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Mitochondrial DNA

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Mitochondrial DNA

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Synonyms

[Eve gene](#); [mtDNA](#)

Definition

Mitochondrial DNA is a small circular DNA found in mitochondria.

Introduction

Mitochondrial DNA (mtDNA), discovered in 1963 by Margit and Sylvan Nass, is a small circular DNA present in the power house (mitochondria) of the eukaryotic cells. It was believed that the mtDNA is only found in the egg and is passed down to both sons and daughters from their mothers until it was found that the copy number of mtDNA is extremely high in oocytes ($\geq 10^5$) as compared to the sperm (50–75), thus explaining the maternal inheritance which could have been a result of dilution of paternal contribution wherein the mitochondria from sperm are lost during embryogenesis. Since

mtDNA is a nonrecombinant DNA, it passes down virtually unchanged through the direct maternal line over the generations (Giles et al. 1980; Pakendorf and Stoneking 2005). Therefore, it is also known as the “Eve gene.”

Need for Mitochondrial DNA

The need for mitochondria to possess its own DNA is still debatable. However, many scientists proposed “theory of endosymbiosis” which suggested that, billion years ago, mitochondria used to be independent single-celled organisms before they were swallowed by larger cells. Nevertheless, these mitochondria were not digested by these cells and developed a mutually beneficial relationship with the host cells. This mutualism further gave rise to more complex life forms over time (Brown et al. 1979). Another group of scientists also believe that mtDNA is present only to provide local control to mitochondria because pivotal proteins that regulate mitochondrial function are created in mitochondria itself and allow quicker and efficient regulation of energy production by the cell (Picard et al. 2013).

Structure of mtDNA

Human mtDNA was the first significant portion of the human genome to be sequenced by Sanger’s

laboratory, Cambridge, in 1981. There are 16,569 base pairs of mitochondrial DNA in human beings which encode for 37 genes. It also comprises of the control noncoding region (Fig. 1). Thirteen genes coded by mtDNA are essential for normal mitochondrial function and involved in making enzymes for oxidative phosphorylation (a process that uses sugar and oxygen to produce ATPs), and the rest of them provide instructions for manufacture of transfer RNA (tRNA) and ribosomal RNA (rRNA) that help in assembly of amino acids into functional proteins. Mutations in mtDNA are generally heteroplasmic, and the wild-type and mutated mtDNA coexist in the same cell. These mutations can be associated to diverse forms of diseases and aging (Pakendorf and Stoneking 2005; Shuwen et al. 2017).

mtDNA Inheritance

Though mtDNA are inherited through generations from mother to child, it still maintains its variability by the occurrence of high mutation rates due to lack of repair mechanisms and proofreading capabilities. The mutation rates of mitochondrial DNA are ten times higher than in nuclear DNA which may be a result of nucleotide imbalance in mitochondria that causes compromised DNA polymerase gamma fidelity and higher mitochondrial DNA mutation rates (Kujoth et al. 2007). This variability in mtDNA can be utilized in human identity tests, to map out ancestry and migration of a population and to evaluate the evolutionary phylogenetic by analyzing the short variable sections present in the noncoding region of mtDNA. Recently, it has been discovered that mtDNA plays crucial role in innate immune responses and inflammatory pathology and can also act as a novel marker for the prognosis of various diseases including cancer (Lee et al. 2016; Mills et al. 2017; Shuwen et al. 2017; West and Shadel 2017).

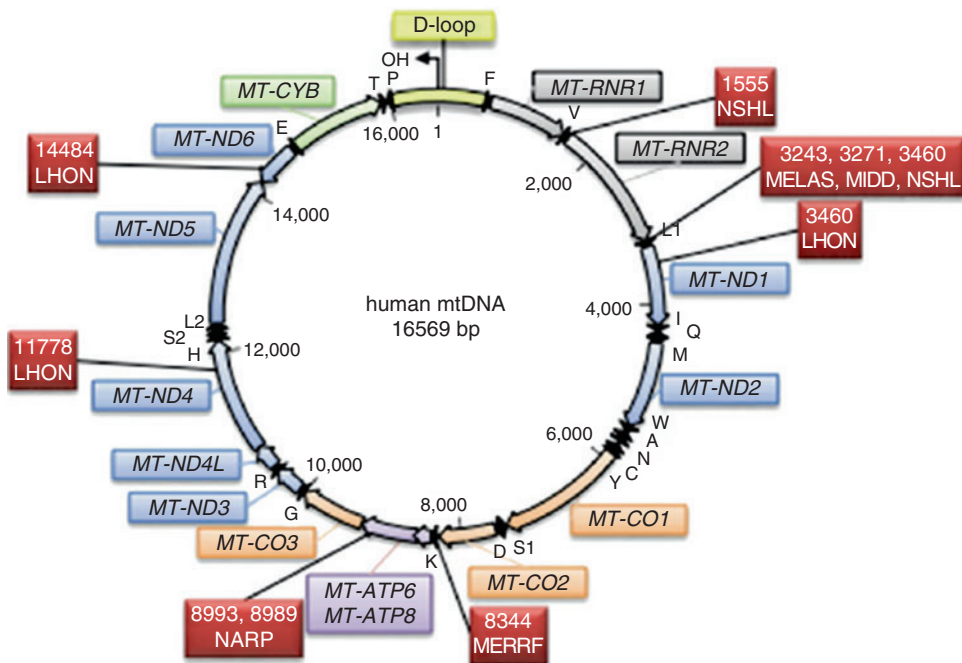
mtDNA Replication

Mechanism of replication in mitochondrial DNA is still being investigated. It was considered for

long that the maintenance of mitochondrial genome was simpler than nucleus for many years. Mammalian mitochondria lack all DNA repair systems and possess an eschewed DNA recombination. Mitochondria have only a single DNA polymerase, polymerase- γ , and it was suggested for long that Poly γ replicates mtDNA exclusively via one mechanism, involving only two priming events and a few proteins which is also referred to as “strand-displacement model.” A mechanism of replication for mammalian mtDNA was elaborated in the early 1970s from EM images of DNA isolated from rodent mitochondria by cesium chloride density centrifugation (Kasamatsu and Vinograd 1973). The EM images of mouse mtDNA suggested a model, whereby leading strand synthesis started at a specific site and advanced approximately two-thirds of the way around the molecule before second-strand DNA synthesis initiated (Kasamatsu and Vinograd 1973). Although it was earlier thought that displaced strand was coated with protein, RNA has more recently been proposed in its place. Furthermore, mtDNA molecules have now been demonstrated to possess all the features of conventional bidirectional replication, suggesting that the process and regulation of replication in mitochondria are complex, as befits a genome that is a core factor in human health and longevity.

Regulating mtDNA Copy Number

A central question in organelle biogenesis is to determine the mechanism by which the cell controls mtDNA copy number. Based on the mechanism of replication found in mtDNA, it is suggested that the rate of mtDNA replication is determined by a balance between transcription initiation from the lagging strand and subsequent RNA processing steps to provide replication primers. It has not been proved yet that mtDNA copy number is regulated by the levels of mtDNA polymerase or other proteins associated with DNA strand elongation; however, mutations in these proteins may not result in less, or even loss of, mtDNA. It has been suggested that direct activation of the nuclear transcription factor



Mitochondrial DNA, Fig. 1 Representative image of human mitochondrial DNA (Adapted from Pinto et al. 2013)

NRF-1 results in stimulation of mitochondrial biogenesis coincident with increased synthesis of mtTFA (mitochondrial transcriptional factor A) owing to the interaction of NRF-1 as an activator of the nuclear gene for mtTFA. This result, along with studies in which loss of mtTFA results in loss of mtDNA and mitochondrial function, raises the probability that mtTFA is a central feature of not only mtDNA transcription and replication but of organelle biogenesis itself (Holt et al. 1988).

can grow anaerobically, hence, it can survive without mtDNA (Goldring et al. 1970). Also, the vertebrate cells cultivated in the laboratory on a diet of glucose far less concentrated than soda can achieve the same feat (Desjardins et al. 1985). Nevertheless, it is impossible for even a simple free-living multicellular organism, such as the nematode worm, to survive without mtDNA (Brown et al. 1979; Pakendorf and Stoneking 2005).

Conclusion

Human mitochondrial DNA (mtDNA) typically forms 5- μ m circles, or 16.5 kilobases, one genome in length. The mtDNA varies largely in size and form outside animal kingdom, yet it exists without fail to provide the cell with essential components of the respiratory chain (and ATP synthase). Therefore, any mutation caused in mtDNA can lead to respiratory chain dysfunction, which results in rare diseases in plants (Levings and Pring 1976; Newton and Coe 1986) and humans (Holt et al. 1988). Since budding yeast

Cross-References

- ▶ [DNA](#)
- ▶ [Mutations](#)
- ▶ [RNA](#)

References

- Brown, W. M., George, M., Jr., & Wilson, A. C. (1979). Rapid evolution of animal mitochondrial DNA. *Proceedings of the National Academy of Sciences of the United States of America*, 76(4), 1967–1971. Available from: PM:109836.

- Desjardins, P., Frost, E., & Morais, R. (1985). Ethidium bromide-induced loss of mitochondrial DNA from primary chicken embryo fibroblasts. *Molecular and Cellular Biology*, 5(5), 1163–1169. Available from: PM:2987677.
- 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. Available from: PM:6256757.
- Goldring, E. S., Grossman, L. I., Krupnick, D., Cryer, D. R., & Marmur, J. (1970). The petite mutation in yeast. Loss of mitochondrial deoxyribonucleic acid during induction of petites with ethidium bromide. *Journal of Molecular Biology*, 52(2), 323–335. Available from: PM:5485912.
- 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. Available from: PM:2830540.
- Kasamatsu, H., & Vinograd, J. (1973). Unidirectionality of replication in mouse mitochondrial DNA. *Nature: New Biology*, 241(108), 103–105. Available from: PM:4512449.
- Kujoth, G. C., Bradshaw, P. C., Haroon, S., & Prolla, T. A. (2007). The role of mitochondrial DNA mutations in mammalian aging. *PLoS Genetics*, 3(2), e24. Available from: PM:17319745.
- Lee, W. T., Cain, J. E., Cuddihy, A., Johnson, J., Dickinson, A., Yeung, K. Y., Kumar, B., Johns, T. G., Watkins, D. N., Spencer, A., & St John, J. C. (2016). Mitochondrial DNA plasticity is an essential inducer of tumorigenesis. *Cell Death Discovery*, 2, 16016. Available from: PM:27551510.
- Levings, C. S., III, & Pring, D. R. (1976). Restriction endonuclease analysis of mitochondrial DNA from normal and Texas cytoplasmic male-sterile maize. *Science*, 193(4248), 158–160. Available from: PM:17759255.
- Mills, E. L., Kelly, B., & O'Neill, L. A. J. (2017). Mitochondria are the powerhouses of immunity. *Nature Immunology*, 18(5), 488–498. Available from: PM:28418387.
- Newton, K. J., & Coe, E. H. (1986). Mitochondrial DNA changes in abnormal growth (nonchromosomal stripe) mutants of maize. *Proceedings of the National Academy of Sciences of the United States of America*, 83(19), 7363–7366. Available from: PM:16593766.
- Pakendorf, B., & Stoneking, M. (2005). Mitochondrial DNA and human evolution. *Annual Review of Genomics and Human Genetics*, 6, 165–183. Available from: PM:16124858.
- Picard, M., Shirihai, O. S., Gentil, B. J., & Burelle, Y. (2013). Mitochondrial morphology transitions and functions: implications for retrograde signaling? *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 304(6), R393–R406. Available from: PM:23364527.
- Pinto, M., et al. (2013). *Biochimica et Biophysica Acta*, 1842(8), 1219.
- Shuwen, H., Xi, Y., & Yuefen, P. (2017). Can mitochondria DNA provide a novel biomarker for evaluating the risk and prognosis of colorectal cancer? *Disease Markers*, 2017, 5189803. Available from: PM:28408773.
- West, A. P., & Shadel, G. S. (2017). Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nature Reviews Immunology*, 17, 363. Available from: PM:28393922.