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Genetics

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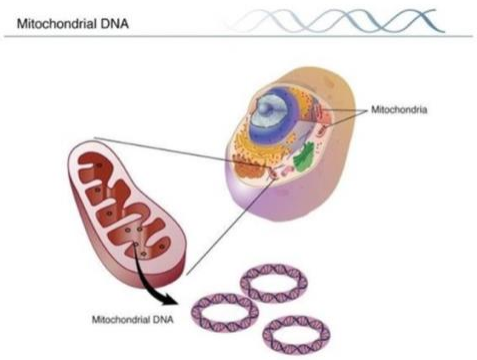
Mitochondrial Diseases

Mitochondrial Genetics

The mitochondria contain its own DNA, and it is independent of the nuclear genomic material.



- Small – 16,569 base pairs.
- Each cell contains different numbers of Mitochondria and its Dna material also vary, 2-10 copies of mtDNA per mitochondria.
- **Maternally inherited**, the mitochondria are inherited from the maternal side.
- Totally there are **37 genes that are encoded** **13 of which are proteins, 2 ribosomal RNAs** and **22 transfer RNAs.**
- **Only 13** of the ~ **1500** mitochondrial structural proteins (which are important for the mitochondria to be able to perform its function) **encoded by the mtDNA**, the rest are encoded by the nuclear DNA.

Mitochondrial DNA may be mutated, and some mutations are more harmful than others depending on **their location** and **which gene** they affect.

However, Mitochondrial disorders are variable, they are not following the typical Mendelian pattern ➔ The mutations are not all or none (And this is called **heteroplasmy**).

Organization of the mitochondrial genome

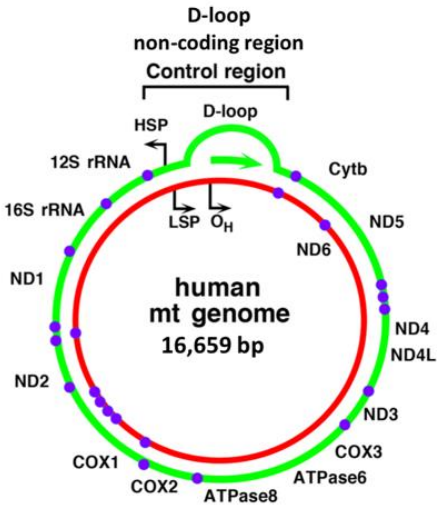
This an illustration of the MtDNA, so as you can see it's **Circular** and **double stranded DNA.**

The **blue dots** are tRNAs.

OH: origin of replication site.

D-loop: displacement loop, it is non-coding region, it is very polymorphic (highly variable) ➔ so it is often used by the Geneticists to classify the population heritage and ethnic background from maternal perspective.

HSP & LSP: heavy- and light- strand promoters for transcription.



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

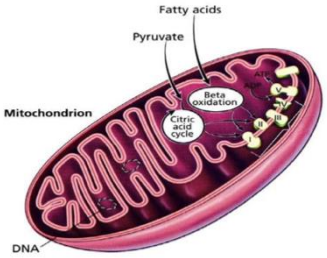
NO INTRONS - **polycistronic mRNAs** [**mRNA that codes for multiple different proteins]**

Thirteen Protein-Coding MT Genes

Mitochondrial Genes	Full Gene Length	Alignment Length
CO1	1,531	1,500
CO2	669	651
ATPF08	165	—
ATPF06	651	651
CO3	783	753
ND3	351	228
ND5	1,113	471
ND4	1,309	669
ND4L	1,308	—
ND6	288	—
CYTB	1,113	1,080
ND1	927	864
ND2	975	690

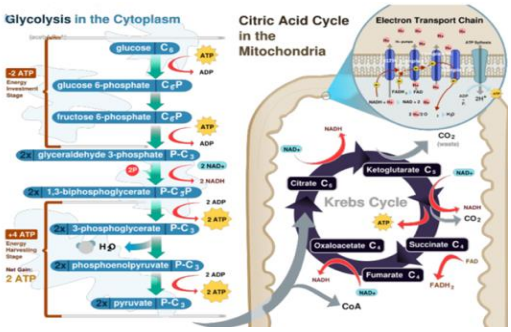
The 13 protein coding genes are listed here, as you can see, they have different sizes and length.

Mitochondria Functions



(1) Generates **ATP** ☀
(2) Critical **component of apoptosis**, It interacts with the caspases.
(3) generate free radicals 02 ➠ 02●
(4) Roles in most neurodegenerative diseases and some cancers.

The synthesis of ATP: From glucose and fatty acids.

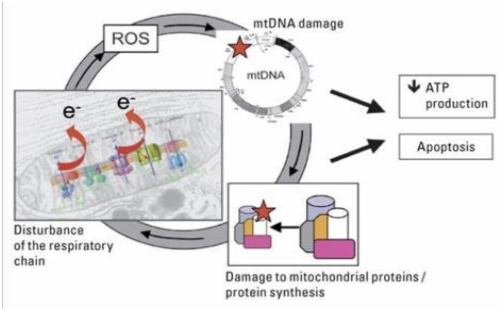


Through 3 main processes:
1. Glycolysis
2. Citric acid cycle
3. Terminal oxidation through phosphoredox complex.

2+3 are taking place inside the mitochondria.

Mutation of mtDNA

In contrast to the nuclear genome, mtDNA has:



- **No histone proteins.**
- **Weak Proofreading and repair**, so there is a higher chance of errors occurring through replication.
- **Free radicals** which are produced by the mitochondria → damage of the DNA, proteins and of the inner membrane.

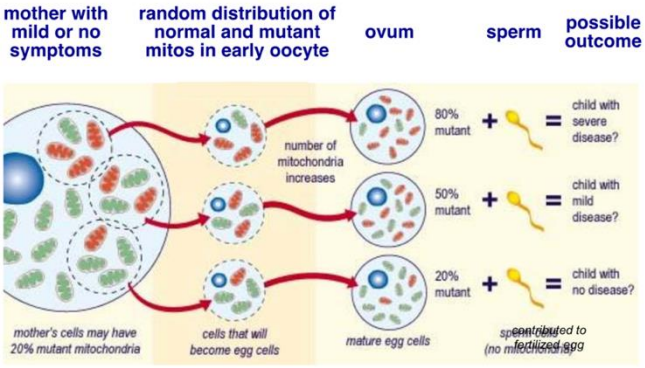
These factors contribute to mutation occurring and the resulting disorders.

MITOCHONDRIAL vs. MENDELIAN GENETICS

- Maternal inheritance
- Heteroplasmy
- Stochastic (random) segregation of mtDNA during cell division.
- Thresholds effect

1) Random segregation of mitochondria and mtDNA

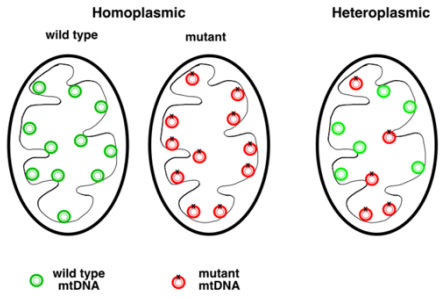
During oogenesis in the ovaries, the oocyte will divide, and the **mitochondrial contents** (the mutants and the normal) **will be distributed randomly** over the daughter cells → so after maturation and fertilization there will be **different possible outcomes [***Cells contain more mutant contents, while other cells contain more normal contents*] as you can see in this pic.



red mitos are mutant, green are normal

2) 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.



3) Threshold Effect

Different tissues have different energy needs and thus, different number of mitochondria per cell hence different amount of mitochondrial DNA in tissues so different levels of tolerance for mtDNA mutations.

➥ This means that tissues differ in their use of mitochondria, so cells that do not need mitochondria so much and have lower number of Mitochondria, even if there is an exciting mutation in them, the accumulative effect of the mutation and the symptoms of the disease will be less.

- It is organ dependent.

Examples:

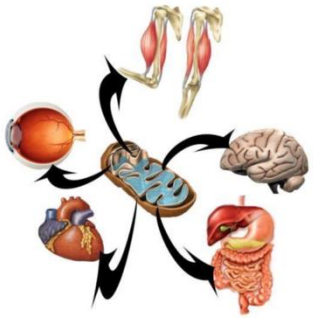
Tissue	Evidence of disease
Fibroblasts	asymptomatic
Liver	asymptomatic
Heart	dysfunction
Brain	dysfunction
Muscle	dysfunction

Threshold sensitivity and disease severity are also affected by nuclear genetics, environment, age.

Mitochondrial diseases

Diseases with many serious symptoms and complications (can be late onset):

extreme tiredness, heart problems, difficulties with mobility and balance,, epilepsy, neurological disorders (deafness, blindness), Diabetes mellitus, and myopathy (muscular weakness).



➥ **So obviously mitochondrial diseases affect many organs:** sensory organs, muscle, heart, nervous system and pancreas → these cells use more energy than other cells.

Symptoms **depend on the ratio between mutated mitochondria to healthy mitochondria.**

Mitochondrial disease can be due to mutations in nuclear DNA or mitochondrial DNA.

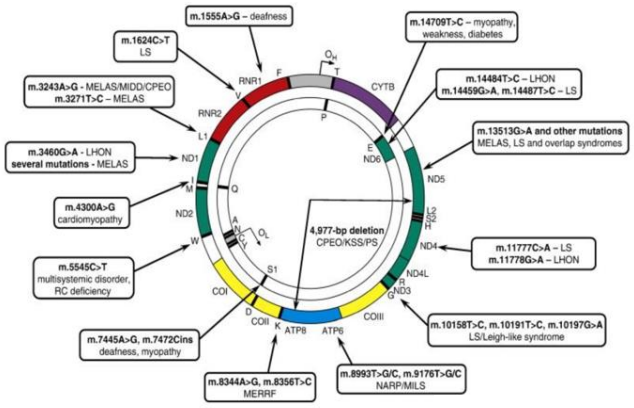
Diseases caused by mutations in mitochondrial DNA are inherited through the maternal line.

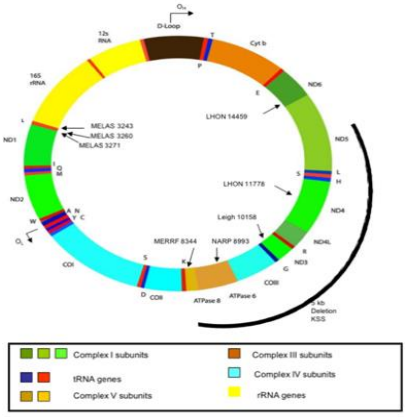
Examples of mitochondrial inherited diseases:

- **Amino-glycoside-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 Fibers.
- **MIDD**: Maternally Inherited Diabetes and Deafness.
- **NARP**: Neuropathy, Ataxia and Retinitis Pigmentosa Pearson syndrome.

Mitochondrial DNA mutations directly linked to human disease.

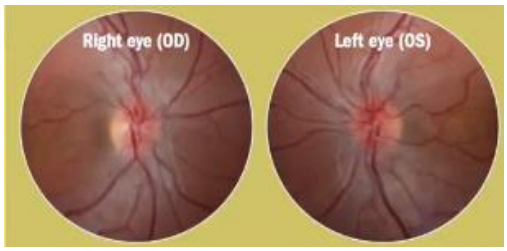
Mutation	Clinical Symptons
MELAS 3243 A→G (tRNA-leu)	Stroke-like episodes, type 2 diabetes, deafness, migraines, short stature, encephalopathy (with stress), exercise intolerance, cardiomyopathy.
MELAS 3260 A→G (tRNA-leu)	Similar to MELAS 3243 but cardiomyopathy more common, exercise induced rhabdomyolysis.
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. 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.





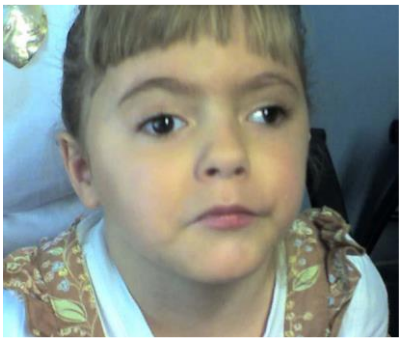
This is definitely not for memorizing, it's just to show you that the mutation may occur anywhere and may affect any gene.

1) Leber hereditary optic neuropathy (LHON) :

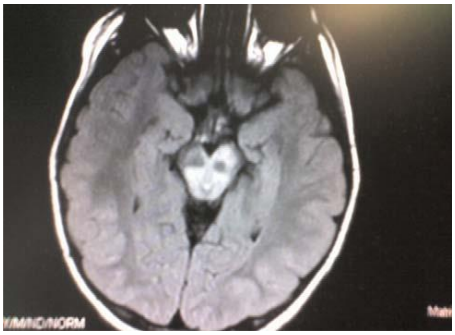


- Mitochondrial inherited degeneration of retinal ganglion cells and their axons resulting in loss of central vision.
- Caused by one of three pathogenic mitochondrial DNA (mtDNA) point mutations (11778 G to A, 3460 G to A, and 14484 T to C respectively) in the ND4, ND1, and ND6 subunit genes of complex 1 of the oxidative phosphorylation.
- The mutations can occur in combination or independently (meaning that one of the mutated genes alone can cause this disease).

2) Leigh syndrome :

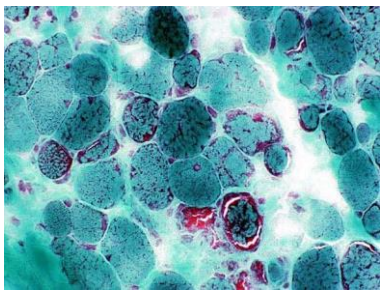


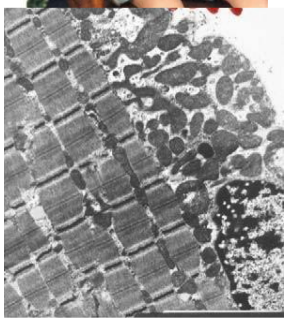
- A severe neurologic disorder manifests in the first year of life.
- Characterized by progressive loss of mental and movement abilities (psychomotor regression).
- Results in death within 2 to 3 years, usually due to respiratory failure.
- While most people with leigh syndrome have a variant in nuclear DNA, about 20% have a variant in mtDNA.
- Disruption of oxidative phosphorylation complex 1 (NADH : ubiquinone oxidoreductase) is the most common cause of this disease.
- The most common mtDNA variant in it affect the ATP6 gene.



3) Pearson syndrome :

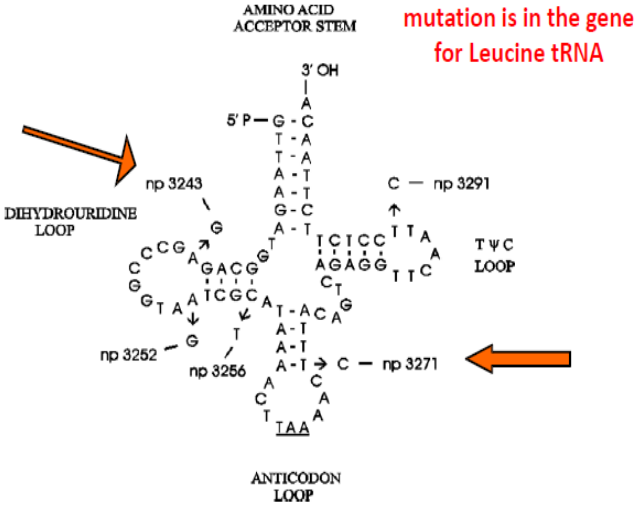
- Caused by single large-scale mtDNA deletion.
- Associated with many symptoms and phenotypes such as :
  a) Anemia (Sideroblastic anemia)
  b) Lactic acidosis
  c) Digestive problems
  d) Moderate mental retardation
  e) Myopathy, neuropathy
  f) Progressive hearing loss
  g) Diabetes mellitus
  h) Heart block, cardiomyopathy





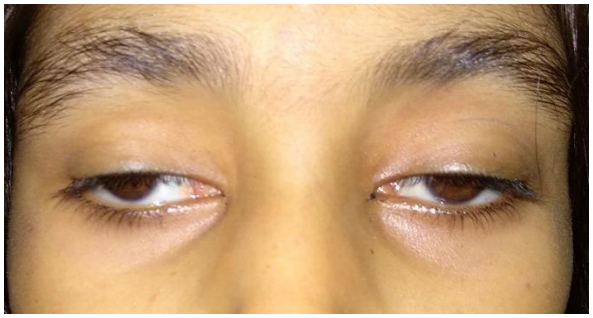
4) Mitochondrial Encephalopathy with Lactic Acidosis and Stroke like episodes (MELAS) :

- A problem caused by a mutation in transfer RNA protein (A3243G tRNALeu / C3271G tRNALeu UUR gene)
- More than 20 other mtDNA mutations can cause this disorder
- Variable Age of Onset (4 months - adult)
- Associated with many symptoms, like :
  a) weakness and fatigability
  b) Short Stature
  c) Strokes and stroke like episodes
  d) Progressive Dementia
  e) Hearing loss and DM
  f) Anorexia from autonomic gut neuropathy
  g) Migraine
  h) Myoclonic or tonic clonic seizures
  i) Hypertrophic > dilated cardiomyopathy
  j) Ophthalmoplegia
  k) renal tubular acidosis
  l) Droopy eyelids

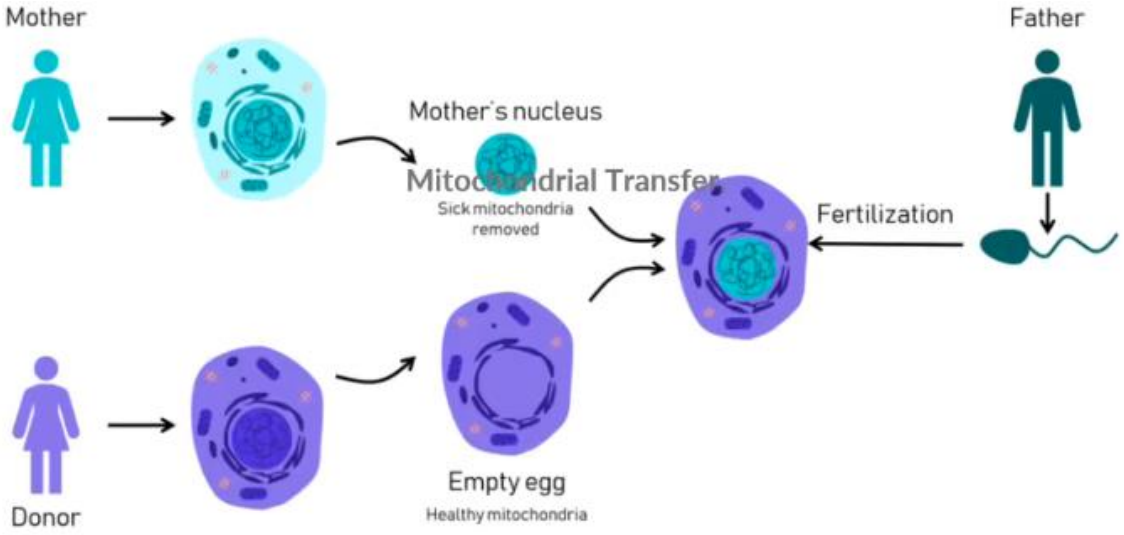


5) Kearns Sayre Syndrome (KSS) :

- Caused by large deletions (1000s bp) of mtDNA ; duplications
- Onset at age 20 (fatal in few years)
- Is not typically inherited, but rather is sporadic (meaning it just seems to show up in people)
- لا تتم وراثته و إنما يظهر فجأة، إذ من الممكن أن يكون فرد واحد من الأسرة مصاب و الباقي طبيعيين
- Manifestations :
  i. Ophthalmoplegia (paralysis or weakness of one or more eye muscles)
  ii. Degeneration of pigment layer of retina
  iii. Cardiac abnormalities
  iv. Neurological abnormalities



Mitochondrial transfer (mitochondrial therapy) :



- ❖ من طرق العلاج أو الوقاية الحديثة أخذ النواة فقط من بويضة الأم المصابة و إدخالها بسايتوبلازم منزوعة النواة من أنثى سليمة أخرى متبرعة.
- ❖ تضمن هذه الطريقة خلو الجنين من الطفرات الوراثية و الأمراض المتعلقة به بما أن مصدر مايتوكندريا الجنين من الأم.
- ❖ **After Frankfort fertilization, the zygote nucleus is a combination from the original mother and the father, while the rest of cellular components are derived from the healthy donor.**

Good Luck