

This fact sheet describes the way in which the genes located within the mitochondria can affect an individual's growth, development and health.

In summary

- Most of our genes are located on the DNA arranged on chromosomes which are found in the nucleus of each cell
- A small number of important genes are also located on the DNA found in another compartment of each cell called the mitochondria
- The mitochondria and the DNA inside it are passed from one generation to the next through the mother's egg cells.

DNA, GENES, CHROMOSOMES AND MITOCHONDRIA

Our bodies are made up of millions of cells. Each cell contains a complete copy of a person's genetic book of life.

Chromosomes can be thought of as being made up of strings of genes (DNA that codes for proteins) with non-coding DNA between them. The chromosomes, including the genes, are made up of a chemical substance called DNA (**D**eoxyribo**N**ucleic **A**cid).

Chromosomes are found in the nucleus of all body cells except for red blood cells which have no nucleus and therefore do not contain chromosomes.

Another place in the cell where DNA is found is in very small compartments called **mitochondria** (the energy centres of the cell) that are found scattered outside the nucleus (*Figure 12.1*). The DNA in mitochondria is much smaller and has very little non-coding DNA.

Mitochondria are found randomly scattered outside the nucleus but still within the cell. The DNA within the mitochondria is arranged as one long circle. The role of mitochondria in each of the cells of the body is mainly to manufacture energy for the cell and therefore the rest of the body.

It is important to remember that while each cell will always have only one nucleus, the number of mitochondria can vary from one cell to another.

A CLOSER LOOK AT MITOCHONDRIAL DNA

The cells in the body, especially in organs such as the brain, heart, muscle, kidneys and liver, cannot function normally unless they are receiving a constant supply of energy. The cell's energy source is a chemical called ATP (*adenosine triphosphate*) that is used to drive the various reactions essential for the body to function, grow and develop.

A number of biochemical reactions that occur in an ordered sequence within the mitochondria are responsible for this process of ATP production. These reactions are under the control of special proteins called enzymes. The genes found within the mitochondria contain the information that codes for the production of some of these important enzymes.

The biochemical processes which occur in the mitochondria and produce energy make up the **mitochondrial respiratory chain**. This 'chain' is made up of five components called complexes 1, 2, 3, 4 and 5. Each of these complexes is made up of a number of proteins. The instructions for these proteins to be produced by the cells are contained in a number of different genes.

There are many different genes needed to produce the components of the mitochondrial respiratory chain. Some of these genes are found in the mitochondria and others are in the nucleus.

A variation in a gene (either in the nucleus or mitochondria) that creates a fault is called a **pathogenic variant** or **mutation**.

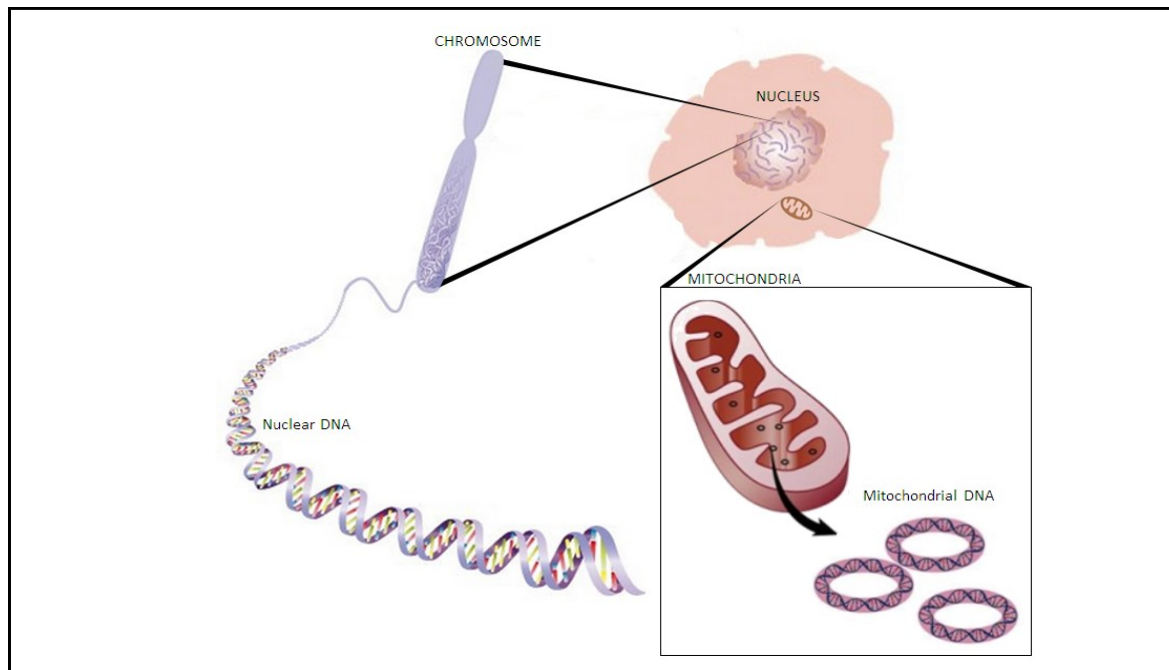


Figure 12.1: Diagram of a human cell showing nuclear DNA which is found on chromosomes in the nucleus of a cell and the mitochondrial DNA which is found in the energy centres of cells known as mitochondria. Figure adapted from the NHS National Genetics and Genomics Education Centre.

A mitochondrial DNA mutation can result in biochemical problems due to absence of enzymes involved in the respiratory chain, or enzymes that are impaired and do not work properly. This leads to a reduction in the supply of ATP, and may result in problems with the body's functions.

WHAT DOES IT MEAN IF YOU HAVE A MITOCHONDRIAL DNA GENE MUTATION?

The number of mitochondria in every cell of a person's body varies from a few to hundreds.

- All of these mitochondria, and therefore the DNA within the mitochondria, descend from the small number of mitochondria present in the original **egg cell** at the time of that person's conception
- The **sperm** contributes very few mitochondria to the baby. An individual's mitochondria are generally only inherited from his or her mother. A variation (*mutation*) in one of the mitochondrial genes that makes it faulty, can therefore be passed by the mother to a child via her egg cells
- This pattern of inheritance is therefore often referred to as **maternal inheritance**.

The egg cell contains many mitochondria. If a particular gene in every mitochondria in an egg cell has a mutation and is therefore sending the incorrect instructions, the disruption to energy production would be so severe that the early embryo would probably not survive.

The fact that a person survives to birth and is affected with a mitochondrial condition means that they must have inherited two types of mitochondria from his or her mother: some containing the working copy of the gene, and some containing the mutation.

The working copy of the mitochondrial gene will still be able to send the right instructions, but the total amount of energy produced may be impacted and may result in a mitochondrial condition.

On the other hand, having some mitochondria with a mutation may not cause a problem at all as described below.

An example of mitochondrial (maternal) inheritance

In some cases, the variation in the mitochondrial gene occurs for the first time in the egg or at the time of fertilisation of the egg.

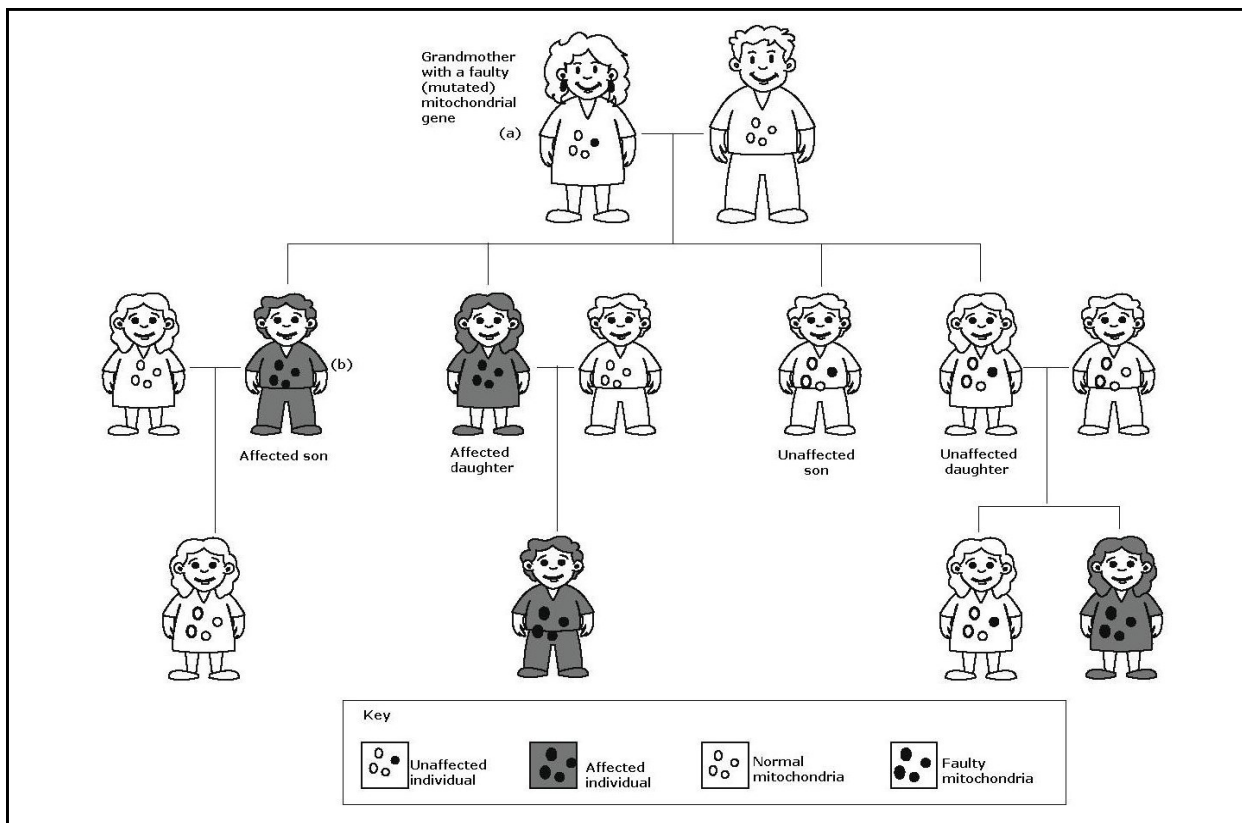


Figure 12.2: Mitochondrial inheritance in a family with a faulty (mutated) mitochondrial gene (Adapted from: Greenwood Genetic Centre (1995): *Counselling Aids for Geneticists*. Greenwood Genetic Centre, USA)

This is a **new** or **spontaneous** change that has occurred to make the particular mitochondrial gene faulty. In this case the affected person is the first in the family to be affected by the condition and the condition is described as **sporadic**. If the affected person is female, she may pass on the mitochondrial gene mutation to her children.

Usually, however, the mitochondrial mutation is inherited from a mother whose own cells, including her egg cells, contain both working and faulty copies of this mitochondrial gene. *Figure 12.2* is an example of a family tree with a pattern of inheritance of a genetic condition caused by a faulty mitochondrial gene.

In *Figure 12.2* the grandmother has one or more faulty mitochondrial genes but is not affected because she has enough working copies to enable most of the mitochondria in her cells to work properly.

- While she has passed on these faulty mitochondrial genes to her children, through her egg, not all are affected by the condition

- One of the reasons for this is thought to be the **threshold effect** of mitochondrial faulty genes.

Due to the way that mitochondria are randomly distributed into the egg cells when the eggs are forming in the ovary, each individual egg cell's mitochondrial make-up may vary from mostly correct to mostly faulty.

- Therefore, all of the children of this grandmother, regardless of the sex of the child, would inherit some faulty mitochondria
- The child would only develop symptoms, however, if the proportion of mitochondria with the faulty gene reached a critical level in enough cells, which would interfere with energy production in the body organ that is vulnerable to the condition
- It is only when there are so many copies of the faulty mitochondrial genes present in the cells that the working copies are unable to provide enough working gene product, that the person will have the condition

- The number of mitochondria that are faulty may also vary from one cell to the next, and so symptoms of the condition will not occur unless there are enough cells, with enough faulty mitochondria (i.e. exceed the critical level).
- The **grandmother's daughters**, however, are at risk of having a child affected with the mitochondrial genetic condition, regardless of whether they themselves are affected. It is difficult to give a precise estimation of their risk as it will depend on how many faulty mitochondria are in the egg at conception, and which tissues and organs will have enough cells with faulty mitochondria over the critical threshold for the condition to occur.

So even though two of the grandmother's unaffected children in *Figure 12.2* have inherited the faulty mitochondrial genes, they have more working copies than faulty copies.

- While the **father (b)** in the family shown in *Figure 12.2* is affected, his children are not at risk for inheriting the condition as the vast majority of the mitochondria are passed to children from their mother through the eggs