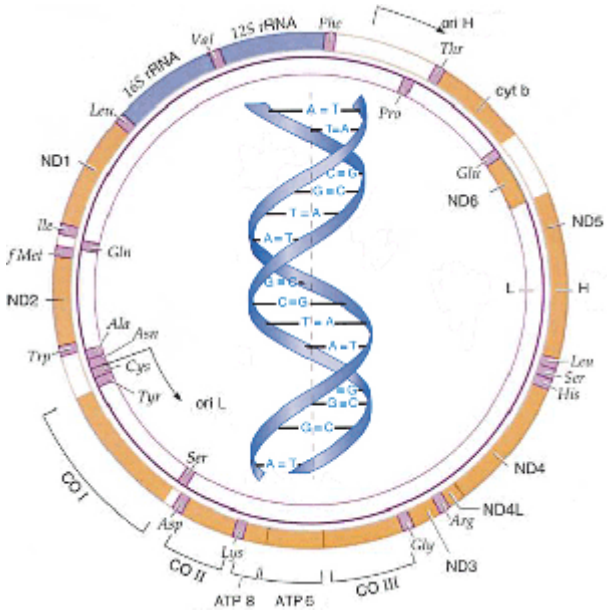

Mitochondrial DNA and its Role

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Mitochondria are extraordinarily complex biochemical structures (“organelles”) located inside eucaryotic cells (Figure 1). Mitochondria convert glucose energy into an energy form that cells can make use of, called ATP. This important process is known as *oxidative phosphorylation*, and it is ultimately controlled by the cell’s intricate genetic machinery.

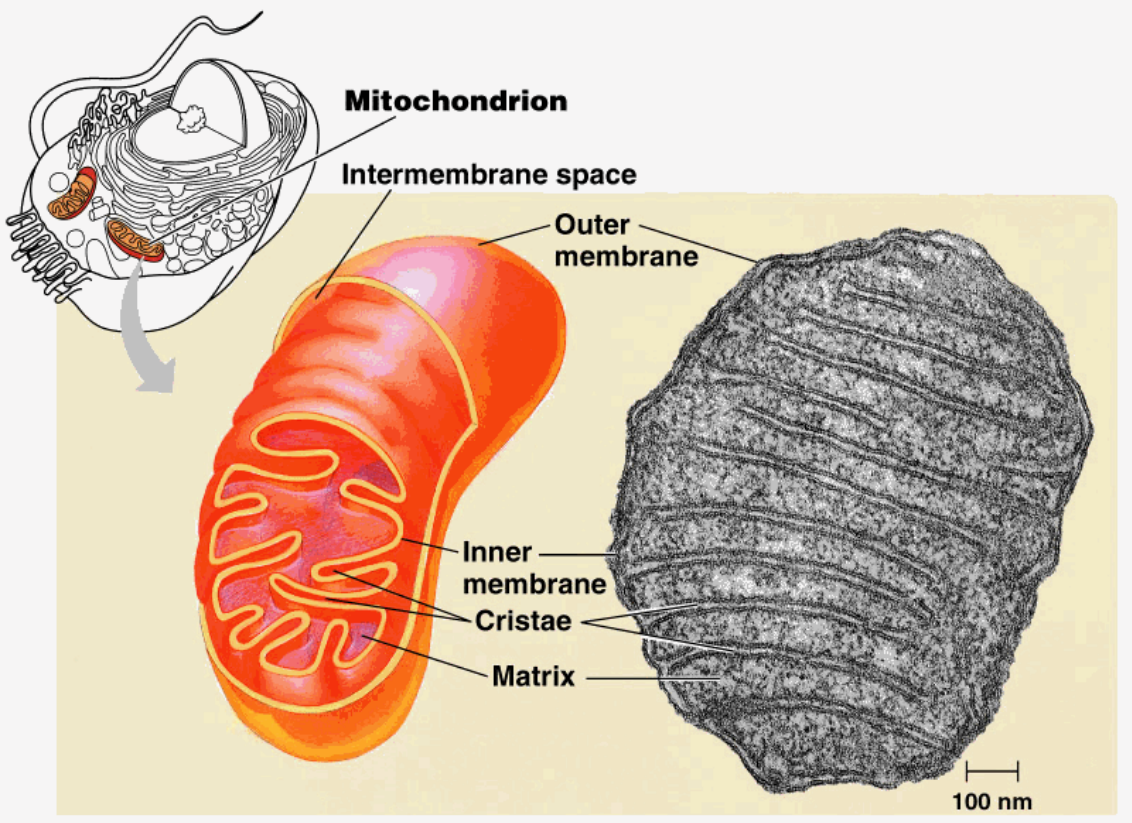


Figure 1: Schematic representation of a mitochondrion. Their position inside a typical eucaryotic cell is shown in the upper left of the figure. Note that **nm** (bottom right) is short for nanometer.

Image Credit: http://kentsimmons.uwinnipeg.ca/cm1504/Image110.gif

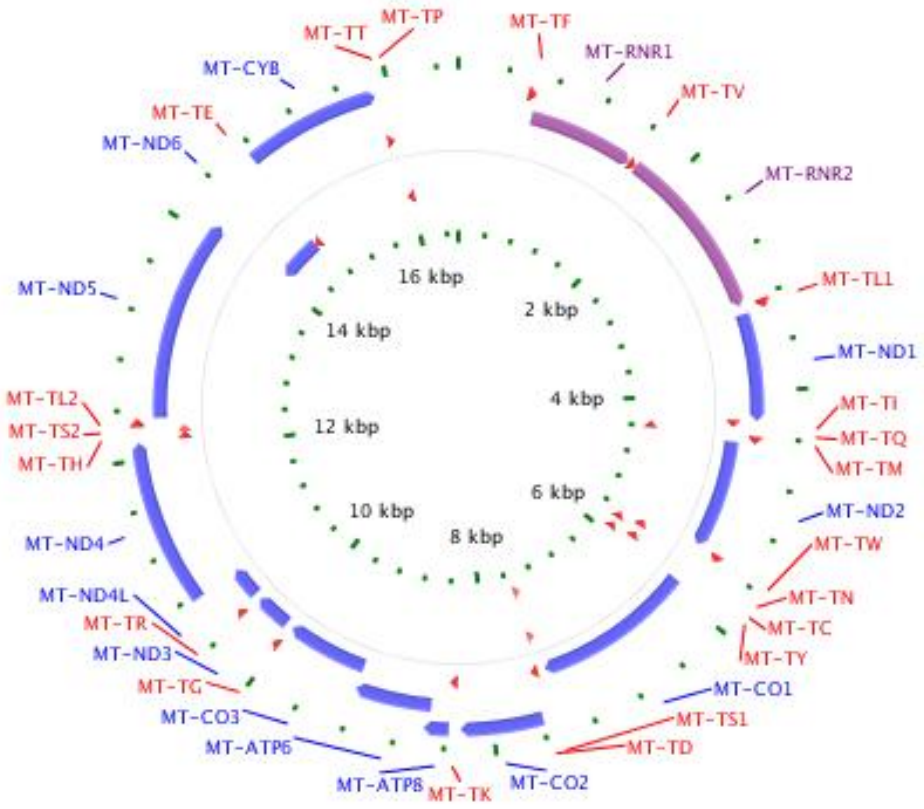
There are an estimated 20,000 to 25,000 genes (3.1 billion base pairs) in the human genome [1]. Of these, a small number are composed of mitochondrial DNA (mtDNA) found in the mitochondria, as opposed to the usual genes based on conventional DNA (nuclear DNA, chromosomal DNA) found in all cell nuclei. In fact, as illustrated in Figure 2, the human mitochondrial genome consists of a mere 37 genes, involving 16,569 base pairs, and these code for 13 proteins, 22 tRNAs (transfer RNAs), and 2 rRNAs (ribosomal RNAs) [2].

Nuclear and mitochondrial DNA are thought to have evolved separately, with mtDNA having developed eons ago from bacteria engulfed by ancestor cells (endosymbiotic hypothesis) [3]. Also, each mitochondrion contains multiple copies of mtDNA, as opposed to only a single copy of regular DNA in cell nuclei.

Conventional (nuclear) DNA in an individual is inherited from both parents, with one chromosome of each chromosome pair coming from each parent. This process results in genes being rearranged, a process known as “recombination”.

Figure 2: Map of human mitochondrial DNA diagrammed as a circular structure with genes and regulatory regions labeled. Note that kbp in the figure stands for *kilo base pairs* (of mtDNA). As an example, mutations of the MT-ATP6 gene (located at 7 o'clock) have been found in some people with neuropathy, ataxia, and retinitis pigmentosa. This gene normally provides instructions for making a component of an enzyme called ATP synthase; mutations in the MT-ATP6 gene reduce the ability of mitochondria to make ATP. (See Appendix for information on other mutations with clinical implications).

Image Credit: http://ghr.nlm.nih.gov/chromosome=MT



By contrast, mtDNA is passed on to an individual only from that person's mother, and it is passed on with (virtually) no change. This point bears emphasizing: all of a person's mitochondria are derived from his or her mother only – there is ordinarily no paternal contribution [4]. Because of this fact (known as *matrilineal descent*) and because the mutation rate of mtDNA is higher than that of regular DNA, mtDNA can be to help track ancestry (*vide infra*).

There are also other reasons why mtDNA is so helpful to scientists. Since most cells contain many mitochondria (sometimes thousands in each cell) and since each mitochondrion contains a number of copies of mtDNA (typically 2 to 10), the end result is that most cells contain thousands of copies of mtDNA but can have only one set of nuclear DNA (Figure 3). As a result, technically adequate samples of mtDNA can usually be obtained using far smaller amounts of tissue than for conventional DNA studies, a point used to advantage in both the genealogical and forensic scientific arenas.

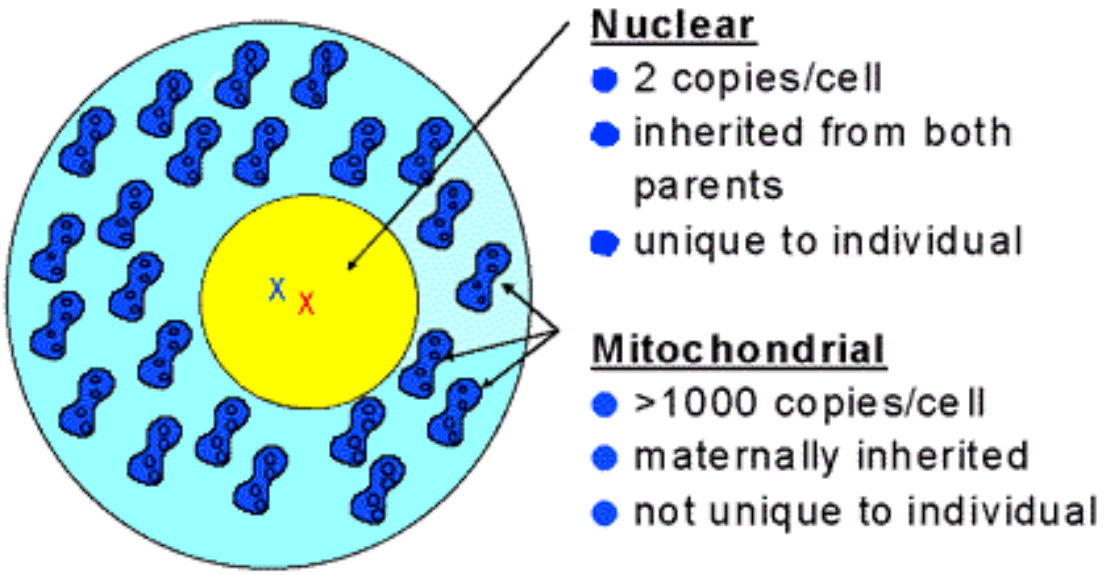


Figure 3: Nuclear DNA has a smaller number of copies per cell than mitochondrial DNA and is inherited from both parents. Mitochondrial DNA is maternally inherited without recombination and, thus, is not unique to an individual.

Image Credit: Image and figure legend from http://www.fbi.gov/hq/lab/fsc/backissu/july1999/dnaf1.htm

In recent years mitochondrial DNA has played a unique role in providing insight into our human origins. One ongoing controversy in paleoanthropology (the study of human origins) concerns the origin of *Homo sapiens* [5]. According to the fossil record, about 100 millennia ago the world was populated by diverse hominids: *Homo sapiens*, *Homo erectus*,

and *Homo neanderthalensis*. However, by about 30 millennia ago this diversity disappeared and humans everywhere evolved into our current modern form. The exact mechanism of this transformation is currently the subject of great debate. One school of thought, the “multiregional continuity model” [6] holds that *Homo erectus* dispersed form Africa into other regions, slowly evolving into modern humans. The other school of thought hold that a single African origin exists for modern humans (“Out of Africa model”) [7].

At the moment, the available scientific evidence seems to favor the latter model (the model of African origin) over the multiregional model on the basis that fossils of modern-like humans have been found in Africa (e.g., “Lucy”), and because of the discovery of early human artifacts in Africa. In particular, recent mitochondrial DNA evidence has become available to even further support the Out of Africa model [8].

For example, mtDNA variation among modern human populations has been shown to be small compared to, for instance, the mtDNA variation between various nonhuman primates,

suggesting that human origins are relatively recent in evolutionary history [9]. In addition, it has been shown that African human populations have more diverse mitochondrial DNA sequences compared to other human populations, a fact suggesting an earlier origin of the African peoples compared to other humans [10]. Finally, judging from recent analyses of mitochondrial DNA from Neandertal bones, it has been established that is unlikely that the Neandertals were ever members of our own species [11].

One particularly interesting notion in genetic paleoanthropology is that of a “molecular clock”. If mutations in human mtDNA are believed to be random events that occur at a roughly uniform rate of (say) one every 3,000 years, then should the mtDNA sequences of two populations differ by, say, 10 nucleotides, it can be inferred that the two populations split from a common ancestral population about 30,000 years ago [12]. This “clock” can even (in principle) be “calibrated” using living species whose date of speciation is known from the fossil record. At the moment, however, the molecular clock concept remains controversial as a result of reports of

non-uniform rates of molecular evolution, species-specific differences in mutation rates, variations in generation times and other recent findings [13].

Another interesting concept in paleoanthropology is “Mitochondrial Eve” [14]. Mitochondrial Eve is the name sometimes given by paleoanthropologists to the woman whose mitochondrial DNA is now found in all living humans. That is, every mtDNA in every living person is ultimately inherited from her mitochondria. Mitochondrial Eve is believed to have lived about 150,000 years ago [14].

Related to this is “Y-chromosomal Adam”: because the Y chromosome present only in males is transmitted unchanged from father to son, all Y chromosomes can presumably be traced back to a single prehistoric father [15].

In conclusion, the analysis of mitochondrial DNA offers a remarkable, if sometimes controversial, anthropological tool for exploring our human origins. In particular, it provides provisional support for the hypothesis that contemporary humans stem from a common African ancestor.

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Appendix: Clinical disorders caused by mutations in mitochondrial DNA

Modified from Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat. Rev. Genet.* 2005; **6**:389–40

Mitochondrial DNA Disorder	Clinical Presentation	mtDNA genotype	Gene	Inheritance
Kearns–Sayre syndrome	Progressive myopathy, ophthalmoplegia, cardiomyopathy	A single, large-scale deletion	Several deleted genes	Usually sporadic
CPEO	Ophthalmoplegia	A single, large-scale deletion	Several deleted genes	Usually sporadic
Pearson syndrome	Pancytopoenia, lactic acidosis	A single, large-scale deletion	Several deleted genes	Usually sporadic
MELAS	Myopathy, encephalopathy lactic acidosis, stroke-like episodes	3243A>G; NOTE 3271T>C	*TRNL1*	Maternal
		Individual mutations	*ND1 and ND5*	Maternal
MERRF	Myoclonic epilepsy, myopathy	8344A>G; 8356T>C	*TRNK*	Maternal
NARP	Neuropathy, ataxia, retinitis pigmentosa	8993T>G	*ATP6*	Maternal
MILS	Progressive brain-stem disorder	8993T>C	*ATP6*	Maternal
MIDD	Diabetes, deafness	3243A>G	*TRNL1*	Maternal
LHON	Optic neuropathy	3460G>A	*ND1*	Maternal
		11778G>A	*ND4*	Maternal
		14484T>C	*ND6*	Maternal
Myopathy and diabetes	Myopathy, weakness, diabetes	14709T>C	*TRNE*	Maternal
Sensorineural hearing loss	Deafness	1555A>G	*RNR1*	Maternal
		Individual mutations	*TRNS1*	Maternal
Exercise intolerance	Fatigue, muscle weakness	Individual mutations	*CYB*	Sporadic
Fatal, infantile encephalopathy; Leigh/Leigh-like syndrome	Encephalopathy, lactic acidosis	10158T>C; 10191T>C	*ND3*	Sporadic

ATP6, ATPase 6; CPEO, chronic progressive external ophthalmoplegia; *CYB*, cytochrome *b*; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy and ragged-red fibres; MIDD, maternally-inherited diabetes and deafness; MILS, maternally-inherited Leigh syndrome; *ND1,3–6*, NADH dehydrogenase subunits 1,3–6; NARP, neurogenic weakness, ataxia and retinitis pigmentosa; *RNR1*, 12*S* ribosomal RNA; *TRNE, TRNK, TRNL1, TRNS1*, mitochondrial tRNAs. **NOTE** 3243A>G means that at base pair position 3243 in the mtDNA sequence, nucleotide A was replaced by nucleotide G in a mutation, and so on.