PNAS COMMENTARY OPEN ACCESS

Incompatibilities between common mtDNA variants in human disease

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Mitochondria are the powerhouses of cells and play important roles in development and health. Besides producing adenosine triphosphate (ATP), mitochondria are also responsible for a number of diverse cellular activities, including reactive oxygen species (ROS) production, calcium signaling, iron homeostasis, steroid synthesis, heme biosynthesis, and programmed cell death (1–3). It is also believed that mitochondria can function as master regulators for immunity and epigenetics (4, 5). Mitochondrial DNA (mtDNA) mutation is one of the major determinants for mitochondrial disorders, which accounts for the vast majority of inborn errors of metabolism with an incidence of 1.6 in 5,000 (6). The advancement of next-generation sequencing techniques enabled us to identify rare variants on both mtDNA and nuclear DNA, and achieved a diagnostic rate of roughly 30%, indicating that mitochondrial diseases may be caused by additional mechanisms (6). In PNAS, Schaefer et al. (7) report a new class of mitochondrial diseases originating from incompatibility between common mtDNA variants, which brings new insights, and complication, for the diagnosis and treatment of mitochondrial diseases.

Incompatible Common mtDNA Variants Lead to Mitochondrial Dysfunction

Each cell has hundreds to thousands of mtDNAs, and given that they are very susceptible to mutation (10- to 100-fold higher than nuclear DNA) (8), it is very likely that both mutant and wild-type mtDNAs coexist in a single cell (mtDNA heteroplasmy). Prior research has concentrated on identifying the pathogenic mtDNA variants and their levels of heteroplasmy in the diagnosis of mitochondrial disorders (6, 9). Schaefer et al. (7) provide a novel paradigm that a common mtDNA mutation, but not a pathogenic one, could also drive mitochondrial abnormalities and cause mitochondrial diseases when presented in an incompatible mtDNA background. This finding echoes an interesting work on incompatibility between two common mtDNA genotypes in mice (10). As a result, the heteroplasmies induced by many common variants may cause mitochondrial dysfunction, indicating that heteroplasmy-induced mitochondrial abnormalities may be more prevalent than we previously thought in mitochondrion-related diseases. Thanks to the advancement of mitochondrial genome editing tools (11, 12), we anticipate being able to edit the mitochondrial genome more precisely and conveniently in the future, further facilitating us to clarify the functional contributions of mitochondrial mutations to both mitochondrial functions and cell phenotypes, and build a solid foundation for our understanding of mitochondrial-related diseases.

Mitochondrial Dysfunctions Trigger Cellular Changes at the Multiomics Level

Due to the central role of mitochondria in cellular energy metabolism, mitochondrial dysfunctions are highly likely to have important implications on epigenome, transcriptome, and metabolome status of cells. For instance, senescent cells are characterized by high levels of DNA and specifically telomere damage, a persistent DNA damage response, an activated senescent-associated secretory phenotypes, shifts in the NAD^+/NADH ratio, activation of innate immune responses, and activation of antiapoptotic mechanisms. Interestingly, mitochondrial dysfunctions contributed to all these phenotypes through multiple pathways (13). Meanwhile, through a multiomics analysis, Silveira et al. (14) have discovered that mitochondrial stress is a central biological hub for spaceflight impact, and uncovered a systemic effect on the body driven by mitochondria.

The current study from Schaefer et al. (7) also performed a multiomics study to evaluate the effects of the ND5 m.13708G>A-H7 mtDNA mutant on cellular physiology. They found significant cell phenotype changes caused by this mtDNA mutation, including downregulation of oxidative phosphorylation and nicotinamide metabolism, reduced NAD^+/NADH ratio, altered methionine degradation and homocysteine degradation, dysregulated one carbon metabolism, abnormal expression of collagen formation, and neurodevelopment-related genes. This study provides sufficient data to support that this common mtDNA mutation, when presented in an incompatible mtDNA background, could have profound effects on cells. It also serves as an excellent reference for future research on the relationships between mitochondrial mtDNA mutations and cellular phenotypes.

Mitochondria–Nuclear Interactions Are Vital in Modifying Cell Phenotypes

Previous studies have highlighted that mitochondria–nuclear genome interactions could modulate cell phenotypes (15, 16). The current study from Schaefer et al. (7) further identified that histidine decarboxylase (HDC) null allele (W317X) could be a beneficial nuclear modifier for the ND5 m.13708G>A-H7 mtDNA mutant. This finding suggests that mtDNA mutations

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Author contributions: Z.G. contributed new reagents/analytic tools; and W.P. and Z.G. wrote the paper.

The authors declare no competing interest.

See companion article, "Combination of common mtDNA variants results in mitochondrial dysfunction and a connective tissue dysregulation," 10.1073/pnas.2212417119.

The authors declare no competing interest.

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Published December 28, 2022.

interact with nuclear mutations and impact cell physiology jointly. In line with this notion, it is conceivable that some nuclear mutations could exacerbate the effects induced by some common mtDNA mutations, which would result in mitochondrial dysfunction and altered cell phenotypes. Due to the possibility that part of mitochondrial diseases might result from these mtDNA-nuclear interactions rather than only mtDNA mutations, future studies should investigate both mtDNA and nuclear DNA mutations in order to correctly pinpoint the origins of mitochondrial-related diseases.

mtDNA Variants Might Be Causes of Disorders that Have Not Been Thought to Result from Mitochondrial Defects Previously

Connective tissue disorders are a heterogeneous group of diseases that affect connective tissue in various organs resulting from inflammation and dysregulated immune responses, which have not been thought from mitochondrial defects previously (17). Recent studies suggest that mtDNA mutations and mitochondrial dysfunctions may contribute to connective tissue disorders (18–20). For the first time, Schaefer et al. (7) identified that common mtDNA mutation, when presented in an incompatible mtDNA background, could alter the nuclear epigenome and expression of numerous multiple extracellular matrix genes. This finding indicates that mtDNA mutation can be an important cause of connective tissue disorders, highlighting the significance of investigating mtDNA mutations in the pathogenesis of connective tissue disorders in elderly, an important but underappreciated field of research. It is also conceivable that mtDNA mutation-induced mitochondrial dysfunction may be one of the etiologies of other complex diseases, which have not been thought to result from mitochondrial defects previously, offering fresh perspectives and new insights to further our understanding on the etiologies of complex diseases.

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