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Mitochondrial DNA Variation in Human Radiation and Disease

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Abstract

Environmental adaptation, predisposition to common diseases, and, potentially, speciation may all be linked through the adaptive potential of mitochondrial DNA (mtDNA) alterations of bioenergetics. This Perspective synthesizes evidence that human mtDNA variants may be adaptive or deleterious depending on environmental context and proposes that the accrual of mtDNA variation could contribute to animal speciation via adaptation to marginal environments.

The mitochondrial DNA (mtDNA) genes of different human populations encompass polymorphisms that alter amino acids, which appear invariant in diverse animal species. Given the functional importance of the 13 mtDNA oxidative phosphorylation (OXPHOS) genes, it would be expected that purifying selection would ensure that the functionally important amino acids would be conserved across species and thus should be invariant among individuals within the same species. Yet this is not the case. Why?

mtDNA Variation and the History of Women

The maternal inheritance of the human mtDNA and its high mutation rate has resulted in the sequential accumulation of mtDNA genetic variants along radiating maternal lineages. The resulting mtDNA mutational tree encompasses clusters of related mtDNA haplotypes, known as haplogroups, which arose in geographically localized indigenous populations. Hence, the human mtDNA phylogeny and the geographic distribution of associated indigenous populations have permitted the reconstruction of the origins and ancient migrations of women (Figure 1).

The mtDNA tree is rooted in Africa about 130,000 and 170,000 years before present (YBP). For the first ~100,000 years, mtDNAs radiated within Africa, generating a plethora of African-specific mtDNA haplogroups (L0, 1, 2, 3, etc.) that, in aggregate, are referred to as macrohaplogroup L. Between 45,000 and 65,000 YBP, two mtDNAs, M and N, emerged from within L3 in northeast Africa and successfully left Africa, founding macrohaplogroups M and N, which colonized the rest of the world. Macrohaplogroup N gave rise to multiple

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SUPPLEMENTAL INFORMATION

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European, Asian, and Native American mtDNA lineages, while macrohaplogroup M gave rise to only Asian and Native American haplogroups.

The migration of women out of Africa and around the world was associated with four striking regional mtDNA discontinuities. First, only M and N mtDNAs colonized Eurasia and the Americas. Second, while N haplogroups dispersed throughout Europe and Asia, M haplogroups were confined to Asia. Third, of all of the Asian M and N mtDNA lineages, only haplogroups A, C, and D became enriched in Northeast Siberia and were poised at around 20,000 YBP to cross the Bering Land Bridge into the Americas. Finally, only haplogroup B mtDNAs colonized the Pacific Islands. Discovery of these striking mtDNA haplogroup regional discontinuities has led to the hypothesis that specific mtDNA haplogroups may have been functionally constrained by regional environmental selection (Cann et al., 1987; Denaro et al., 1981; Kivisild et al., 2006; Merriwether et al., 1991; Mishmar et al., 2003; Wallace, 2005, 2013a, 2013b).

Mitochondrial Genetics and Bioenergetics

The mtDNA codes for the most important polypeptides of the mitochondrial energy generating system OXPHOS: the *ND1*, *2*, *3*, *4*, *4L*, *5*, and *6* genes of complexes I; the *cytochrome b* gene of complex III; the *COI*, *COII*, and *COIII* genes of complex IV; and the *ATP6* and *ATP8* genes of complex V. In addition, the mtDNA codes for the 22 tRNAs and two rRNAs for mitochondrial protein synthesis plus an ~1,000 nucleotide “control region” that regulates mtDNA transcription and replication (Wallace et al., 2013).

Mitochondrial OXPHOS generates much of cellular energy by the oxidation of dietary calories with oxygen. As electrons pass down the electron transport chain (ETC) through complexes I, III, and IV to reduce oxygen, the energy released is used to pump protons out across the mitochondrial inner membrane to generate a proton electrochemical gradient. This electrochemical gradient can be employed by the ATP synthase (complex V) to drive ATP synthesis. However, mitochondria OXPHOS also modulates cellular REDOX and reactive oxygen species (ROS) production, pH and Ca^{2+} levels, apoptotic initiation, and, via tricarboxylic cycle intermediates, signal transduction pathways and the epigenome (Picard et al., 2014; Wallace, 2005; Wallace and Fan, 2010; Wallace et al., 2010, 2013).

The critical role played by the mtDNA genes in OXPHOS means that the mtDNA polypeptide genes should be highly evolutionary conserved. Yet the mtDNA has a very high sequence evolution rate. Since most functional mtDNA mutations would be deleterious, the high mutation rate should create a high genetic load and imperil the survival of the species (Wallace, 2013a). This conundrum is resolved by the unique intracellular mtDNA population genetics of the female germline (Wallace and Chalkia, 2013).

Maternally inherited mtDNA mutations arise among the hundreds to thousands of mtDNAs within the female germline cells, each new mutation creating a mixture of normal and mutant mtDNAs, a state known as heteroplasmy. As a heteroplasmic mitotic or meiotic cell divides, the mutant and normal mtDNAs undergo replicative segregation, becoming randomly distributed among the daughter cells. The mammalian occyte contains several hundred thousand mtDNAs, which do not actively replicate after fertilization until the

blastocyst stage. Hence, the resulting primordial germ cells contain only a couple of hundred mtDNAs. Subsequent mtDNA replication in the derived oogonia leads to proto-oocytes with re-expanded mtDNA populations of several thousand mtDNAs. This repeated contraction and expansion of the intracellular mtDNA populations causes rapid genetic drift of heteroplasmic mtDNAs generating proto-oocytes enriched for either the mutant or normal mtDNAs (Wallace and Chalkia, 2013).

The proto-oocytes and/or oocytes with the most severe mtDNA mutations are then selectively eliminated prior to or soon after fertilization. This is possible because, unlike anatomical alterations that require developmental elaboration of structures before they can be acted on by selection, mitochondrial physiological alterations are expressed at the single-cell level. Hence, cells with highly deleterious mtDNA mutations and associated bioenergetic perturbations can be detected and eliminated within the ovary. This permits the mtDNA to have a high mutation rate without the species acquiring excessive genetic load (Fan et al., 2008; Sharpley et al., 2012; Stewart et al., 2008). Through this system, bioenergetic variation is continuously introduced into the population, thus providing a powerful tool for animal adaption to changing environments.

Regional mtDNA Variation and Functional Consequences

The central role of the mtDNA genes in OXPHOS and of OXPHOS in cellular physiology means that functional variants in the mtDNA can have profound effects on human biology. For example, the efficiency with which the ETC generates the proton gradient and by which the proton gradient is converted into ATP is referred to as the coupling efficiency, and humans can differ in their coupling efficiency due to mtDNA polymorphisms. Since a dietary calorie is a unit of heat, every calorie burned by the mitochondrion generates one calorie of body heat. Tightly coupled mitochondria generate the maximum ATP and minimum heat per calorie burned and thus could be beneficial in warmer climates, while loosely coupled mitochondria must burn more calories for the same amount of ATP, generating more heat, and could be of benefit in colder climates. Variation in OXPHOS can also affect ROS production, which affects cell growth, signaling, inflammation, and predilection to infection; Ca^{2+} levels, which regulate cellular and organ homeostasis; and high-energy intermediate levels that can regulate the epigenome.

Consistent with the proposed importance of mtDNA variation in human adaptation, regional haplogroups are generally founded by one or more functionally significant polypeptide, tRNA, rRNA, and/or control region variants. These variants are retained in the descendant mtDNAs creating the haplogroups. For example, at the macrohaplogroup level, the out-of-Africa macrohaplogroup N was founded by two amino acid variants: *ND3* nucleotide (nt) 10389G>A (A114T) and *ATP6* nt 8701 G>A (A59T). These variants alter mitochondrial membrane potential and Ca^{2+} regulation (Kazuno et al., 2006), potentially changing the coupling efficiency and being advantageous in colder climates. The European macrohaplogroup N-derived haplogroup J was founded by the reversion of the N-defining *ND3* 10389G>A variant and the acquisition of a new *ND5* 13708G>A (A458T) variant. Haplogroup J radiation gave rise to subhaplogroup J1c founded by a *cytochrome b* variant at 14798T>C (F18L) and subhaplogroup J2 with a *cytochrome b* variant at 15257G>A

(D171N). European haplogroup U was founded by the *tRNA*$^{Leu(CUN)}$ 12308A>G variant and gave rise to subhaplogroup Uk, which encompasses the *ATP6* 9055G>A (A177T) variant and an independent recurrence of the *cytochrome b* 14798T>C (F18L) variant (Ruiz-Pesini et al., 2004; Ruiz-Pesini and Wallace, 2006). These haplogroup-founding polypeptide variants change amino acids that otherwise show high interspecific evolutionary conservation — in some cases, even to bacteria. Yet these and multiple other variants of highly conserved amino acids have been retained in the human population in the face of purifying selection for tens of thousands of years, recurred multiple times, and have become enriched in regional populations to generate regional haplogroups (Kivisild et al., 2006; Mishmar et at., 2003; Ruiz-Pesini et al., 2004, 2007; Ruiz-Pesini and Wallace, 2006; van Oven and Kayser, 2009).

That haplogroups have physiological consequences is suggested by haplogroups T and U, which are associated with reduced sperm motility (Montiel-Sosa et al., 2006; Ruiz-Pesini et al., 2000); haplogroups J and Uk being enriched in Finnish sprinters and haplogroup I in distance runners; and haplogroup L0 being enriched in Kenyan elite distance runners (Table S1). Moreover, climatic differences correlate with mtDNA rather than nDNA variation (Balloux et al., 2009), and the basal metabolic rate of Siberian populations that are enriched for haplogroups A, C, and D is higher than that of more southern populations (Leonard et al., 2002; Snodgrass et al., 2005, 2008).

A more direct demonstration of the adaptive importance of mtDNA variants comes from studies on the mtDNA *ND1* nt 3394T>C (Y30H) variant. In high-altitude Tibetans, the rare 3394C allele is greatly enriched over low altitude Asians (OR ~24), arose three independent times on macrohaplogroup M mtDNAs, and increases in frequency with the altitude of Tibetan villages; an analogous variant *(ND1* Y30C) having been found in the high-altitude Ethiopian monkey, *Theropithecus gelada.* This suggests that the 3394C allele is adaptive at high altitudes when it arises on M haplogroups. However, the 3394C allele has not been observed in Tibetan N haplogroups, suggesting that it may be deleterious when it arises on macrohaplogroup N mtDNAs (Ji et al., 2012).

To determine the physiological consequences of the 3394C variant in association with various mtDNA haplogroups, the mtDNAs of interest have been established in cultured cell lines by transmitochondrial cybrid production (Trounce et al., 1996). Transfer of 3394T>C (Y30H) mtDNAs into an osteosarcoma nuclear environment revealed that the *ND1* 3394C allele on macrohaplogroup N haplogroup B or F mtDNAs reduced complex I activity between 7% and 28%. However, the complex-l-specific activity between haplogroups B and F harboring the 3394T allele differed by 30%, a greater difference than seen for either haplogroups B or F when comparing the 3394T versus C allele. Moreover, when the 3394C variant occurred on the macrohaplogroup M background, as in Tibetan haplogroup M9, the complex-l-specific activity was as high as that of the most active macrohaplogroup N haplogroup B mtDNA with the 3394T allele (Ji et al., 2012). Hence, both individual mtDNA single-nucleotide polymorphisms, as well as the haplogroup background, interact to modulate mitochondrial bioenergetics.

Functional differences have been observed between other haplogroups with the osteosarcoma cybrids. Comparison of H versus J cybrids revealed that J mtDNA cells have reduced mtDNA, mtDNA transcripts, mitochondrial translation products, oxygen consumption, membrane potential, and ATP levels (Gómez-Durán et al., 2012). Haplogroup H cybrids differ from Uk cybrids by the Uk cybrids having lower mtDNA, mitochondrial RNA, and mitochondrial protein synthesis levels; reduced complex IV activity; increased oxygen consumption; and reduced inner membrane potential, suggesting reduced coupling efficiency (Gómez-Durán et al., 2010). The control region variant, 295C>T, is associated with increased TFAM transcription factor binding to the L-strand promoter, increased L-strand transcripts, and increased mtDNA copy number (Suissa et al., 2009).

Comparison of haplogroup H and J mtDNAs on a retinal pigment epithelial (RPE) nuclear background revealed that J mtDNA cells have reduced ATP, ROS, and reactive nitrogen species levels; increased lactate and growth rate; reduced expression of macular degeneration gene CFH; altered expression of genes involved in cell signaling, inflammation, and metabolism; and altered UV exposure response (Kenney et al., 2014a; Malik et al., 2014). Comparison of European H versus African L mtDNAs in RPE cells showed that the L mtDNA cells had lower ATP turnover rates; reduced spare respiratory capacity; reduced mtDNA copy number; increased mtDNA mRNA levels; and altered expression of nuclear complement, inflammation, and autoimmunity genes (Kenney et al., 2014b). Transfer of mouse mtDNAs from one inbred nucleus to another or mixing of two normal mtDNAs within the mouse germline resulted in significant phenotypic differences (Fischer Lindahl etal., 1991; Roubertoux et al., 2003; Sharpley et al., 2012), an effect also seen in *Drosophila* (Meiklejohn et al., 2013; Zhu et al., 2014). Therefore, naturally occurring mtDNA variation can have profound effects on cellular physiology, growth characteristics, and inflammatory systems.

While the population substructure of mtDNA variation can result from genetic drift (Cann et al., 1987; Kivisild et al., 2006; Wallace, 2013a), in this Perspective, I am exploring the hypothesis that a portion of mtDNA sequence variation, particularly among the haplogroup-founding functional mtDNA variants, has been acted on by adaptive selection. This is because these mtDNA variants fulfill all of the criteria currently used to argue for positive selection acting on protein-coding genes (Nielsen et al., 2007). They change evolutionary conserved amino acids; they have recurred multiple times throughout human radiation; they are associated with expansion of a rare haplotypes into regional polymorphic haplogroups; they lead to geographically constrained population haplogroups; they increase in frequency in cases in which the environmental challenge is apparent (e.g., altitude); and they change physiological phenotypes, cellular functions, and nuclear gene expression profiles of direct relevance to regional environmental challenges (Nielsen et al., 2007).

mtDNA Variation in Disease

The importance of mtDNA variation is demonstrated by the wide range of common clinical phenotypes that have been associated with mtDNA haplogroups. The penetrance of the milder Leber hereditary optic neuropathy (LHON) complex I gene mtDNA mutations is increased if the LHON mutation arose on haplogroup J or a *ND1* 3394C-bearing mtDNA (Ji

et al., 2012; Sadun et al., 2011; Wallace et al., 1988). In fact, mtDNA haplogroups have been associated with a wide range of metabolic, degenerative, infectious, and autoimmune diseases, selected examples of which are listed in Table S2.

Specific mtDNA haplogroups have also been associated with predisposition to various cancers (Table S2). Additionally, cancer cells can acquire de novo mtDNA mutations within the control region and the tRNA, rRNA, and protein-coding genes, a subset of which may be the same or similar to variants associated with regional haplogroups (Brandon et al., 2006).

One mechanism by which mtDNA variation can have such profound effects on cellular and organismal phenotypes is through retrograde signaling to the nucleus. Patients heteroplasmic for the mtDNA $tRNA^{Leu(UUR)}$ nt 3243A>G mutation harboring 20%–30% mutant (3243G) mtDNAs can present with diabetes, 50%–90% of mutant mitochondria with neuromuscular degenerative disease, and ~100% with lethal perinatal disease. Relative to osteosarcoma cybrids with 0% mutant mtDNAs, physiological and molecular analysis of 20%–30% mutant cybrids revealed reduced OXPHOS without glycolytic compensation; 50%–90% mutant cybrids showed strong glycolytic gene induction with declining OXPHOS; and 100% mutant cybrids experienced severe reductions in both glycolysis and OXPHOS. These marked changes in patient phenotypes associated with mtDNA genotypes correlate with four dramatic phase changes in transcriptional patterns corresponding to 0%, 20%–30%, 50%–90%, and 100% 3243 mutant. Thus, the continuous changes in the mtDNA genotype must signal to the nucleus through the cellular signal transduction pathways and epigenome to regulate gene expression. However, the nucleus appears to only be able to respond in four finite ways, thus creating the abrupt phase changes in gene expression and phenotype (Picard et al., 2014).

mtDNA Variation and Speciation

The discoveries that the female germline generates a high frequency of mild functional mtDNA variants, that functionally important OXPHOS gene variants have arisen repeatedly within the mtDNA phylogeny throughout human history, and that selected variants become regionally enriched has led to the hypothesis that the mtDNA provides a powerful adaptive engine for mammals to cope with environmental change (Figure 2). As a corollary to this hypothesis, the rapid elaboration of adaptive mtDNA variants could permit subpopulations of a species to survive and prosper in “marginal” environments, becoming progressively isolated from parent populations. These meta-stable peripheral populations could then, in theory, have sufficient longevity for the much slower accumulation of adaptive nDNA gene mutations in both bioenergetic (Gershoni et al., 2010, 2014; Mishmar et al., 2006) and structural genes (Nielsen et al., 2007; Sabeti et al., 2007). Ultimately, the accumulated mtDNA and nDNA adaptive variants could alter a subpopulation’s physiology and anatomy sufficiently to permit a switch to a new primary food source (energy resource), resulting in a new niche and thus speciation.

How then could the conservation of mitochondrial DNA sequence be explained? With the acquisition of a more abundant energy resource, many of the selective pressures that originally drove the enrichment of regional mtDNA variants would be relieved for the new

species. The high mtDNA sequence evolution rate plus adaptive selection would then favor in the new species the reversion of previously adaptive but now maladaptive variants back to more commonly optimal bioenergetics alleles. By sequencing only mtDNAs from the central populations of different species, only the common optimal allele would be observed, thus giving the false impression of the invariance of the amino acid at that site.

Conclusion

The process of mtDNA adaptive radiation, combined nDNA-mtDNA coevolution to speciation, and reversion of intraspecific adaptive mtDNA mutations can explain several seemingly anomalous facts. These include why mutations in apparently highly conserved OXPHOS amino acids can occur multiple times within a species and repeatedly increase to polymorphic frequencies; why mtDNA phylogenies coalesce with the origins of species (Cann et al., 1987; Merriwether et al., 1991; Mishmar et al., 2003) while nDNA variants such as HLA alleles or the Tibetan Denisovan *EPAS1* allele (Huerta-Sánchez et al., 2014) are retained across related species; and why a mtDNA variant can be advantageous in one environmental context and deleterious in another. This later phenomenon may be relevant to the rise of common disease phenotypes such as diabetes, obesity, and neurodegenerative disease, as globalization of regional diets encompasses non-regional mtDNA haplogroups or as migration transfers regional mtDNA haplotypes to new environments, thus converting an adaptive mtDNA genotype into a maladaptive one. Thus, the unique features of the mtDNA may require a reassessment of some of our core assumptions about human genetics and evolutionary theory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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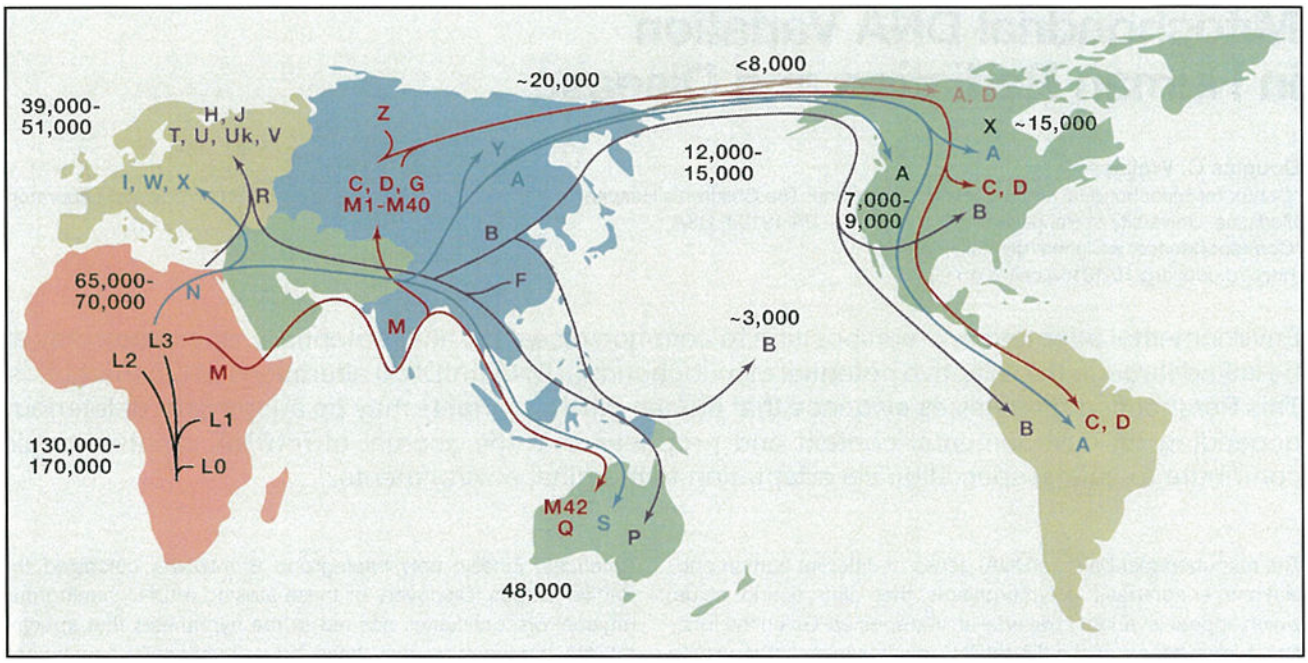

Figure 1. Regional Radiation of Human mtDNAs from their Origin in Africa and Colonization of Eurasia and the Americas Implies that Environmental Selection Constrained Regional mtDNA Variation

All African mtDNAs are subsumed under macrohaplogroup L and coalesce to a single origin about 130,000–170,000 YBP. African haplogroup L0 is the most ancient mtDNA lineage found in the Koi-San peoples, L1 and L2 in Pygmy populations. The M and N mtDNA lineages emerged from Sub-Saharan African L3 in northeastern Africa, and only derivatives of M and N mtDNAs successfully left Africa, giving rise to macrohaplogroups M and N. N haplogroups radiated into European and Asian indigenous populations, while M haplogroups were confined to Asia. Haplogroups A, C, and D became enriched in northeastern Siberia and were positioned to migrate across the Bering Land Bridge 20,000 YBP to found Native Americans. Additional Eurasian migrations brought to the Americas haplogroups B and X. Finally, haplogroup B colonized the Pacific Islands. Figure reproduced from (MITOMAP, 2015).

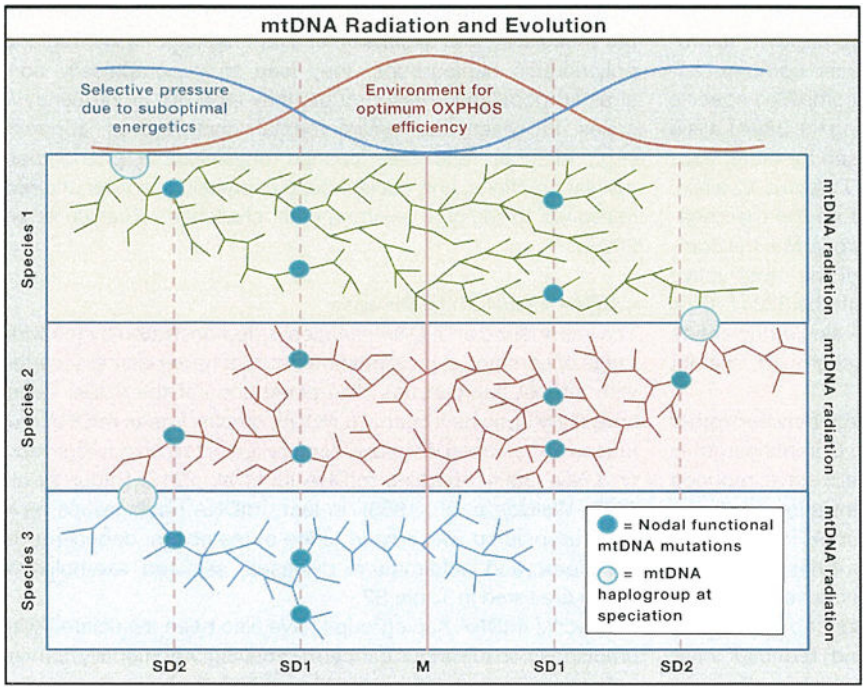

Figure 2. Hypothetized Role of mtDNA Variation in Animal Environmental Adaptation and Speciation

This figure portrays the environmental space (niche) of successively evolving species (green, orange, and blue horizontal bands). The left-to-right expanse represents the range of ecological zones for each species, with the center (M) being the optimal environment and the two left and right vertical dashed lines (SD1 and SD2) representing increasingly marginal environments. Successive mtDNA mutations occurring over time are represented by branch points on black lines, with most of them being neutral. As a new species expands from its optimal niche into more marginal environments, occasional mtDNA mutations arise, which are physiologically beneficial in the suboptimal environment (blue circles at branch points). These lineages become enriched by adaptive selection with additional neutral and adaptive mutations accumulating, creating a haplogroup. The same environmental constraint can select for the same mutation on different mtDNA lineages. Occasionally, one mtDNA lineage located at the extreme edge of the species' niche (left and right edges) permits a subpopulation to persist long enough for nDNA variants to arise that permit switching of food source (energy reservoir), leading to speciation (open circle crossing species boundaries). Previously adaptive mtDNA variants now become suboptimal in the new niche and revertants are selected, permitting energetic re-adaptation back to M.