Oxford Cambridge and RSA

Friday 16 October 2020 – Morning

A Level Biology B (Advancing Biology) H422/02

Scientific literacy in biology

Advance Notice

Time allowed: 2 hours 15 minutes

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INFORMATION
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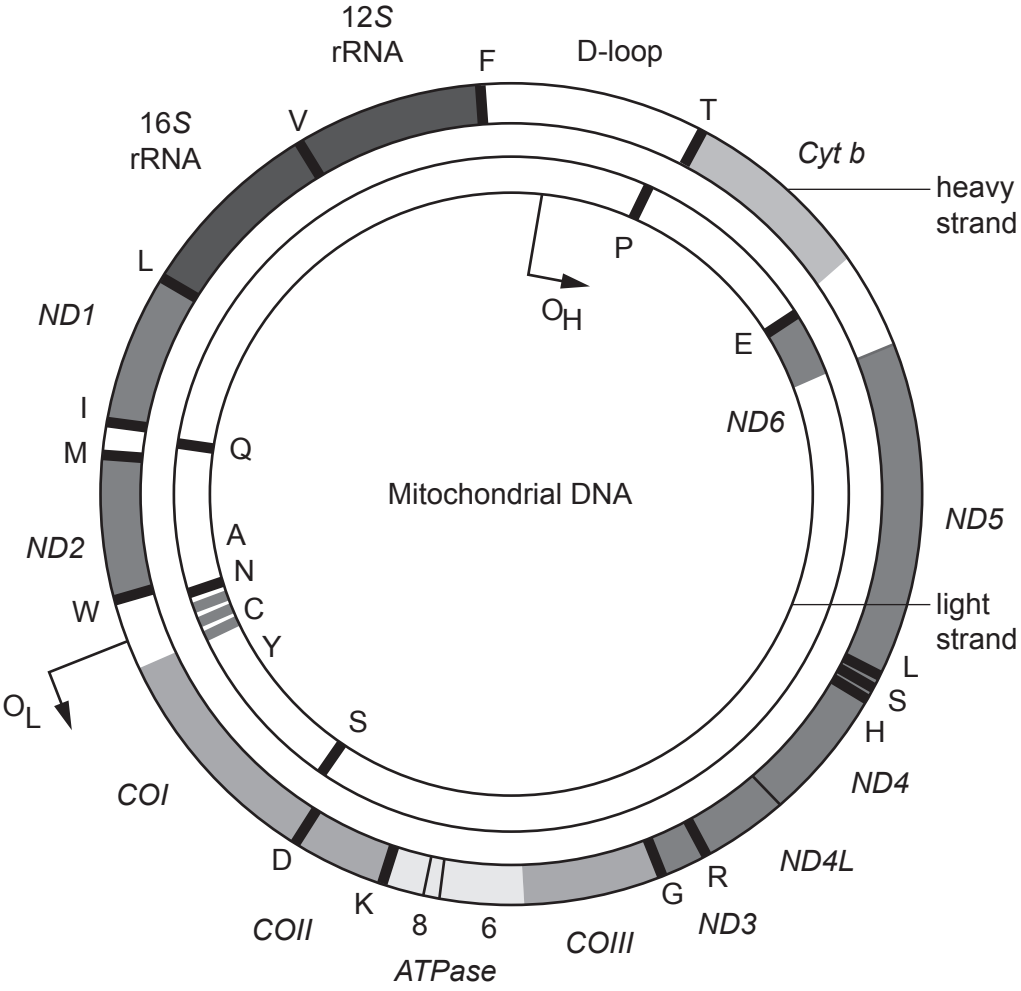
Mitochondrial DNA and mitochondrial disease

Mitochondrial DNA (mtDNA) is much smaller than the DNA within chromosomes; it contains only 16 500 base pairs compared to over 3 billion pairs in nuclear DNA. The DNA within mitochondria is more similar to the DNA within bacteria than nuclear DNA. Each mitochondrion contains many copies of the mtDNA, and there are many mitochondria in each cell.

The mitochondrial genome contains 37 genes that encode 13 proteins (see diagram below). The 13 mitochondrial gene-encoded proteins are subunits of enzyme complexes in the oxidative phosphorylation system. The small mitochondrial genome is not able to independently produce all of the proteins needed for functionality; thus, mitochondria rely heavily on imported nuclear gene products.

The mitochondrial genome contains few non-coding DNA sequences. Three percent of the mitochondrial genome is non-coding DNA, whereas 93% of the nuclear genome is non-coding DNA.



A map of the human mitochondrial genome. The 37 genes include genes encoding for cytochrome c oxidase, cytochrome b and subunits of ATP synthase. The D-loop is a non-coding control region.

The DNA contained within your nucleus comes from both your parents; you inherit half your nuclear DNA from your mother and half from your father. However, the situation with mtDNA is different. Children inherit mtDNA from their mothers only. Sperm contain mitochondria, but they are broken down shortly after fertilisation. Since children inherit all of their mtDNA from the mother, only women can pass on mutations within this DNA.

The mitochondrial genome has a higher mutation rate (about 100-fold higher) than the nuclear genome. What explains the high mutation rate of mtDNA? Two nuclear genes, TWNK and POLG, encode enzymes for replicating the mitochondrial genome. TWNK encodes a helicase enzyme and POLG encodes DNA polymerase gamma. The POLG protein consists of two regions: a catalytic region that exhibits polymerase activity, and an exonuclease region that is involved in the recognition and removal of DNA base-pair mismatches that occur during DNA replication. A recent study suggests that mitochondria may have a nucleotide imbalance that leads to decreased POLG fidelity and higher mtDNA mutation rates.

What is mitochondrial disease?

When a person has mitochondrial disease, the mitochondria in the cells fail to produce enough energy. They are either inefficient or they do not work at all. There is huge variety in the symptoms and severity of mitochondrial disease. It depends on how many cells are affected and where they are in the body. Each person with mitochondrial disease will have a different combination of functional and non-functional mitochondria within each cell. However, there are times when particular body systems are affected in a recognisable pattern and these diseases have specific names. One example is Alper's disease.

Alper's disease

Alper's disease is a mitochondrial disease that affects the brain and liver. Symptoms of the disease include severe epilepsy, loss of developmental skills and liver failure.

Alper's disease is caused by mutations in the nuclear gene called POLG. The mutations are present in both the catalytic and exonuclease regions of POLG. The faulty product of POLG – the polymerase gamma enzyme – fails to produce sufficient amounts of functioning mtDNA in the liver and brain.