
# Mitochondrial Diseases

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## Genetics in Medicine - 0504321

2022-2023 Second Semester

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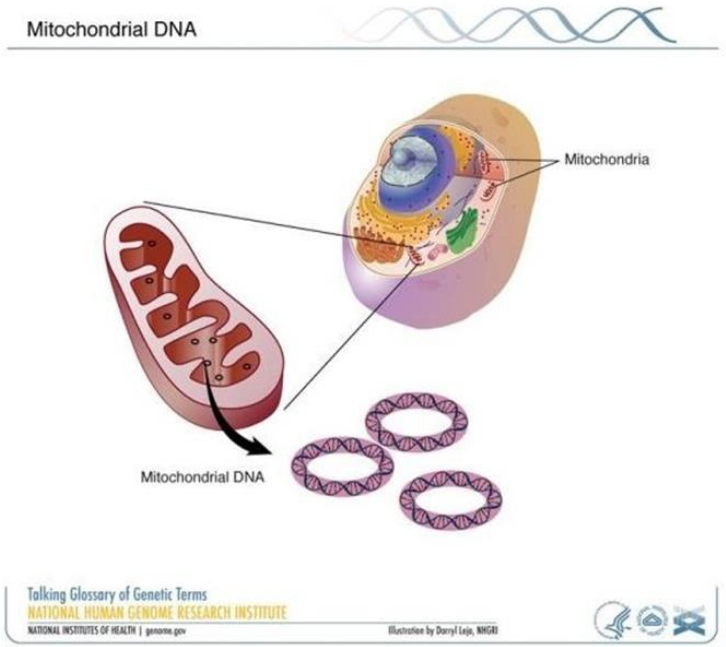
# What is Mitochondrial disease?

- Range of symptoms  (can be late onset) –  extreme tiredness, heart problems, diabetes, difficulties with mobility/ balance, deafness, epilepsy
- Symptoms depend on the ratio between mutated mitochondria to healthy mitochondria
- Mitochondrial disease can be due to mutations in nuclear DNA or mitochondrial DNA
- Diseases caused by mutations in mitochondrial DNA are inherited through the maternal line.

# Mitochondrial Genetics

- The mitochondria contain its own DNA
  - Small – 16,569 base pairs
  - 2-10 copies of mtDNA per mitochondria
  - maternally inherited
  - 37 genes
    - 22 tRNAs
    - 2 rRNA
    - 13 proteins
  - some mutations are more harmful than others
  - mutations are not all or none (heteroplasmy)
- Only 13 of the ~ 1500 mitochondrial structural proteins are encoded by the mtDNA



# Organization of the mitochondrial genome

**Mitochondrial genetic code has different genetic code as compared to that in nucleus**

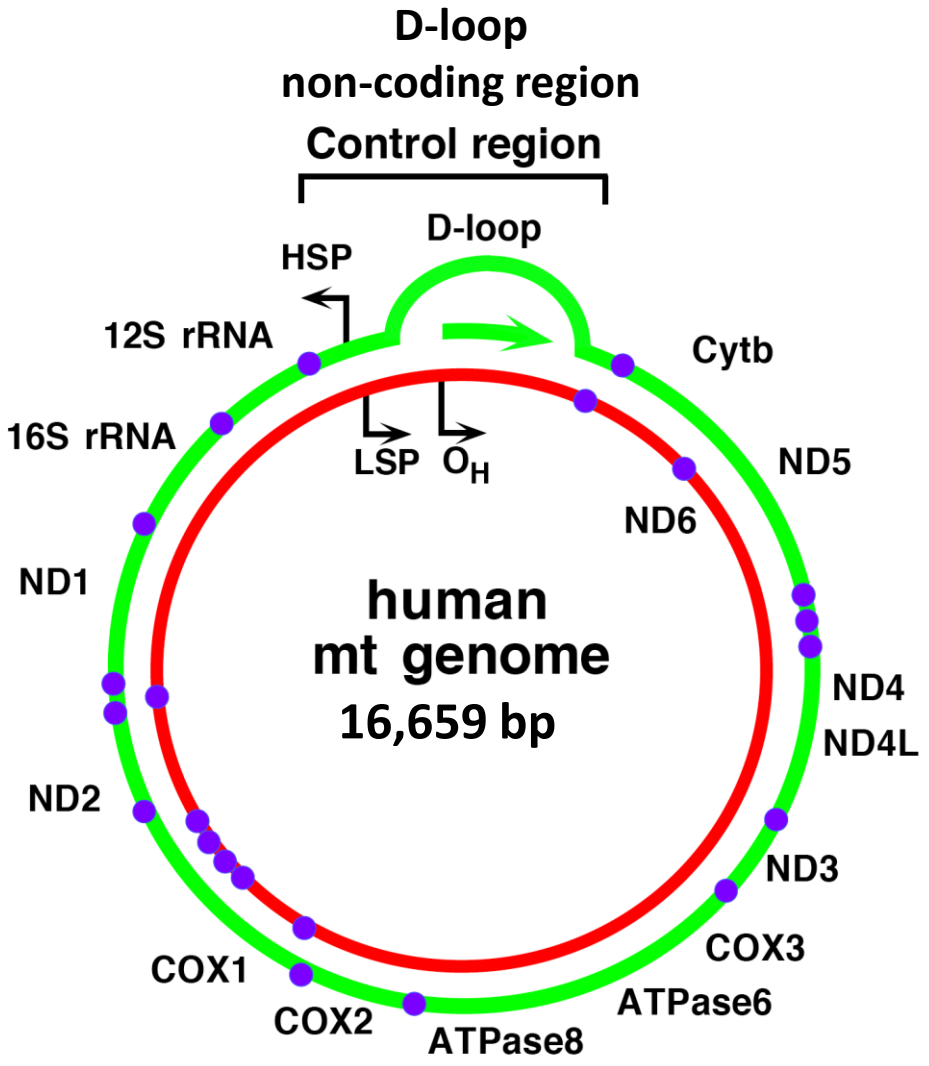
**UGA = tryptophan not STOP**

**AGA = STOP not arginine**

**AUA = methionine not isoleucine**

**NO INTRONS- polycistronic mRNAs**

- **tRNAs**




**D-loop: displacement loop**
**HSP and LSP: heavy- and light- strand promoters for transcription**
**$O_H$: origin of replication**

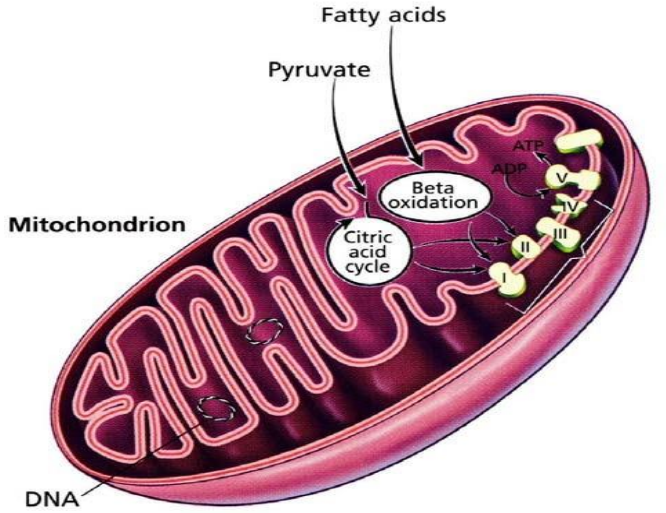
# Mitochondria Functions

(1) generate ATP ☀

(2) critical component of apoptosis

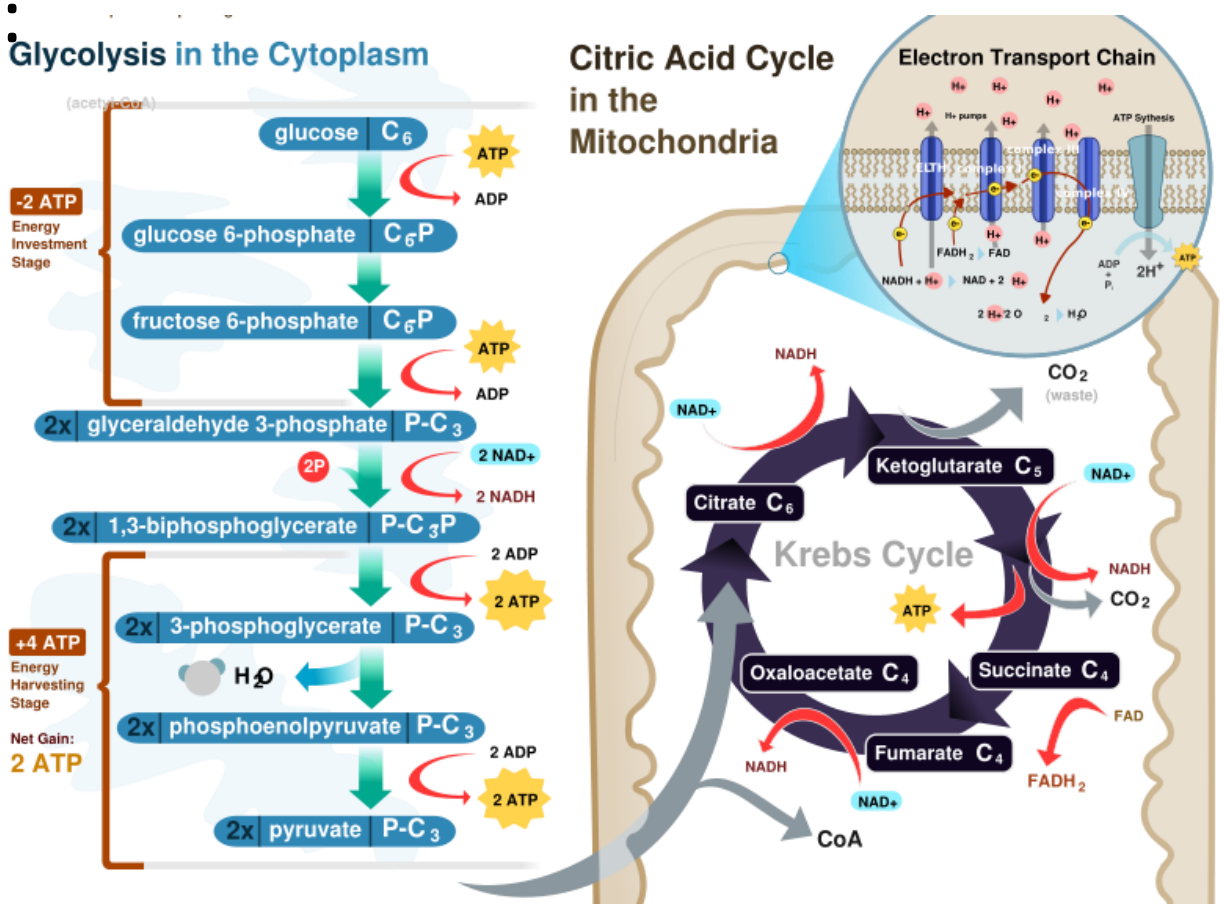
(3) generate free radicals $0_2$ ➠ $0_2$●

(4) Roles in most neurodegenerative diseases and some cancers



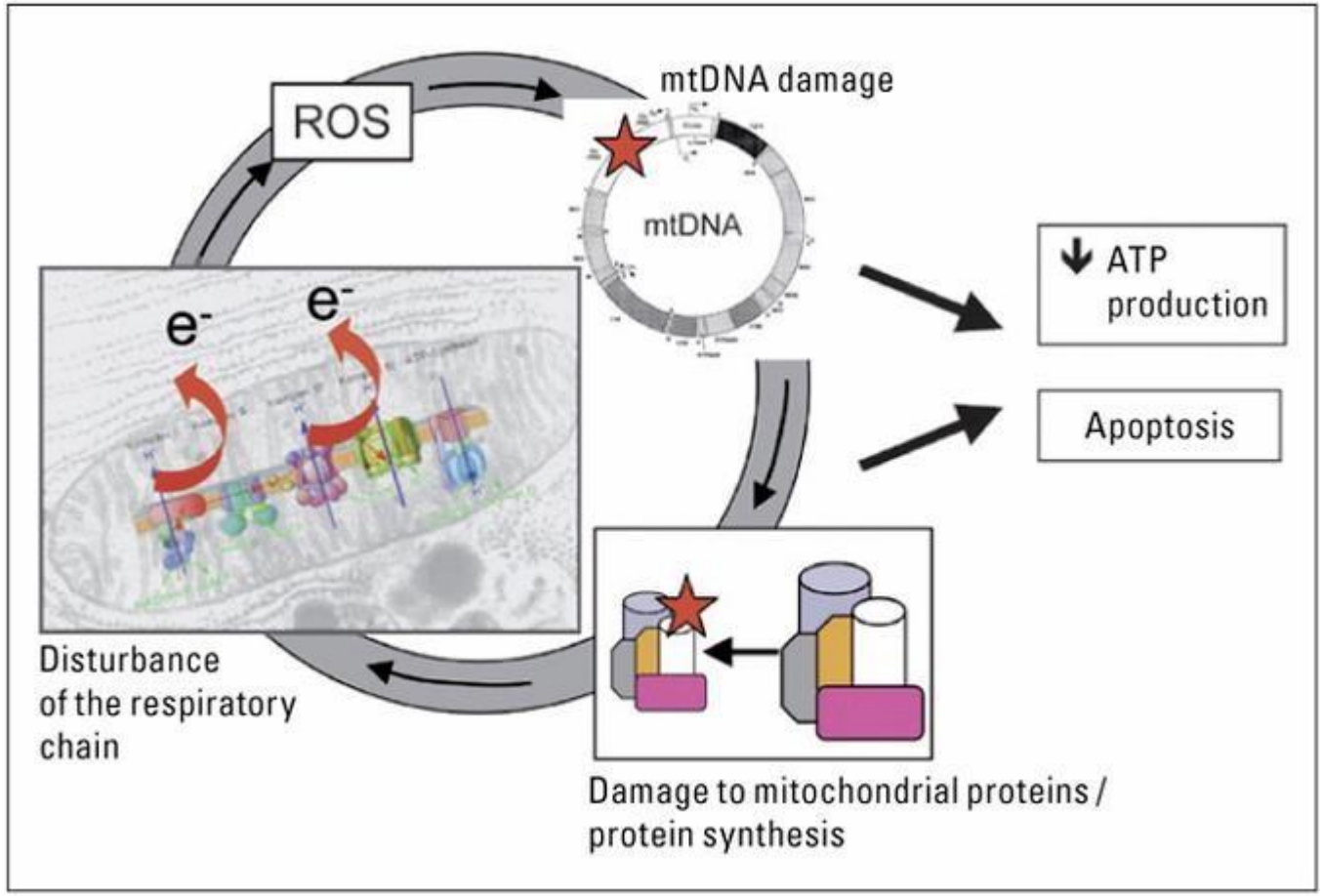
# The synthesis of ATP

- From glucose and fatty acids
- 3 main processes:
  1. Glycolysis
  2. Citric acid cycle
  3. Terminal oxidation



# Mutation of mtDNA

- No histone proteins
- Weak Proofreading and repair
- Free radicals → damage of the DNA, proteins and of the inner membrane

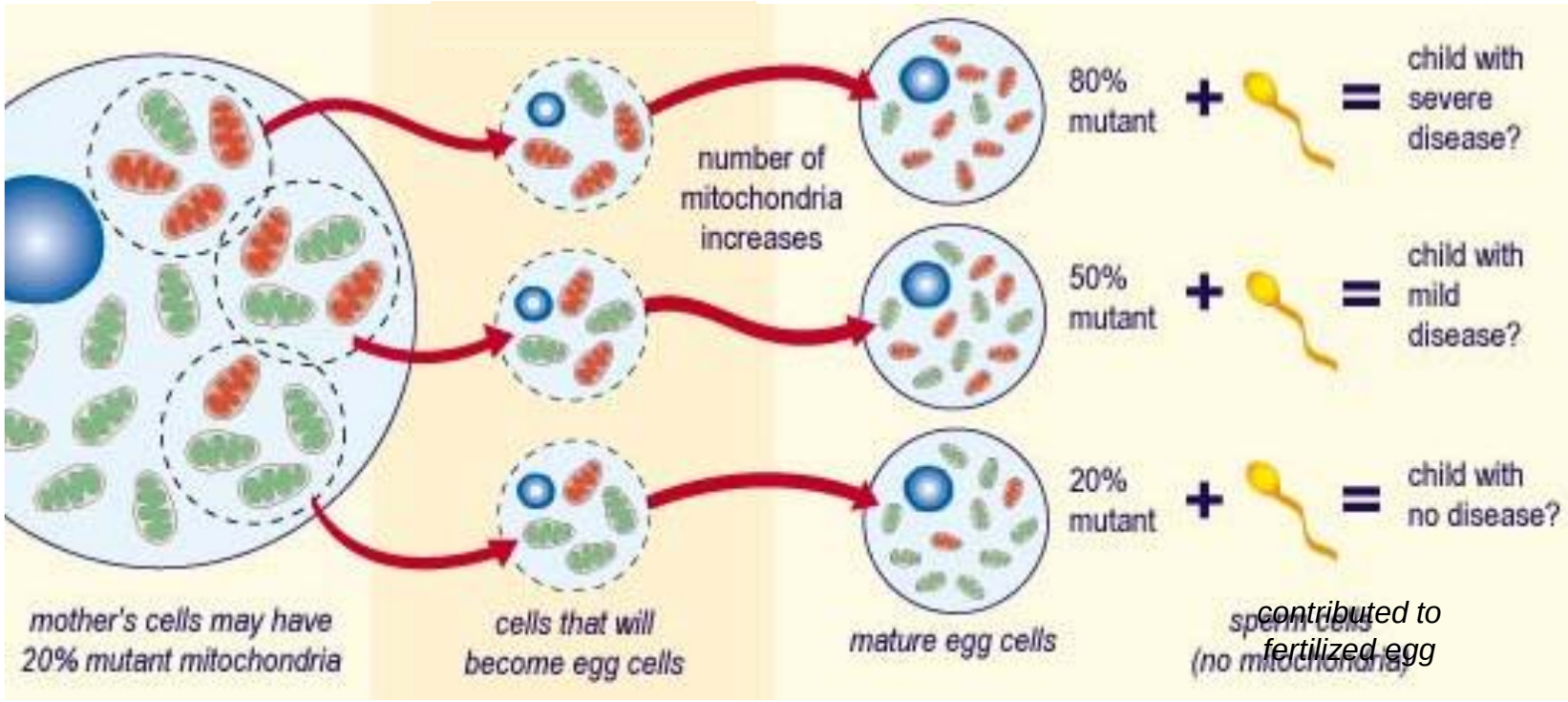


# MITOCHONDRIAL vs. MENDELIAN GENETICS

- Maternal inheritance
- Heteroplasmy
- Stochastic (random)  segregation of mtDNA
- Threshold effect

# Random segregation of mitochondria and mtDNA

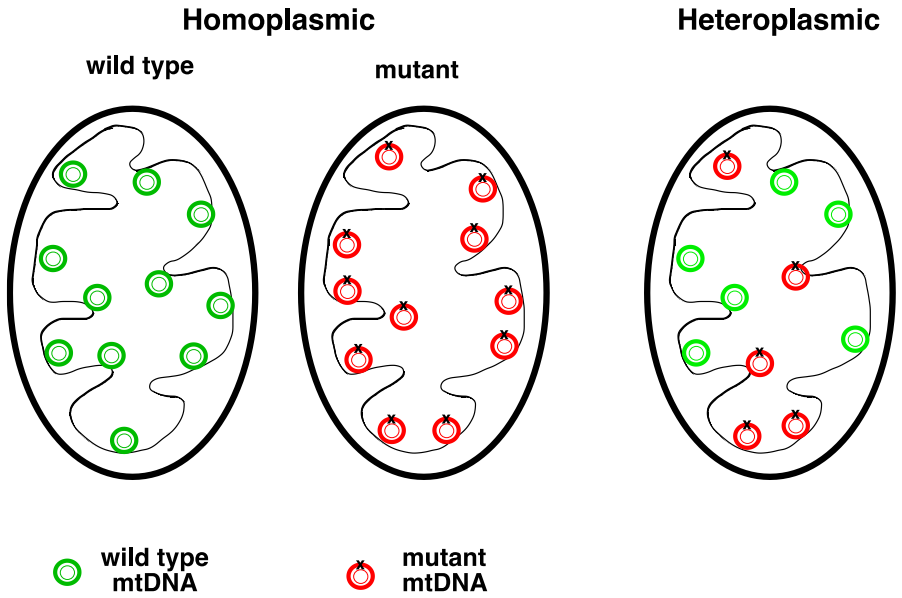
**mother with mild or no symptoms** | **random distribution of normal and mutant mitos in early oocyte** | **ovum** | **sperm** | **possible outcome**




**red mitos are mutant, green are normal**

# Mitochondrial DNA Mutations and Heteroplasmy

- An individual cell may contain normal and mutated mtDNA at different proprtions
- Proportions may change as cells divide and mitochondria proliferate
- Generally, the larger the percentage of mutant mtDNA molecules, the more severe the expression of the disease is



# Threshold Effect

**Different tissues have different energy needs and thus, a different levels of tolerance for mtDNA mutations**

**Examples:**

| Tissue | Evidence of disease |
|---|---|
| Fibroblasts | asymptomatic |
| Liver | asymptomatic |
| Heart | dysfunction |
| Brain | dysfunction |
| Muscle | dysfunction |

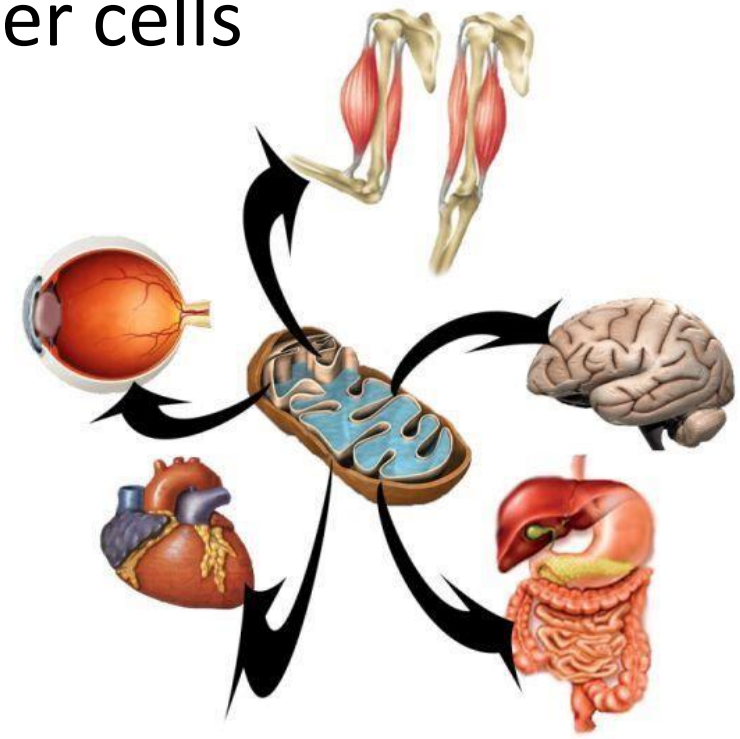
**Threshold sensitivity is also affected by nuclear genetics, environment, age.**

# Examples of mitochondrial inherited diseases:

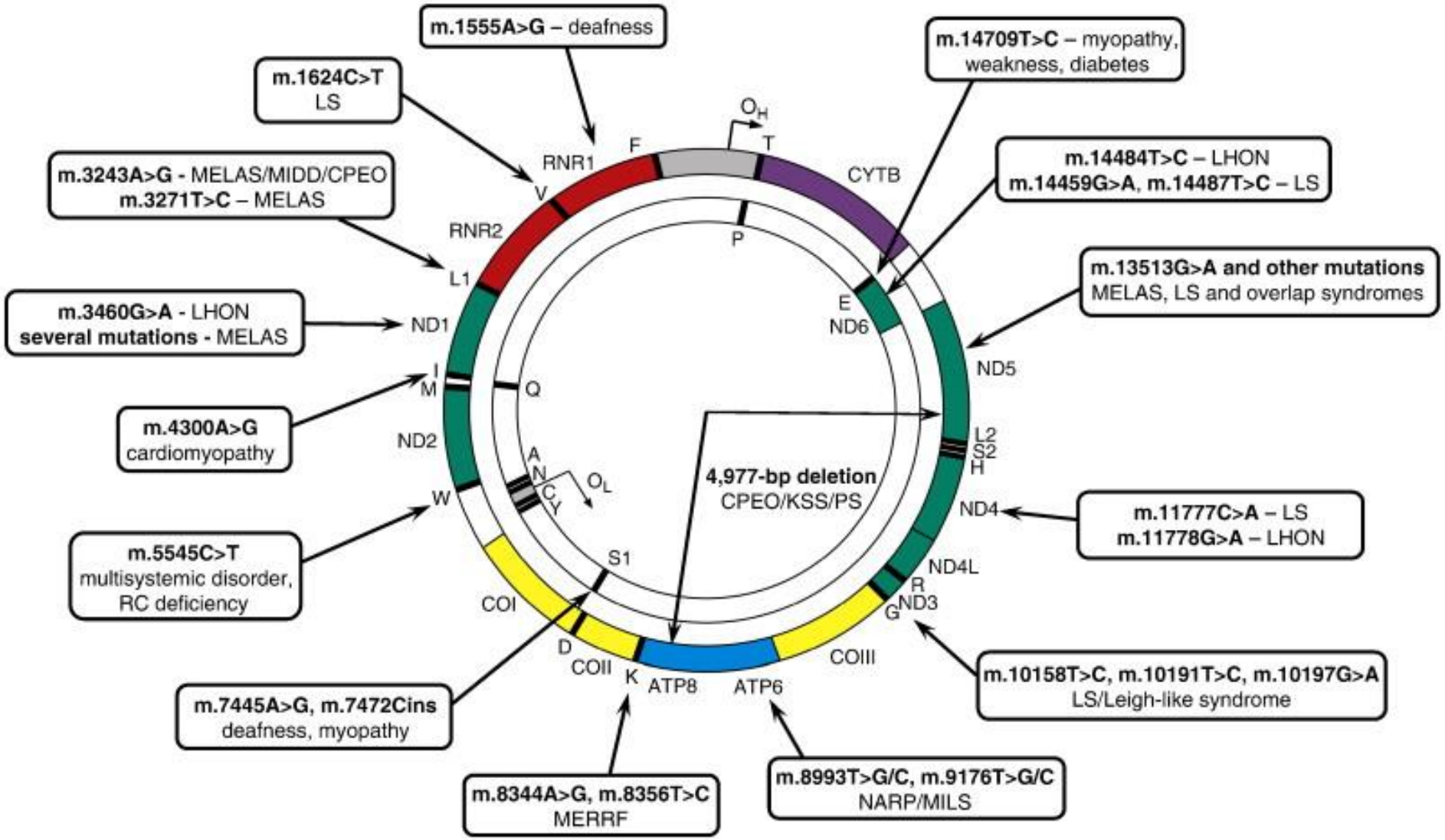
- Aminoglycoside-induced Deafness
- KSS: Kearns-Sayre Syndrome
- LHON: Leber's Hereditary Optic Neuropathy
- MELAS: Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes
- MERRF: Myoclonic Epilepsy with Ragged-Red Fibres
- MIDD: Maternally Inherited Diabetes and Deafness
- NARP: Neuropathy, Ataxia and Retinitis Pigmentosa
- Pearson syndrome

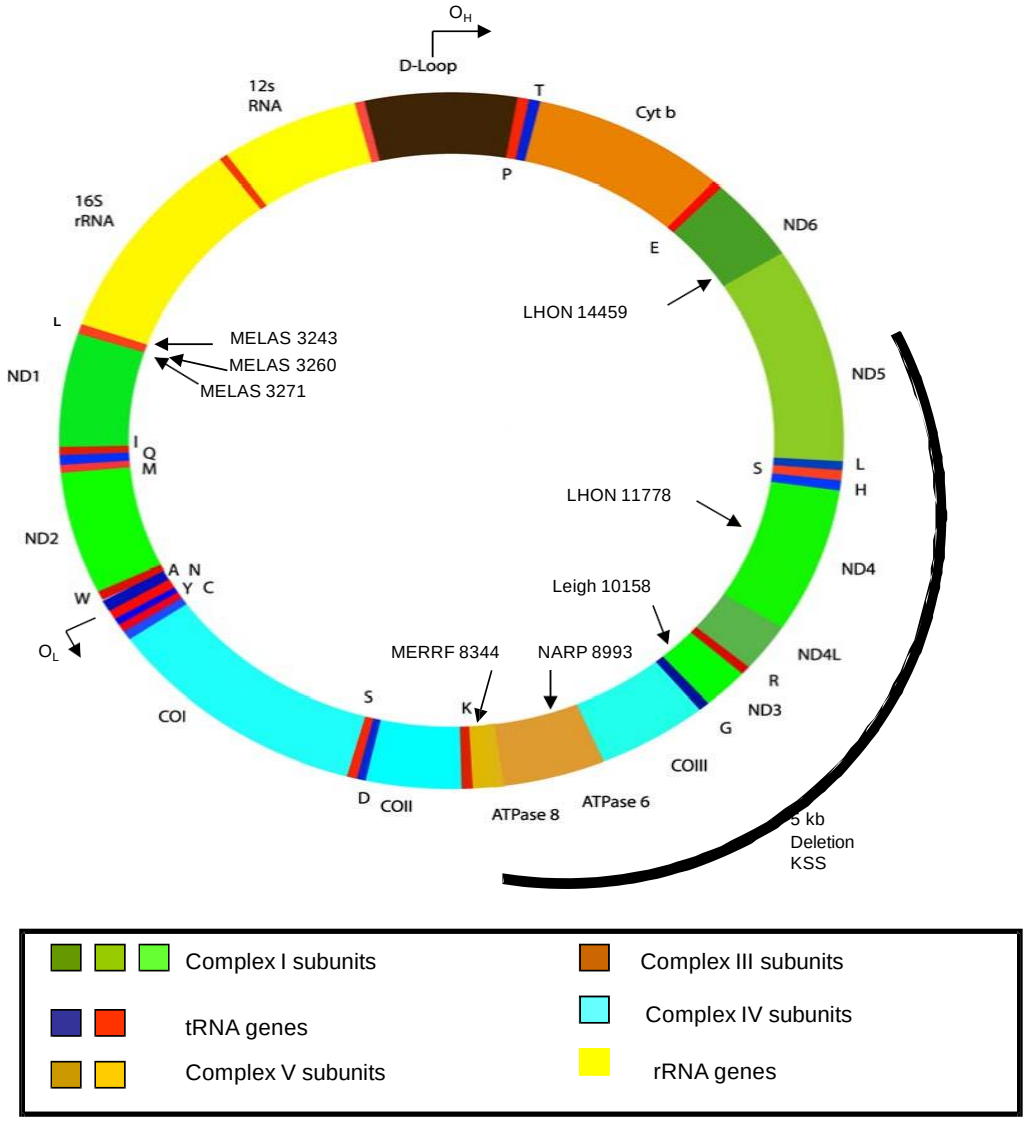
# Mitochondrial diseases

- Sensory organs, muscle, heart, nervous system, pancreas,… are affected → these cells use more energy than other cells
- neurological disorders
- Diabethes mellitus
- blindness
- myopathy (muscular weakness)



# Mitochondrial DNA mutations directly linked to human disease

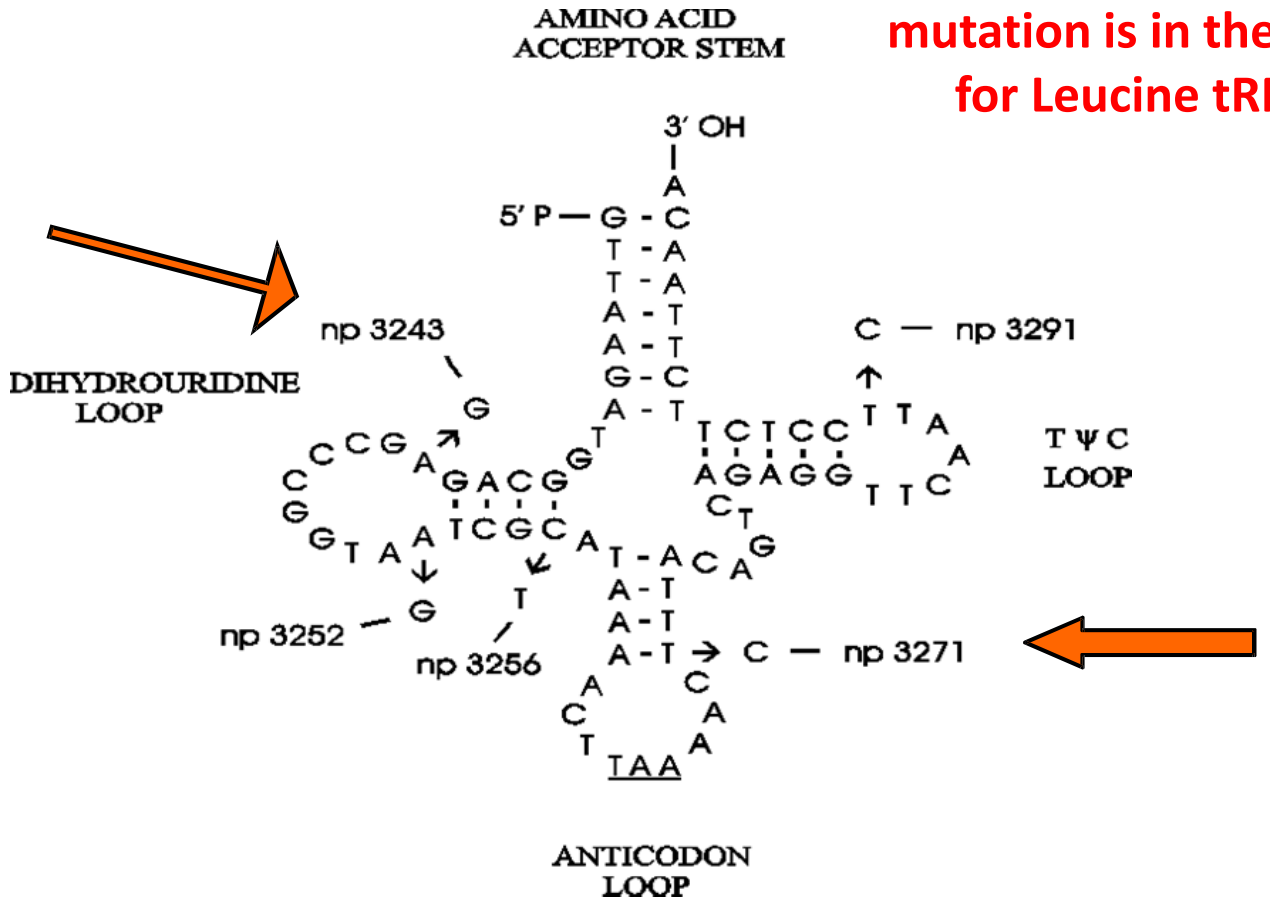





| Mutation | Clinical Symptons |
|---|---|
| MELAS 3243 A→G (tRNA-leu) | Stroke-like episodes, type 2 diabetes, deafness, migraines, short stature, encephalopathy (with stress), exercise intolerance, cardiomyopathy. |
| MELAS 3260 A→G (tRNA-leu) | Similar to MELAS 3243 but cardiomyopathy more common, exercise induced rhabdomyolysis. |
| MELAS 3271 T→C (tRNA-leu) | Similar to MELAS 3243 (less common). |
| MERRF 8344 A→G ((tRNA-Lys) | Myoclonus, epilepsy, ataxia, dementia, deafness, neuropathy. |
| NARP 8993 T→C or T→G NARP/MILS | Adult: Retinitis pigmentosa, ataxia, neuropathy.<br>Child (Leigh's syndrome): Psychomotor regression, ataxia, ophthalmoparesis, ataxic breathing, episodic vomiting and encephalopathy. |
| Leigh 10158 T→C ND3 | Leigh's disease as above for MILS 8993. |
| LHON 11778 G→A ND4 | Painless visual loss over weeks > months, more common in men (onset 20s). |
| LHON 14459 G→A ND6 | LHON as above +/- dystonia. |

# Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes (MELAS)

- Variable Age of Onset (4 months through adult)
  - weakness and fatigability
  - Short Stature
  - Strokes and stroke-like episodes
  - Progressive Dementia
  - Hearing loss and DM
  - Anorexia from autonomic gut neuropathy
  - Migraine
  - Myoclonic or tonic-clonic seizures
  - Hypertrophic > dilated cardiomyopathy
  - Ophthalmoplegia
  - renal tubular acidosis
  - Droopy eyelids, Short stature




**mutation is in the gene for Leucine tRNA**

- A3243G tRNALeu (UUR) gene;
- C3271G tRNALeu (UUR) gene
- > 20 other mtDNA mutations causing this disorder


- Pavlakis SG, Phillips PC, DiMauro S, et al: Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984 Oct; 16(4): 481-8

# Kearns-Sayre Syndrome = KSS (pp. 358-359)

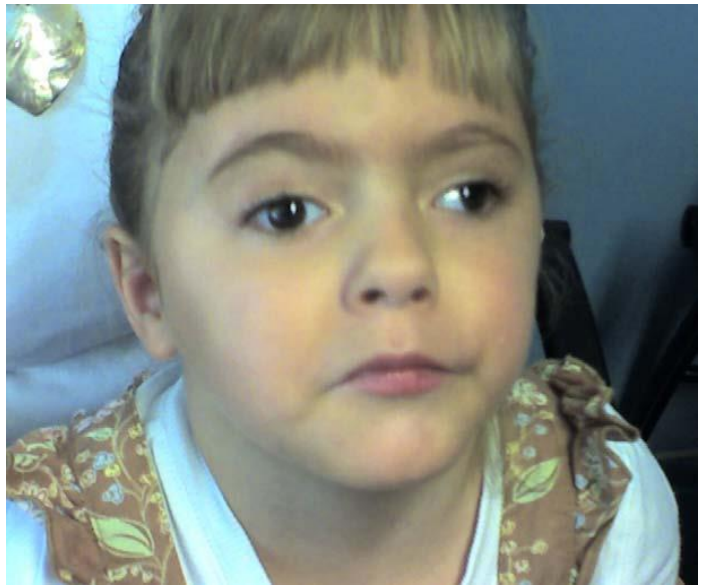
- Ophthalmoplegia (paralysis or weakness of one or more
- eye muscles)
- Degeneration of pigment layer of retina
- Cardiac abnormalities
- Neurological abnormalities
- Onset at age 20 (fatal in few years)

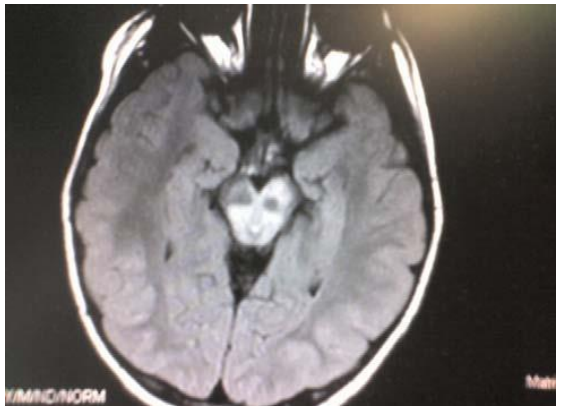
- Large deletions (1000s bp) of mtDNA; duplications

- Is not typically inherited, but rather is ‘sporadic’ (meaning
- it just seems to show up in people)

# Leigh Syndrome

- Healthy child until age 3
- Non-specific viral infection
- Lost the ability to ambulate due to ataxia, hemiparesis then bilateral hemiparesis
- lactic acidosis
- eye movement and bulbar dysfunction
- dystonia
- neuropathy
- some recovery over 6 months followed by deterioration
- muscle biopsy may be normal unless due to complex IV defects
- clinical: heavily CNS/PNS during the natural life span
- host of mtDNA, nDNA mutations result in this presentation
- not clear why some mutations cause Leigh Syndrome and others do not

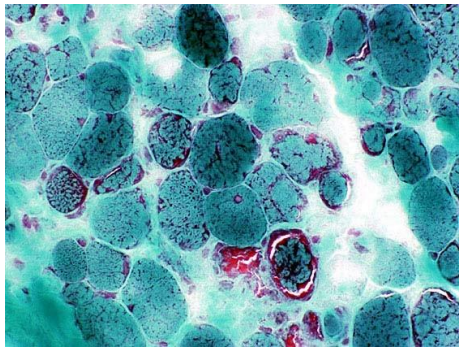


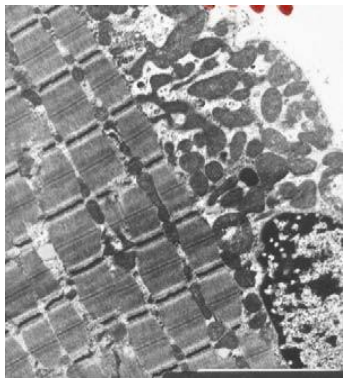



- Leigh, D. :
  - Subacute necrotizing encephalomyelopathy in an infant. J. Neurol. Neurosurg. Psychiat. 14: 216-221, 1951

# Pearson Syndrome

- Anemia
- Lactic acidosis
- Sideroblastic anemia
- digestive problems
- moderate mental retardation
- Myopathy, neuropathy
- progressive hearing loss
- diabetes mellitus
- heart block,
- cardiomyopathy





# Mitochondrial Transfer (Therapy options)