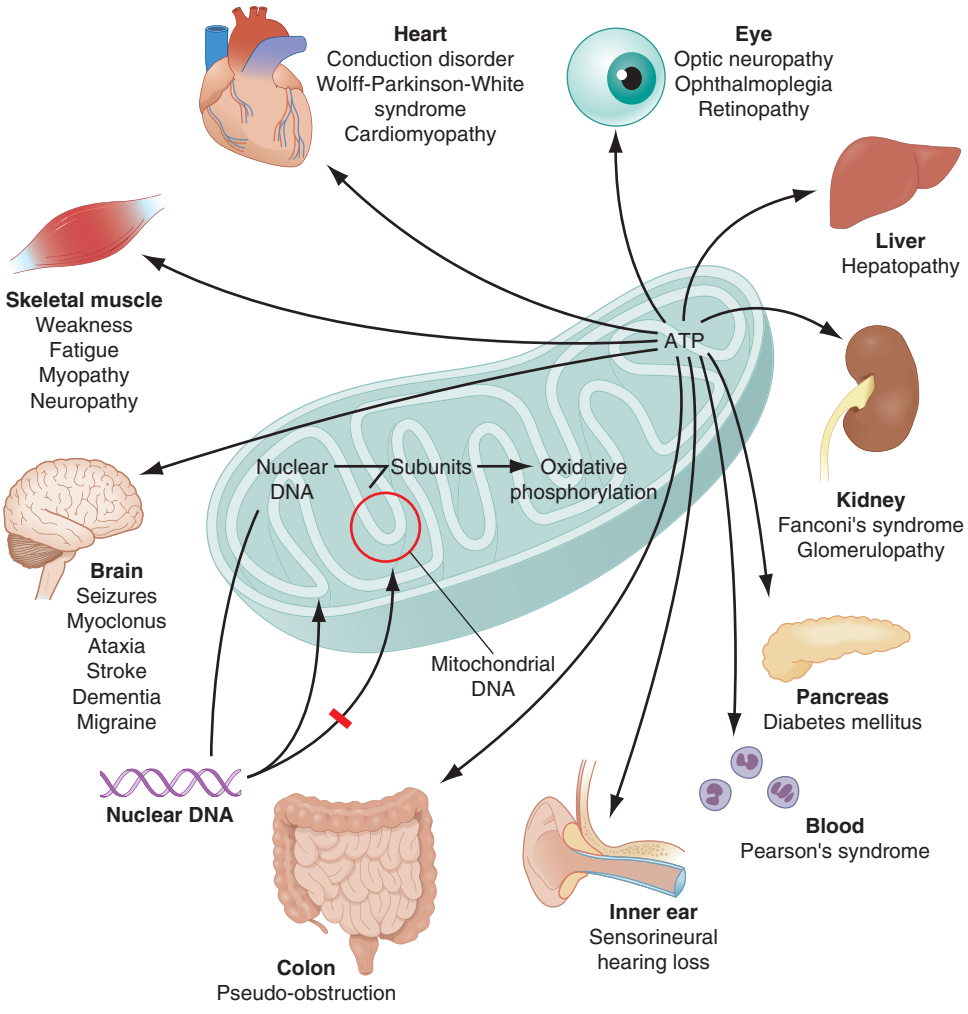


**FIGURE 85e-1 Dual genetic control and multiple organ system manifestations of mitochondrial disease.** *(Reproduced with permission from DR Johns: Mitochondrial DNA and disease. N Engl J Med 333:638, 1995.)*

hereditary impact of mtDNA mutagenesis requires separate consideration of events in the female germline.

The multiple mtDNA copy number within each cell, including the maternal germ cells, results in the phenomenon of heteroplasmy, in contrast to much greater uniformity (homoplasy) of somatic nuclear DNA sequence. Heteroplasmy for a given mtDNA sequence variant or mutation arises as a result of the coexistence within a cell, tissue, or individual of mtDNA molecules bearing more than one version of the sequence variant (Fig. 85e-3). The importance of the heteroplasmy phenomena to the understanding of mtDNA-related mitochondrial diseases is critical. The coexistence of mutant and nonmutant mtDNA and the variation of the mutant load among individuals from the same maternal sibship, and across organs and tissues within the same individual, play a pivotal role in the manifestation and severity of disease and are crucial to understanding the complexity of inheritance of mtDNA disorders. At the level of the oocyte, the percentage of mtDNA molecules bearing each version of the polymorphic sequence variant or mutation depends on stochastic events related to partitioning of mtDNA molecules during the process of oogenesis itself. Thus, oocytes differ from each other in the degree of heteroplasmy for that sequence variant or mutation. In turn, the heteroplasmic state is carried forward to the zygote and to the organism as a whole, to varying degrees, depending on mitotic segregation of mtDNA molecules during organ system development and maintenance. For this reason, in vitro fertilization, followed by preimplantation genetic diagnosis (PGD), is not as predictive of the genetic health of the offspring in the case of mtDNA mutations as in the case of the nuclear genome. Similarly, the impact of somatic mtDNA mutations acquired during development and subsequently also shows an enormous spectrum of variability.

*Mitotic segregation* refers to the unequal distribution of wild-type and mutant versions of mtDNA molecules during all cell divisions that occur during prenatal development and subsequently throughout the lifetime of an individual. The phenotypic effect or disease impact will, thus, be a function not only of the inherent disruptive effect (pathogenicity) on the mtDNA-encoded gene (coding region mutations) or integrity of the mtDNA molecule (control region mutations), but also of its distribution among the multiple copies of mtDNA in the various mitochondria, cells, and tissues of the affected individual. Thus, one consequence can be the generation of a bottleneck due to the marked decline in given sets of mtDNA variants, consequent to such mitotic segregation. Heterogeneity arises from differences in the degree of heteroplasmy among oocytes of the affected female, together with subsequent mitotic segregation of the pathogenic mutation during tissue and organ development, and throughout the lifetime of the individual offspring. The actual expression of disease might then depend on a threshold percentage of mitochondria whose function is disrupted by mtDNA mutations. This in turn confounds hereditary transmission patterns and hence genetic diagnosis of pathogenic heteroplasmic mutations. Generally, if the proportion of mutant mtDNA is less than 60%, the individual is unlikely to be affected, whereas proportions exceeding 90% cause clinical disease.

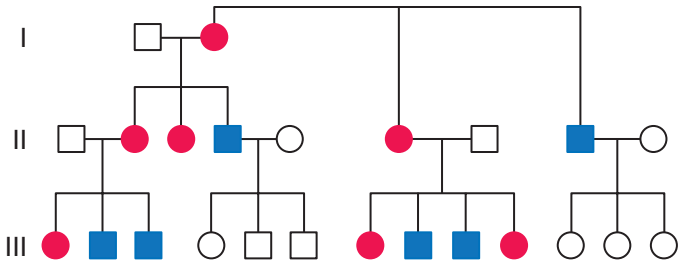


**FIGURE 85e-2 Maternal inheritance of mitochondrial DNA (mtDNA) disorders and heritable traits.** Affected women (*filled circles*) transmit the trait to their children. Affected men (*filled squares*) do not transmit the trait to any of their offspring.

## HOMOPLASMIC VARIANTS AND HUMAN MTDNA PHYLOGENY

In contrast to classic mtDNA diseases, most of which begin in childhood and are the result of heteroplasmic mutations as noted above, during the course of human evolution, certain mtDNA sequence variants have drifted to a state of homoplasmy, wherein all of the mtDNA molecules in the organism contain the new sequence variant. This arises due to a "bottleneck" effect followed by genetic drift during the very process of oogenesis itself (Fig. 85e-3). In other words, during certain stages of oogenesis, the mtDNA copy number becomes so substantially reduced that the particular mtDNA species bearing the novel or derived sequence variant may become the increasingly predominant,