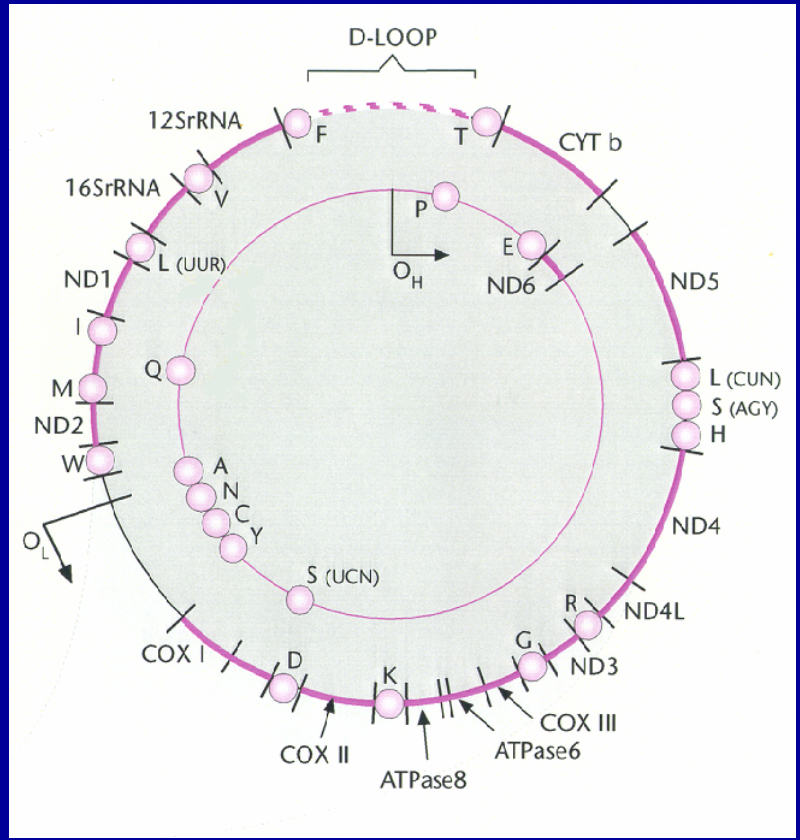
Mitochondrial DNA Disease: Clinical and histochemical features

Human mtDNA

- Located in mitochondrial matrix
- Circular genome with short non-coding region (D-loop)
- Multiple copies in single cell
  Approx. 700 in fibroblasts to >200,000 in mammalian oocytes
- Maternally inherited



Mitochondrial DNA Disease

Clinical features

- Classic syndromes
- Clinical syndromes with a high risk of mtDNA involvement
- Involvement in common disease phenotypes
- Mitochondrial DNA variants as a predisposition for common disease

Mitochondrial DNA Disease

Classic syndromes

- Kearns Sayre syndrome – mtDNA deletion
- MELAS – 3243A>G
- MERRF – 8344A>G
- Leber's Hereditary Optic Neuropathy – 3460G>A, 11778G>A, 14484T>C
- NARP – 8993T>G/C

Mitochondrial DNA Disease

Clinical syndromes with a high risk of mtDNA involvement

- Progressive external ophthalmoplegia
- Leigh's disease
- Exercise induced muscle pain and fatigue
- Heart failure with biventricular cardiomyopathy

Mitochondrial DNA Disease

Involvement in common disease phenotypes

- Diabetes
- Migraine
- Deafness
- Ataxia

Mitochondrial DNA Disease

Mitochondrial DNA variants as a predisposition for common disease

- Diabetes
- Neurodegenerative disease

Mitochondrial Diseases

What types of symptoms are seen?

Mitochondrial Disease

- Audiology
- Cardiology
- Clinical Genetics
- Clinical Neurophysiology
- Dermatology
- Endocrine/Diabetes
- Gastroenterology
- Geriatrics
- Haematology
- Neurology
- Rehabilitation
- Renal Medicine
- Respiratory Medicine
- Rheumatology

Sciencexpress Report

A Cluster of Metabolic Defects Caused by Mutation in a Mitochondrial tRNA

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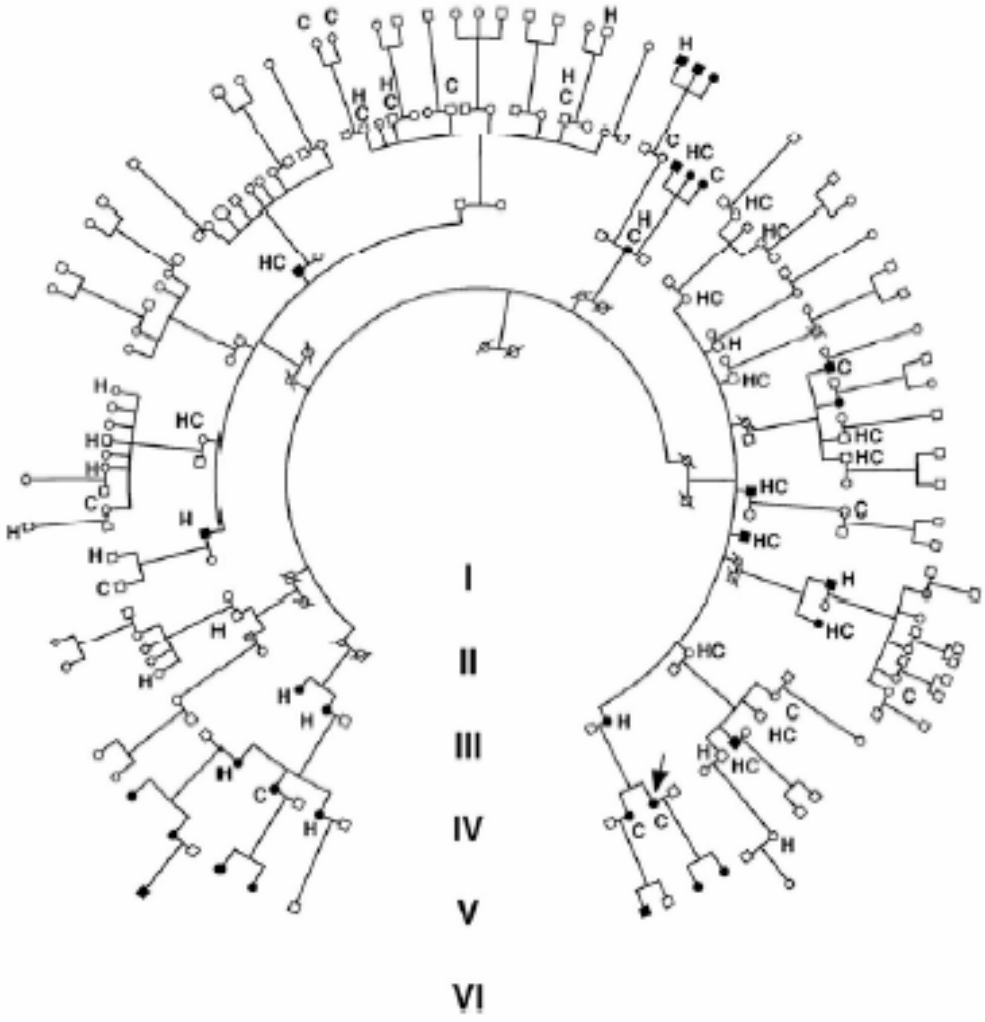
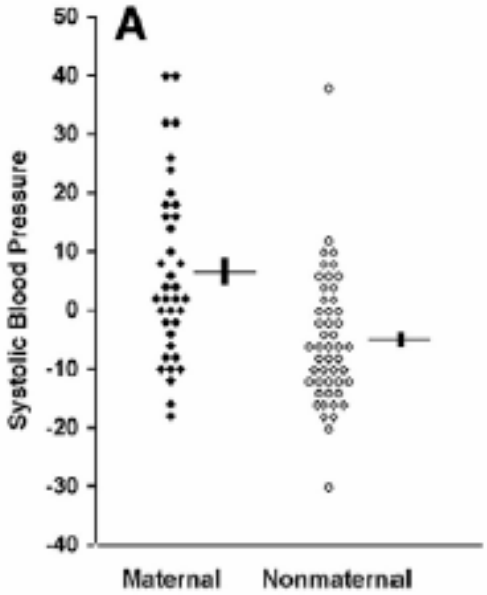
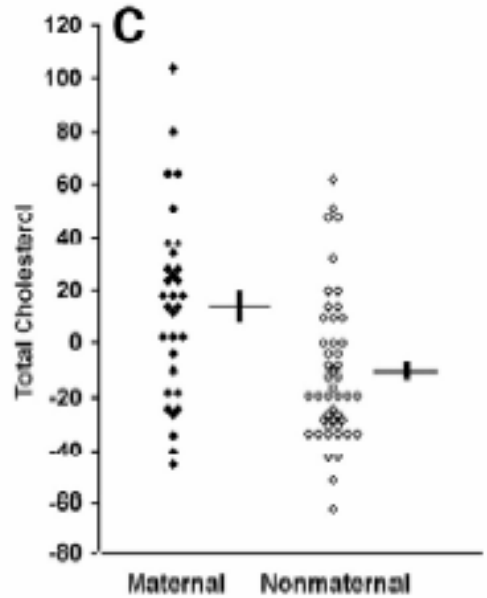

I
II
III
IV
V
VI


A
Systolic Blood Pressure
50
40
30
20
10
0
-10
-20
-30
-40
Maternal
Nonmaternal


C
Total Cholesterol
120
100
80
60
40
20
0
-20
-40
-60
-80
Maternal
Nonmaternal

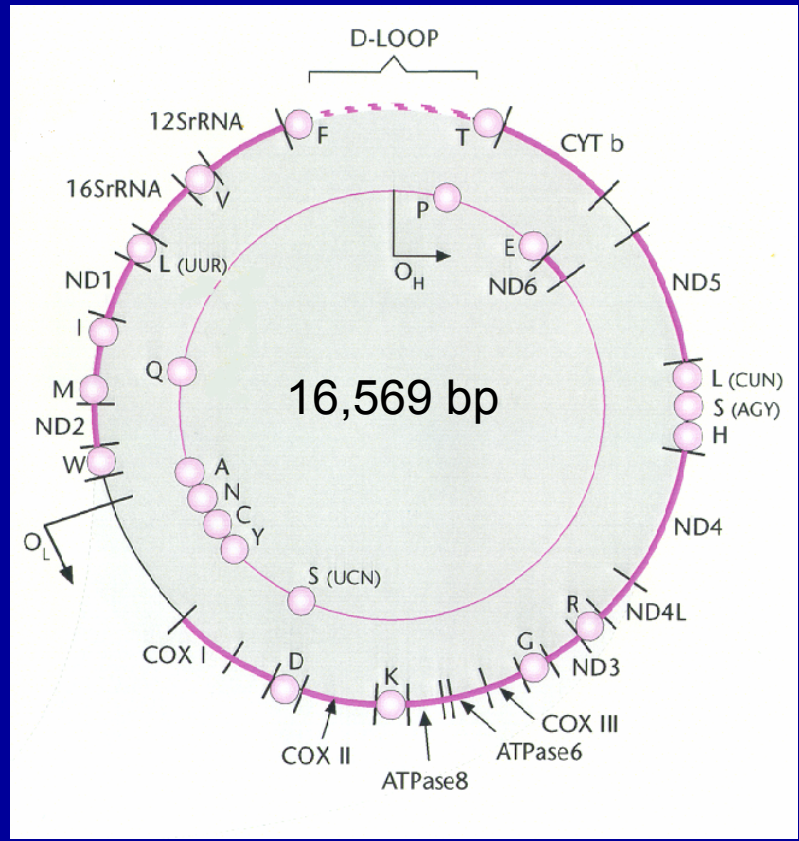
Mitochondrial Diseases

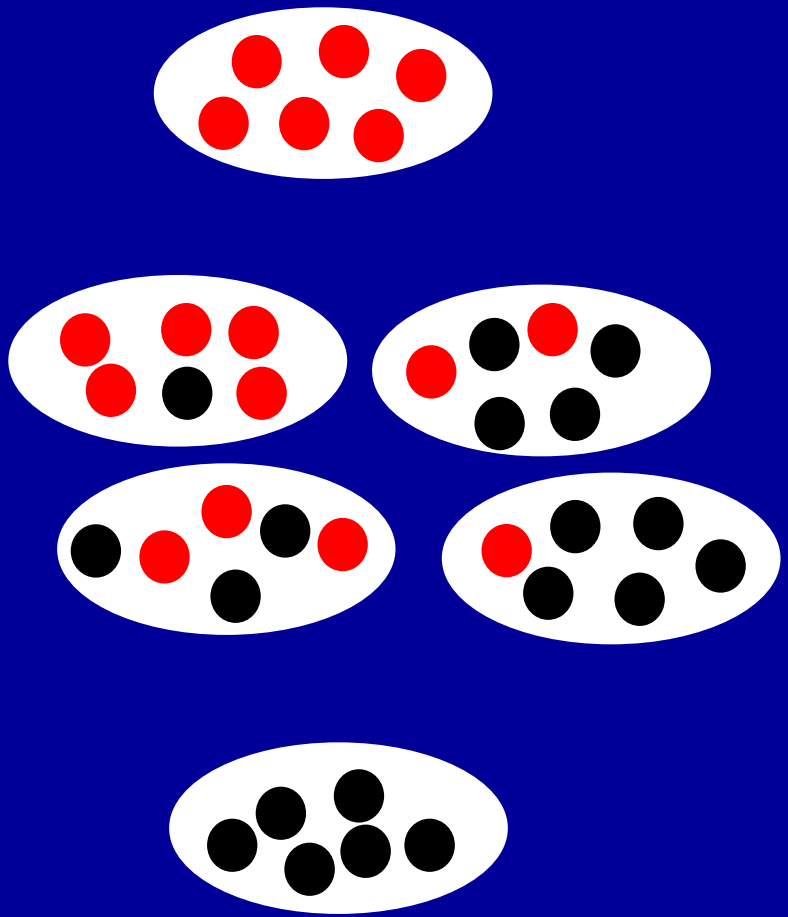
What cause the clinical variability?

Human mtDNA

>150 Different mtDNA point mutations

>100 Different deletions

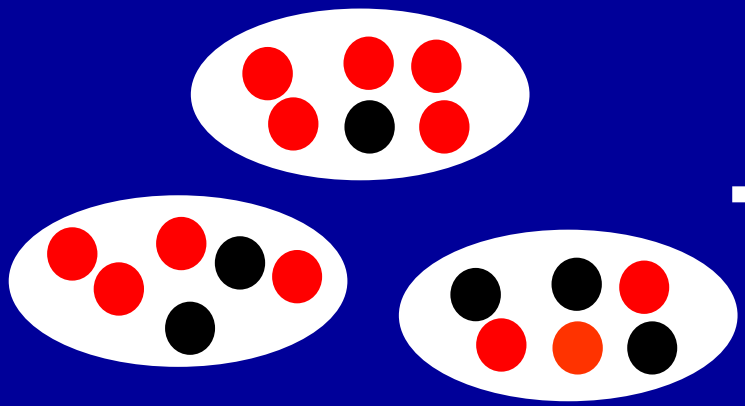




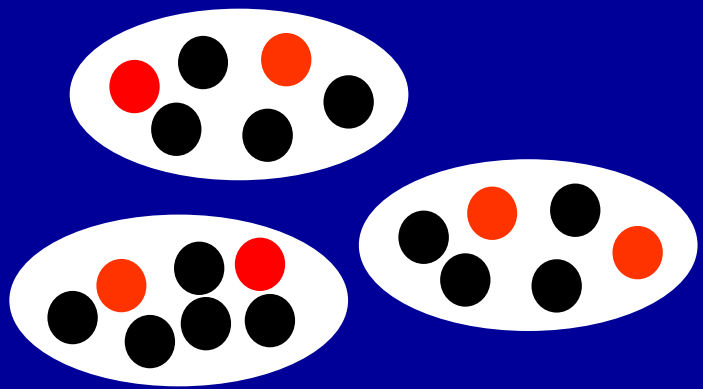
Homoplasmic wild-type

HETEROPLASMIC

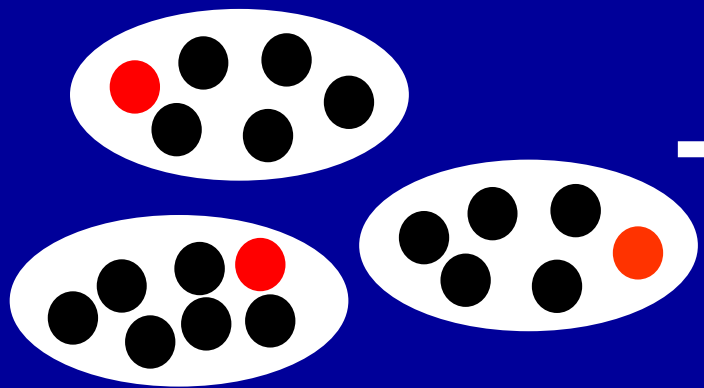
Homoplasmic mutant



normal phenotype



mild phenotype

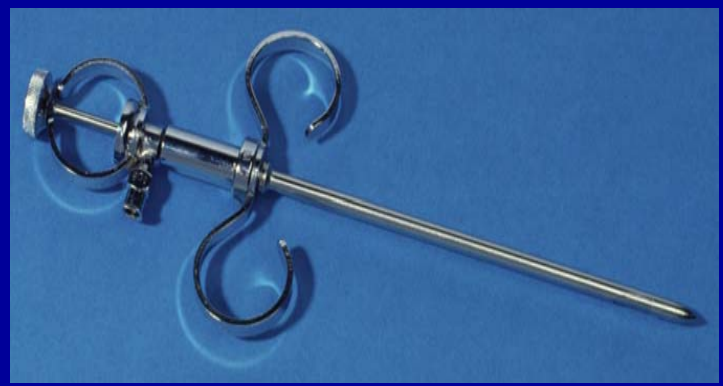


severe phenotype

Mitochondrial DNA Disease

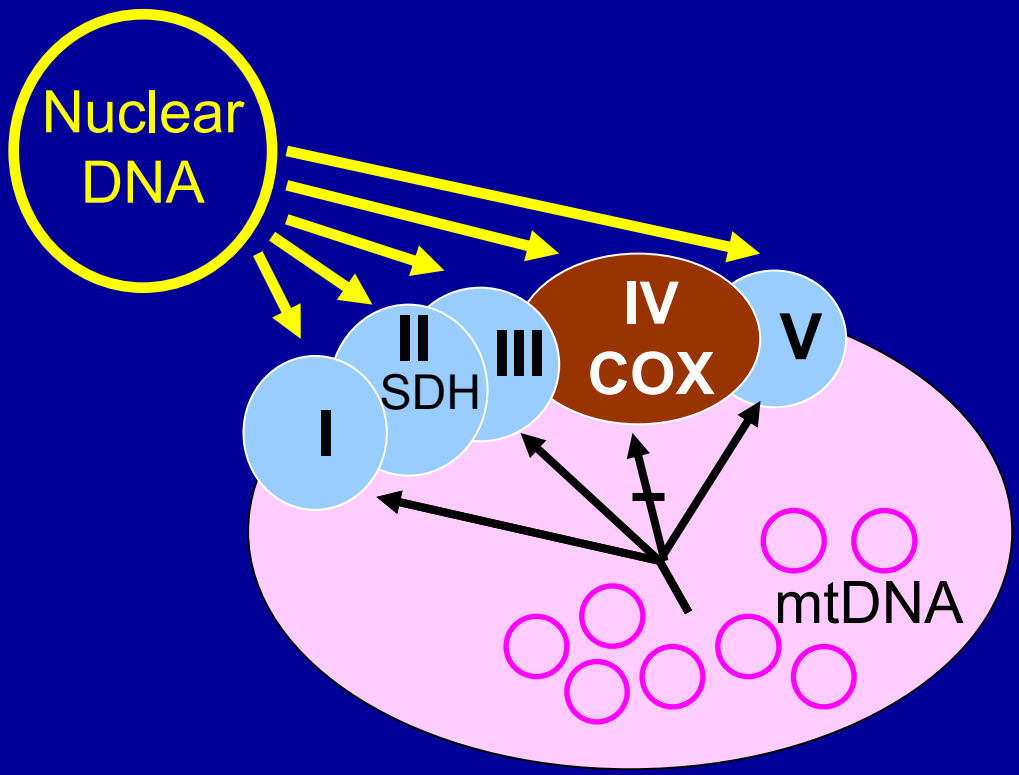
Investigation

Histochemistry



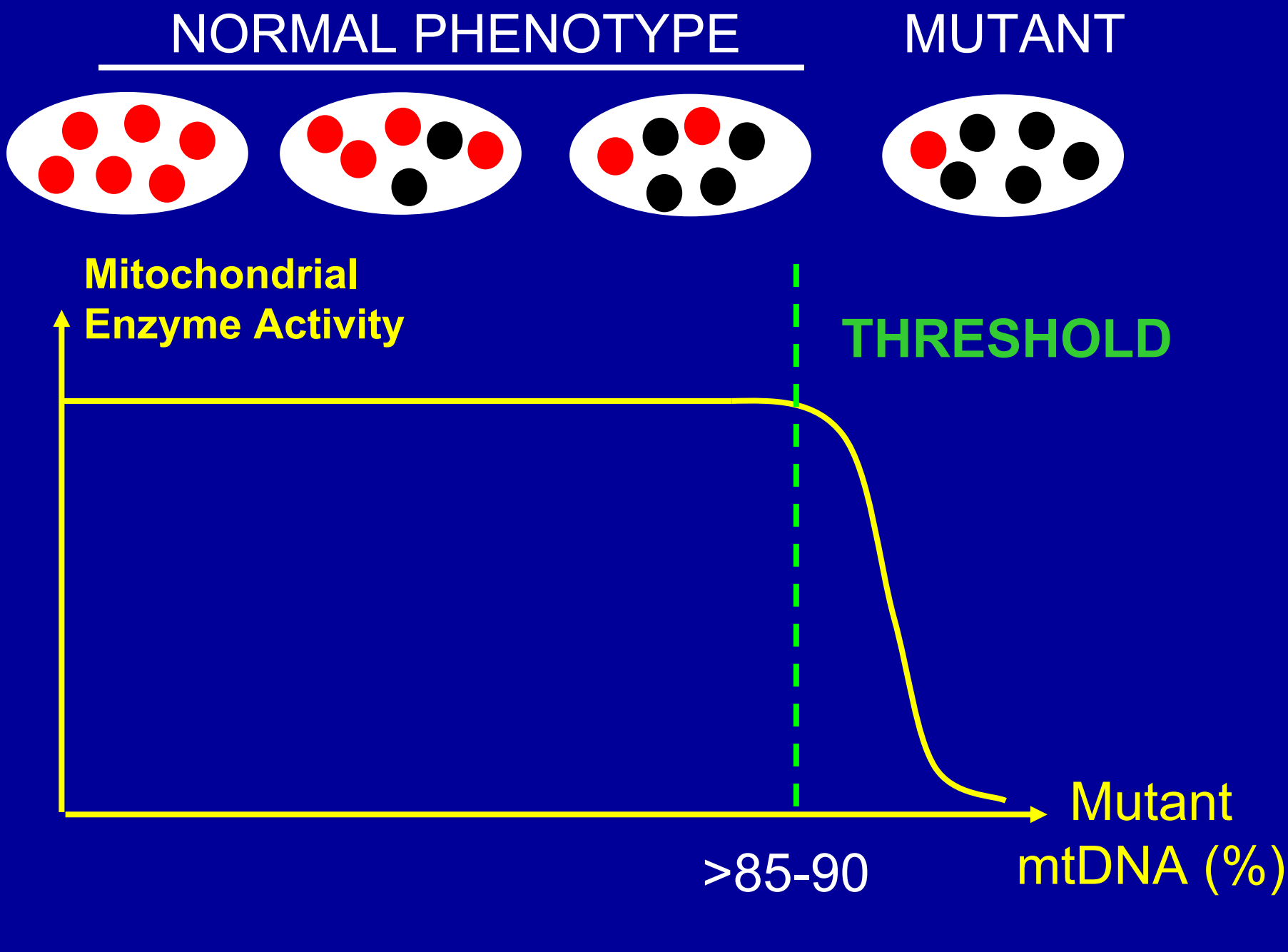
Cytochrome *c* oxidase (COX) Histochemistry

Measures mitochondrial enzyme activity



COX activity ✓

= Brown


NORMAL PHENOTYPE
MUTANT
Mitochondrial
Enzyme Activity
THRESHOLD
>85-90
Mutant
mtDNA (%)