S., Carr, K., Reiley, L., Diaz, K., Guerra, O., Altamirano, P. F., Pagani, W., Lodin, D., Orozco, G., & Chinea, A. (2015). A comprehensive review of amyotrophic lateral sclerosis. *Surgical Neurology International*, *6*(1), 171. https://doi.org/10.4103/2152-7806.169561

Zierath, J. R., & Hawley, J. A. (2004). Skeletal muscle fiber type: Influence on contractile and metabolic properties. *PLoS Biology*, *2*(10), e348.

How to cite this article: Friedrich, V. K., Rubel, M. A., & Schurr, T. G. (2021). Mitochondrial genetic variation in human bioenergetics, adaptation, and adult disease. *American Journal of Human Biology*, e23629. https://doi.org/10.1002/ajhb.23629