HST.161 Molecular Biology and Genetics in Modern Medicine
Fall 2007

Lecture 7 Mitochondrial Disorders

Mitochondria:

- possess their own genome; mtDNA contains 16,569 bp. It's very compact, with an absence of introns.
- outer membrane, inner membrane, cristae, matrix
- clustered in muscle sarcolemma to provide energy to muscles
- also located in photoreceptors

Oxphos pathway:

- produces ATP
- generation of reactive oxygen species – toxic byproducts of respiration
- initiation of apoptosis

Mitochondrial inheritance:

- track along maternal germline; no male to male transmission
- heteroplasmy: mixing of WT and mutant mitochondria
- only when mutant DNA reaches a "critical level" will cellular phenotype change from normal to abnormal
- the more abnormal mitochondria you have, the more abnormal your phenotype will be
- disease expression may require other factors, such as hormonal, genetic, or immunological factors

Many mitochondrial disorders have neurological symptoms
Mitochondrial disease map [good figure; redraw? P. 13]

High mutation rate; 10X that of nuclear DNA

- Large numbers of polymorphisms in coding regions
- Absence of protective histones (histones protect against oxidative damage, and mitochondria help produce, and are therefore near, oxidative species)
- Lack of DNA-excising repair mechanisms

Phenotypic heterogeneity of mitochondrial syndromes: can affect many different organs

- Cardinal feature: large, ballooned cells in muscle. "Ragged red fibers." To diagnose a mitochondrial disease, do a muscle biopsy and look for these cells.
    - In children, this can be unreliable; sometimes the ragged red fibers will only be apparent after attacks