Support, Educate, Advocate

Mitochondrial Disease Action Commitee

MITOCHONDRIAL GENETICS

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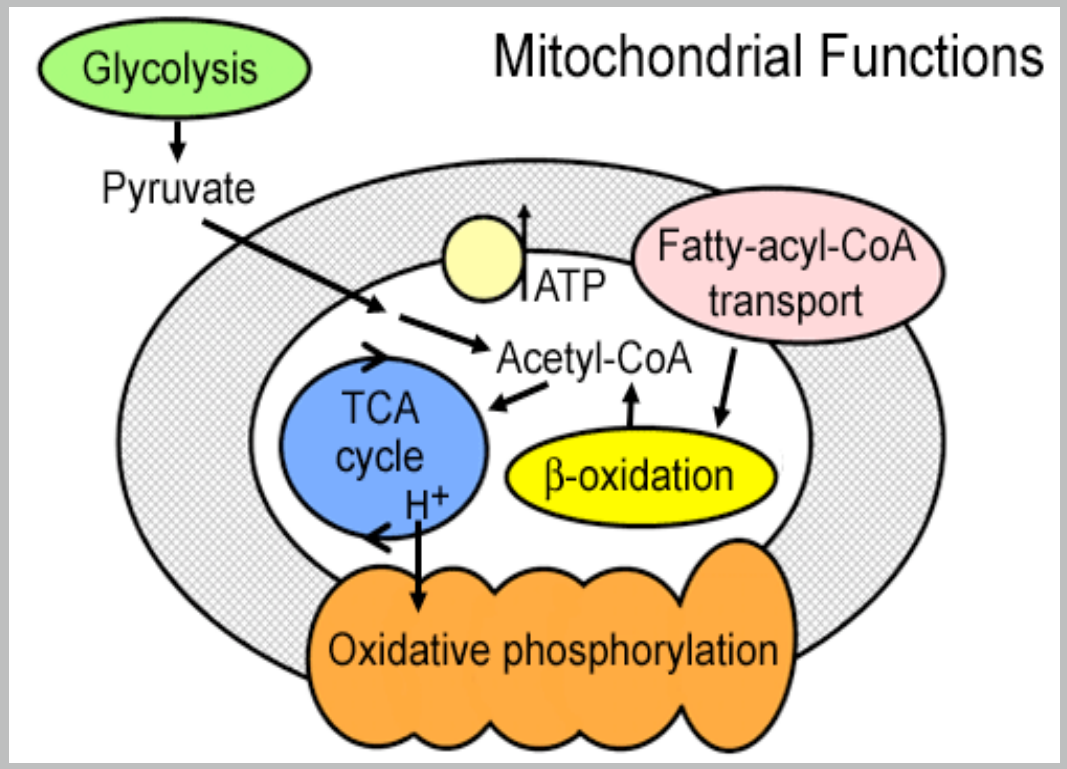
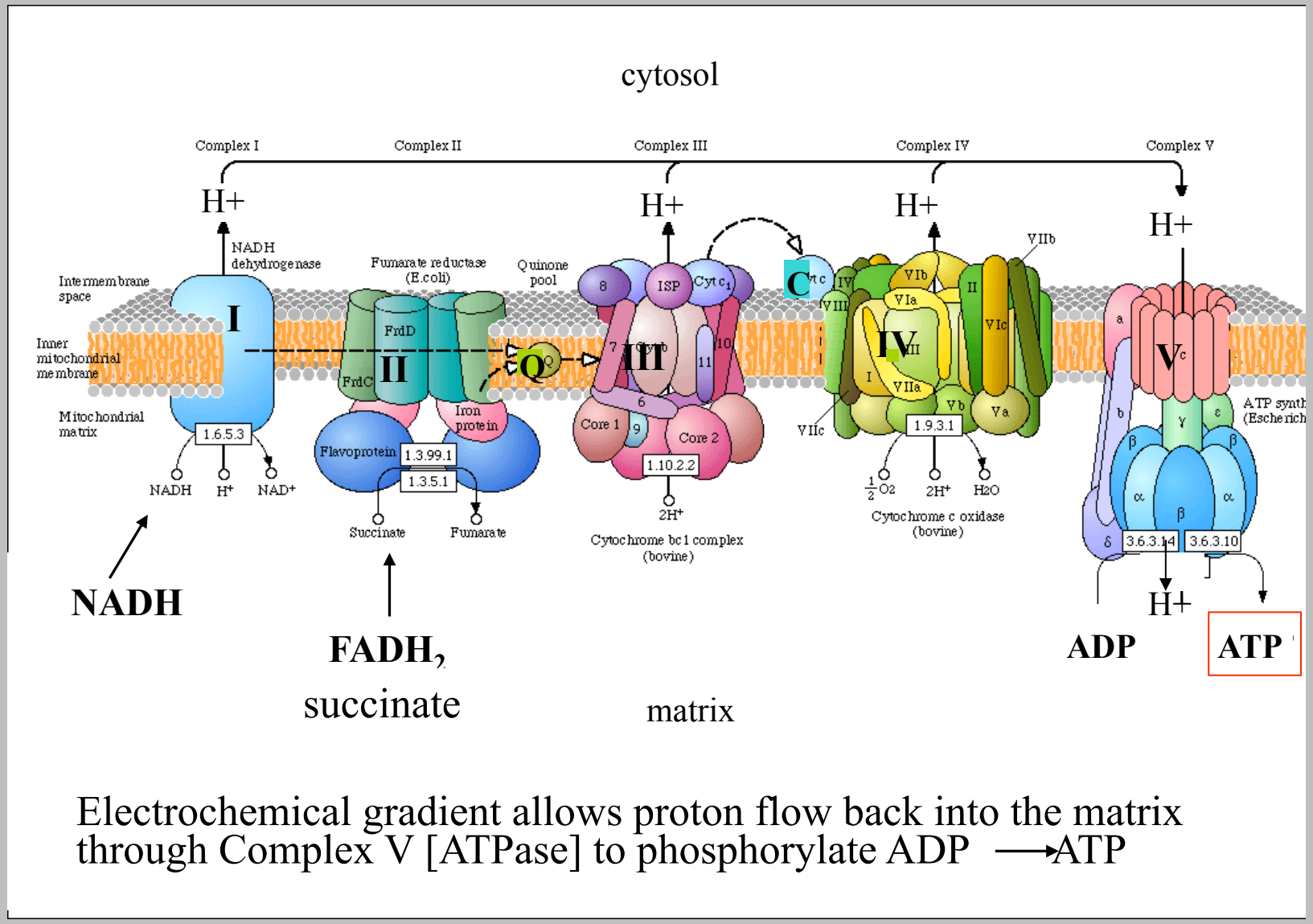
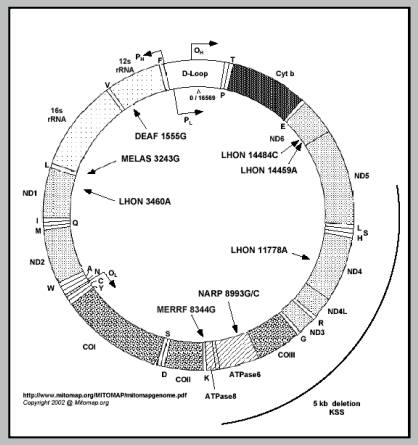

Glycolysis
Mitochondrial Functions
Pyruvate
ATP
Fatty-acyl-CoA transport
Acetyl-CoA
TCA cycle
H+
β-oxidation
Oxidative phosphorylation

Electron Transport Chain



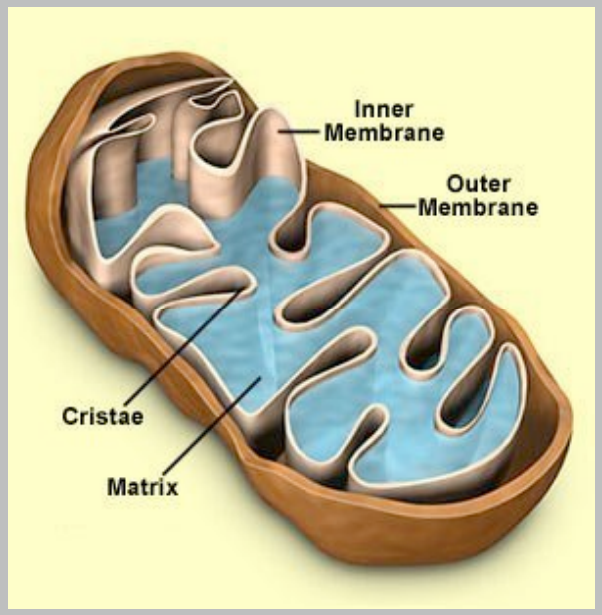
Electrochemical gradient allows proton flow back into the matrix through Complex V [ATPase] to phosphorylate ADP ⟶ ATP

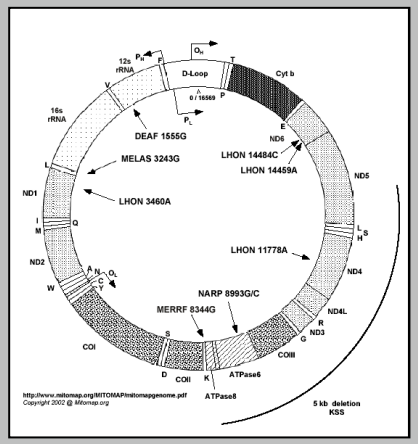
Bi-genomic Input



mtDNA

nDNA

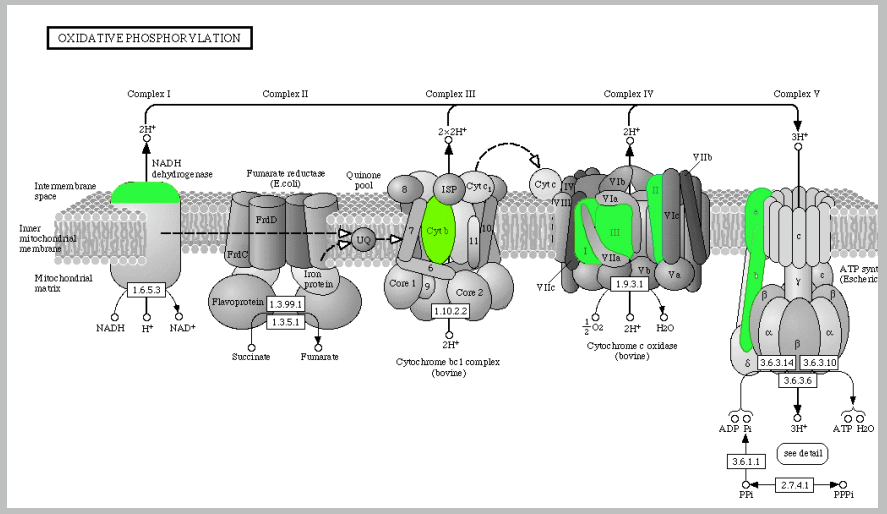


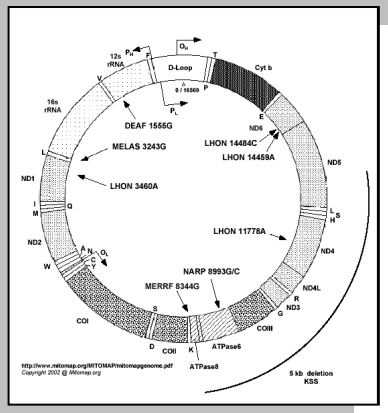


mtDNA genes

13-ETC structural proteins

22-tRNAs, 2-rRNAs

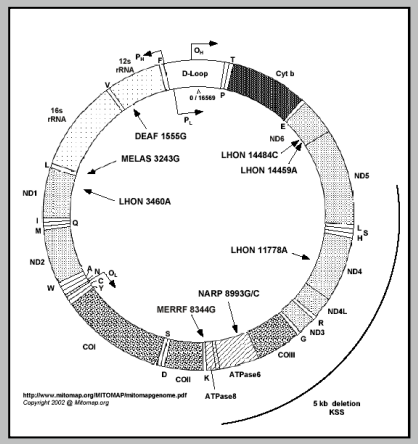




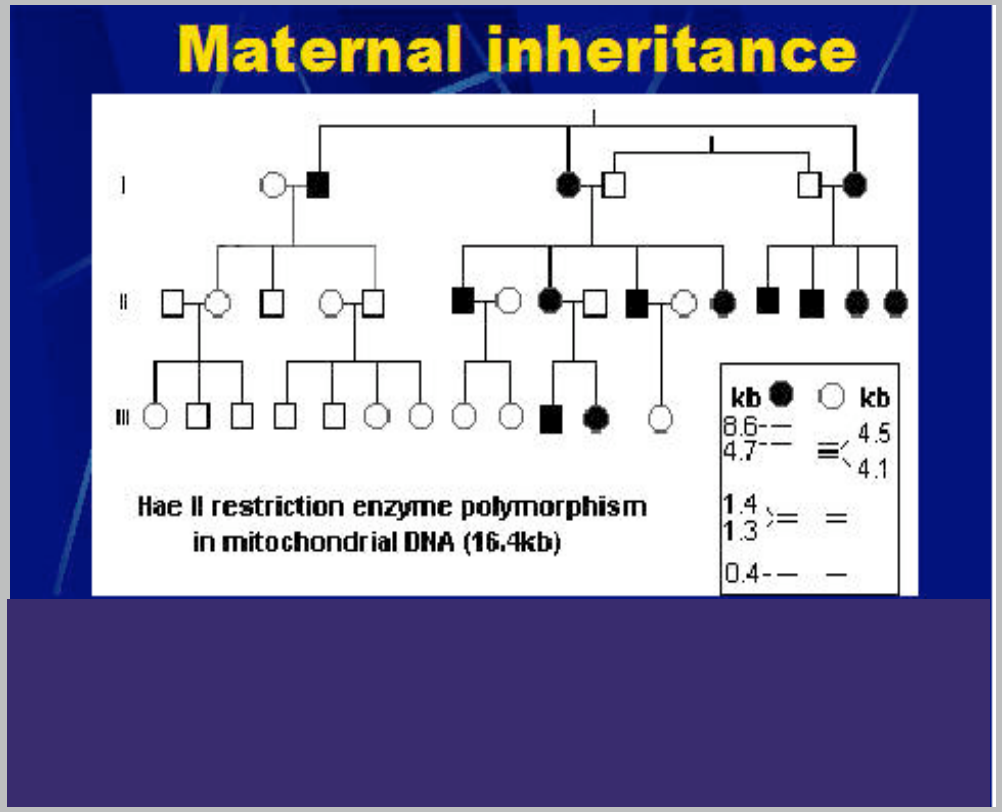
Phenotypes associated with mtDNA point mutations

Clinical Phenotype	Nucleotide	Mutation	Gene
LHON (primary mutations)	3460	G→A	ND1
-	11778	G→A	ND1
-	14484	A→G	ND6
-	15257	G→A	Cyt b
LHON (secondary mutations)	3394	T→C	ND1
-	4160	T→C	ND1
-	4216	T→C	ND1
-	4917	A→G	ND2
-	5244	G→A	ND2
-	7444	G→A	COX I
-	9438	G→A	COX III
-	9804	G→A	COX III
-	13708	G→A	ND5
-	15812	G→A	Cyt b
MELAS	3243	A→G	$tRNA^{Leu(UUR)}$
-	3271	T→C	$tRNA^{Leu(UUR)}$
-	3291	T→C	$tRNA^{Leu(UUR)}$
-	8356	T→C	$tRNA^{Lys}$
-	9957	T→C	COX III
-	11084	A→G	ND4
MERRF	8344	A→G	$tRNA^{Lys}$
-	8356	T→C	$tRNA^{Lys}$
NARP/MILS	8993	T→G	ATPase 6
-	8993	T→C	ATPase 6
PEO	3243	A→G	$tRNA^{Leu(UUR)}$
-	3256	C→T	$tRNA^{Leu(UUR)}$
-	5703	G→A	$tRNA^{Asn}$
Myopathy	3250	T→C	$tRNA^{Leu(UUR)}$
-	3260	A→G	$tRNA^{Leu(UUR)}$
-	3302	A→G	$tRNA^{Leu(UUR)}$
-	15990	G→A	$tRNA^{Pro}$
Cardiomyopathy	3260	A→G	$tRNA^{Leu(UUR)}$
-	3303	C→T	$tRNA^{Leu(UUR)}$
-	4269	A→G	$tRNA^{Ile}$
-	9997	T→C	$tRNA^{Gly}$

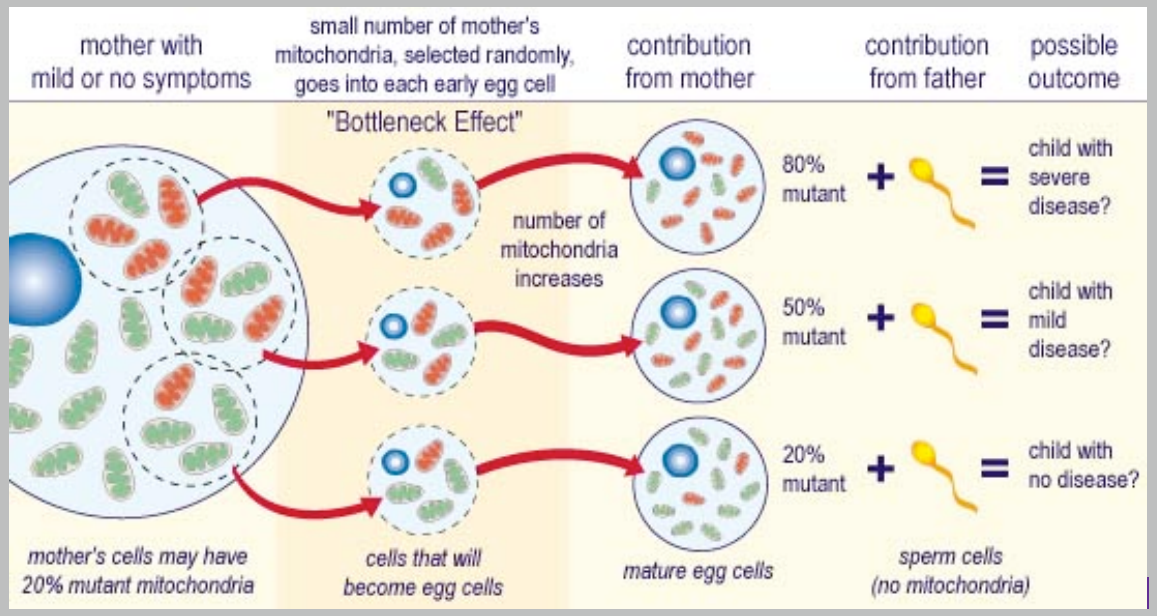
mtDNA deletions – KSS, PEO

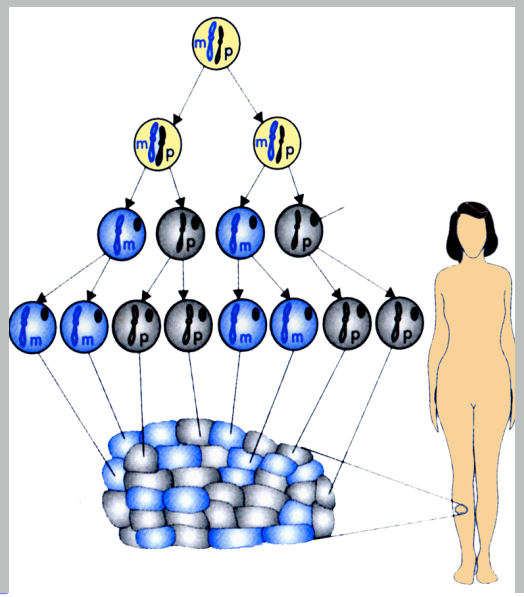

12s rRNA
D-Loop
Cyt b
16s rRNA
DEAF 1555G
MELAS 3243G
LHON 14484C
LHON 14459A
ND5
ND1
LHON 3460A
LHON 11778A
ND4
ND2
NARP 8993G/C
MERRF 8344G
ND4L
ND3
COI
COIII
ATPase6
COII
ATPase8
5 kb deletion
KSS

mtDNA


Maternal inheritance
I
II
III
kb
kb
8.6
4.7
4.5
4.1
1.4
1.3
0.4
Hae II restriction enzyme polymorphism
in mitochondrial DNA (16.4kb)

Heteroplasmy



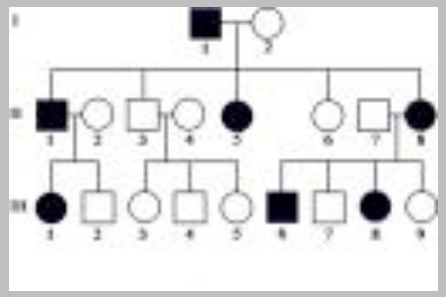


Mitochondrial nDNA genes

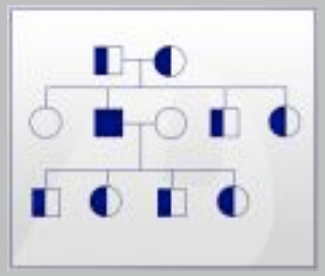
estimated >1200 genes

- Structural subunits of ETC complexes
- Assembly of ETC complexes
- Intergenomic signaling nDNA ⟷ mtDNA
- Mitochondrial assembly & stability
- Mitochondrial replication/biogenesis
- Fusion ⟷ Fission
- Fatty acid oxidation pathway
- Krebs cycle proteins

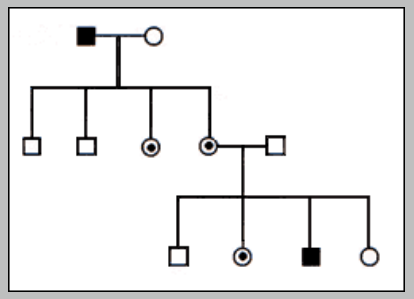
nDNA genes [Mendelian inheritance]



autosomal dominant



autosomal recessive



X-linked

Mito nDNA genes

ETC structural components

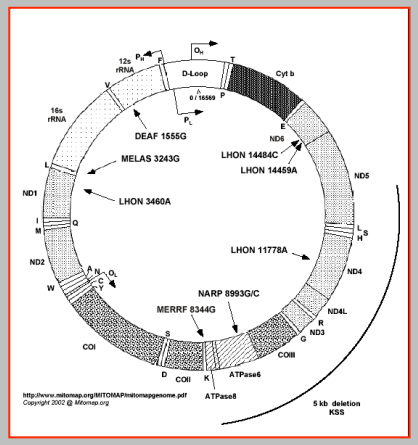
NDUFV1	Complex I	Leukodystrophy, myoclonic epilepsy; LD
NDUFV2		Leigh disease
NDUFS1		Leigh disease
NDUFS2		cardiomyopathy, encephalopathy
NDUFS4		FTT, hypotonia, Leigh-like
NDUFS6		Leigh disease; adult myopathy
NDUFS7		Leigh disease
NDUFS8		Leigh disease
Flavoprotein	Complex II	Leigh disease
SDHD		Hereditary paraganglioma
Synthesis of CoQ10	Complex I, II, III	Ataxia, myopathy, seizures

Mito nDNA genes

Factors of mitochondrial assembly/stability, ox-phos

SURF1	COX assembler	Leigh syndrome
SCO1	COX assembler, Cu^{+2}	Infantile encephalopathy
SCO2	COX assembler, Cu^{+2}	Infantile cardiomyopathy
COX10	COX assembler Heme A synthesis	Infantile encephalopathy
ANT1	Nucleotide pool	adPEO
Thymidine phosphorylase	Nucleotide pool	MNGIE

Bi-genomic Input

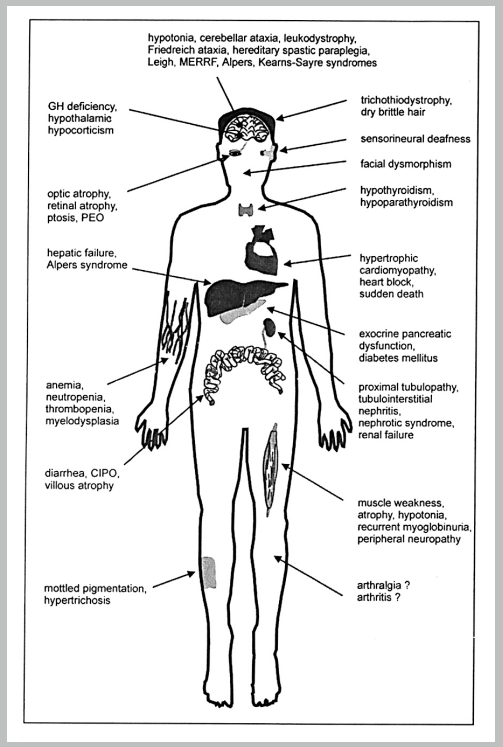


mtDNA

maternal inheritance

nDNA

mendelian inheritance



Diagnosis of Mitochondrial Disorder

- Clinical multi-system problems
- Physiologic abnormalities
- Biochemical abnormalities
- Pathologic features
- ETC dysfunction
- Molecular diagnosis
  - mtDNA
  - nDNA