# MITOCHONDRIAL DNA- REVOLUTIONARY EVOLUTION

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**ABSTRACT**

**BACKGROUND**

Mitochondrion, the sausage-shaped organelle residing in the cytoplasm of all eukaryotic cells, apart from being the power house, represents endosymbiotic evolution of a free living organism to intracellular structure. Anthropologically, mitochondrial DNA is the fossilised source to trace the human ancestry particularly of maternal lineage. This article attempts to highlight the various biological functions of mitochondrial DNA (mtDNA) with a note on its forensic application.

**KEYWORDS**

Mitochondria, Mitochondrial DNA, Genetics, Forensics.

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## BACKGROUND

Mitochondrion is a unique cell organelle, which functions to provide energy in all eukaryotic organisms. Its number varies from a few in skin cells to numerous in muscle tissue. Anthropologically, mt gene is called Eve gene, since it is inherited and transmitted by maternal genes. MtDNA is unique and distinctive from nuclear DNA. It is the only source of DNA available when considerable tissue damage has occurred. These features make it a useful tool in forensic investigations. Nonforensic uses of mtDNA has been in the study of diseases inherited by mutation in the mtDNA, ageing, genealogy and human evolution.

## REVIEW LITERATURE

### Structure of mtDNA

The human mtDNA is a double-stranded circular molecule having 16569 bps. These nucleotide base pairs code for 13 polypeptide chains, most of it is involved in aerobic respiration (oxidative phosphorylation complex OXPHOS). A small part of mtDNA also codes for 22 transfer RNAs and 2 ribosomal RNAs.[1]

Displacement loop or D-loop is a region in the mtDNA structure. It consists of a stretch of 1123 base pair sequences. This region is close to the area of mtDNA replication and transcription. It bears two variable regions- HV1 at position 16024-16383 and HV2 at position 57-372.[2] Progressive mutations and accumulation in this region has been observed in cancers and ageing.[3,4,5] Studies have shown mutations in mtDNA in cases of oral squamous cell carcinomas.[6,7] It has found application in forensics, medical diagnosis, cancer research and therapy.

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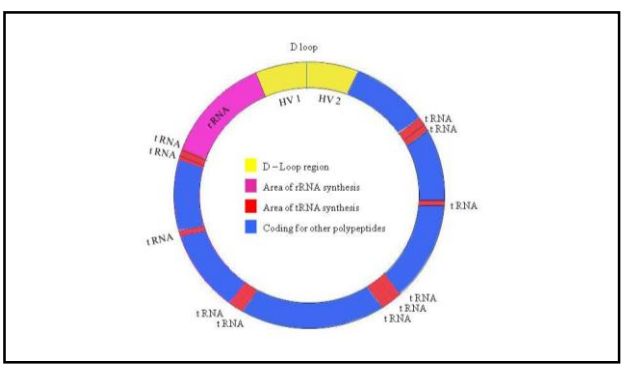


***Figure 1. Structure of mtDNA showing Hypervariable Regions (HV1, HV2) in D Loop Area Susceptible to Mutations***

### Genetics of mtDNA

Mitochondria once a free living organism through endosymbiosis gets into eukaryotic cell.[8] This evolutionary change is evident by the unique genetic features the mtDNA possesses, few of which has been listed below.

Mitochondrion has its own circular genomic DNA (mtDNA). Its replication is independent and partly controlled by nuclear DNA. There are multiple copies of mtDNA, which can be homoplasmy (has single type of DNA) or heteroplasmy (has wild and mutant DNA). MtDNA is devoid of introns and histones. Few of the genetic codes is different in the mtDNA; e.g.- AUA codes for methionine, which is represented as AGA in universal code.[9] The inheritance of the mtDNA is uniparental coming exclusively from mother to children and does not follow the Mendelian Patterns of Inheritance.[10]

### Mitochondrial Eve

Mitochondrial DNA is of anthropological value in tracing the first humans. The first ancestral woman is traced back to Africa based on two strong findings. Firstly, because mtDNA

is maternally inherited, tracked through mother to grandmother to great grandmother and so on, it is less complicating while reconstructing the phylogenetic tree. Since, there is no mixing of maternal and paternal genes as in nuclear DNA, it is a simpler tracing method.

Secondly, mitochondrial DNA offers a more sensitive clock by which the genetic distance between individuals are determined. The degree of genetic relatedness between individuals is determined by the number of mutations that separate them.

Based on these anthropological studies, it has been concluded that Africa is the likely source of the human mitochondrial gene, which later spreads to the rest of the world.[11,12]

**Mitochondrial Disease**

Although, the mtDNA genome is very small compared to the nuclear DNA, the mutations in this region are a cause to many inherited diseases. Since, mtDNA are present in all nucleated cells, the mutation in the mtDNA causes varied phenotypic expressions. Mitochondrial disease transmission is governed by 3 rules-

1. Heteroplasmy and threshold effect- As each cell contains many mitochondria with multiple copies of mtDNA, it is possible that wild and mutant mtDNA coexist. The presence of wild and mutated DNA in a cell is called heteroplasmy. The presence of mutated DNA itself does not cause disease. The accumulation of mutant mtDNA should reach a threshold level for the disease expression to occur.
2. Mitotic segregation- The number of mtDNA received by the daughter cells during cell division is a random process and has implication on clinical manifestations. It is also responsible for phenotypic shift as the patient grows older.
3. Maternal inheritance- During fertilisation, all of the sperm mitochondria are killed and so the zygote gets its mitochondria from the ovum. This kind of inheritance from mother to children is called maternal inheritance, also known as matrilineal inheritance.[13]

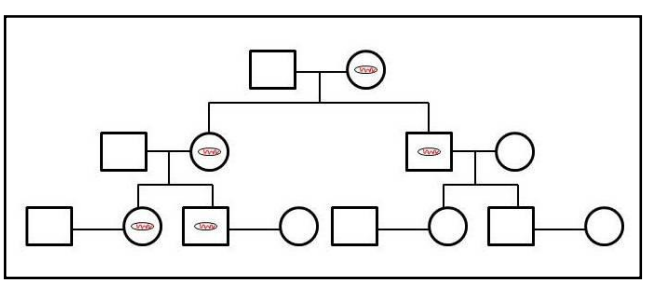

***Figure 2. Pedigree Chart Showing Transfer of mtDNA Mutations along Maternal Lineage***

A disease expressed in both sexes, but with no evidence of paternal transmission is strongly suggestive of mtDNA point mutation. The clinical features of mitochondrial diseases are nonspecific, which makes diagnosis difficult. Diseases of the mitochondria affect organs, which require high energy such as brain, heart, liver, skeletal muscles, kidney endocrine and respiratory systems.[14]

Most commonly encountered mitochondrial disease include Leber's Hereditary Optic Neuropathy (LHON), Leigh disease, pyruvate dehydrogenase complex deficiency and autosomal dominant optic dystrophy.[15]

Treatment of mitochondrial disease has been with use of vitamins, cofactors and nutritional supplements with very little benefit. Newer therapies at molecular level are still in preclinical stage.[14]

**Mitochondrial DNA and Cancer**

Among the two genetic systems, mtDNA is more prone to damage. It is more vulnerable to mutations than nuclear DNA, because it lacks histone protection has limited repair capacity and has close proximity to the electron transport chain, which constantly generates superoxide radicals.

Also, mtDNA lacks introns, most mutations occur in the coding sequences and are thus likely to be of biological consequence.

Somatic mitochondrial DNA mutations have been observed in primary human cancers like breast cancer, colorectal cancer, ovarian cancer, gastric carcinoma, hepatocellular carcinoma, pancreatic cancer, prostrate cancer, lung cancer, renal carcinoma, thyroid cancer, brain tumours and other solid tumours.[16,17]

Mitochondrial factor assay is accepted diagnostic procedure for many metabolic disorders. Many mitochondrial markers have been developed for early cancer detection. Detection of mtDNA alterations offers the advantage of allowing low invasive methods including analysis in urine for bladder cancer or saliva for head and neck cancers.[18] Most popular mitochondrial marker is the MitoChip array.

MitoChip oligonucleotide arrays is a sequencing tool for identification of mtDNA mutations. It contains oligonucleotide probes, which can sequence >29 kb of double stranded DNA in a single assay, which makes it possible to screen for many factors at the same time.[19,20]

Mitochondria have also become cellular targets for future cancer therapy. Mitocans, that is, anticancer agents that act through the mitochondria provide a strategy for targeting of mitochondrial metabolism and apoptotic processes.[21]

**mtDNA in Forensic**

mtDNA has become a useful tool in forensic science. With the development of Polymerase Chain Reaction (PCR) and direct DNA sequencing, rapid and reliable characterisation of the mtDNA has become possible and is gaining popularity. The fact that there are hundred copies of mtDNA in a cell as compared to 2 copies of nuclear DNA makes mtDNA an easy source when limited biological sample is obtained or in cases of mass disaster and criminal investigations. The most noted case solved by mtDNA isolation has been the finding of Russian Tsar and his family during the Bolshevik revolution. Since then, many cases have been using mtDNA for victim identification especially when nucleated cellular material is lacking like hair, bone and dental remains.[22]

**Method**

Following the sample collection, DNA extraction is done, which removes impurities, debris and other interfering proteins, thus obtained DNA is amplified by using PCR machine. With this, the region of interest (hypervariable region HV I, HV II present in the D loop region of the mtDNA) are amplified to many copies. The amplified DNA is sent for DNA sequencing, which reveals the nucleotide sequence. This is used to match and compare with known samples.[23]

**Advantages and Limitations of mtDNA**

Mitochondrial DNA testing lacks specificity as all maternally related females will show the same mtDNA. Hence, it can only be reliable as to exclude the person in question from the suspect list. The mtDNA examination is useful, if the victim or the suspect is long deceased, then the surviving maternal relative becomes useful source of DNA for compare and identification.

**CONCLUSION**

Since, its time of sequencing by Sanger and colleagues, mtDNA has revealed its significant roles in human genetics, diseases evolution, etc. It has proved to be useful tool in forensics for human remains identification. Further studies on pathogenesis and research at molecular level for treatment of mitochondrial disease are required.

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