This fact sheet talks about the way in which the genes located within the mitochondria can affect a person'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.

CHROMOSOMES, GENES, DNA AND MITOCHONDRIA

Our bodies are made up of billions 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. Red blood cells 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** (*Figure 12.1*). The DNA in mitochondria is much smaller and mostly non-coding DNA.

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.

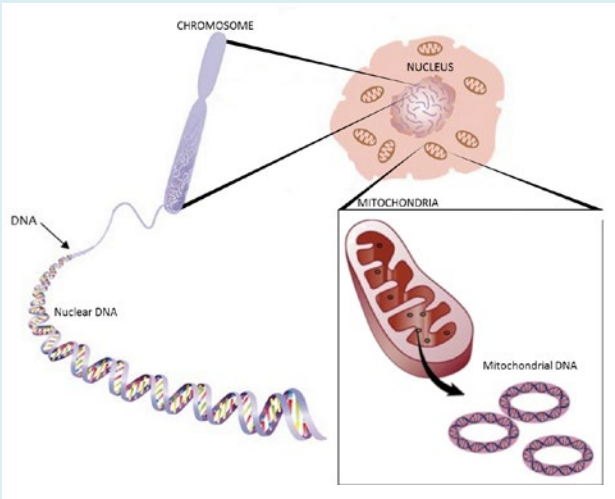


Figure adapted from the NHS National Genetics and Genomics Education Centre, https://www.genomicseducation.hee.nhs.uk/image-library

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

Content updated October 2021
OCT21/V1 NS12656
SHPN: (HETI) 240983

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***). ATP is broken down to release the energy needed for the body to work properly, grow and develop.

A number of chemical reactions that happen in an ordered sequence in the mitochondria control the process of making ATP. These reactions are under the control of special proteins called enzymes. The genes found within the mitochondria contain DNA coding for making some of these important enzymes.

The chemical processes which happen in the mitochondria to make energy are part of the **mitochondrial respiratory chain**. This 'chain' is made up of five parts 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 make the parts of the mitochondrial respiratory chain. Some of these genes are found in the DNA of the mitochondria and others are found in the DNA in the nucleus (chromosomes).

The genes in our DNA provide the instructions for proteins, which are the building blocks of the cells that make up our body. Although we all have variation in our genes, sometimes this can affect how our bodies grow and develop. Generally, DNA variations that have no impact on our health are called **benign variants** or **polymorphisms**. These variants tend to be more common in people. Less commonly, variations can change the gene so that it sends a different message. These changes may mean that the gene does not work properly or works in a different way that is harmful. A variation in a gene that causes a health or developmental condition is called a **pathogenic variant** or **mutation**.

A mitochondrial gene variant can sometimes result in enzymes involved in the respiratory chain not being produced properly. This leads to not enough ATP being made, which can be harmful to the body.

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

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 inside the mitochondria, come from the mitochondria present in the original **egg cell** from a mother, at the time that a person is first made (conception)
- It is likely to be rare that the **sperm** from the father passes on mitochondria to the baby. A person's mitochondria are generally only inherited from their mother. A variant in one of the mitochondrial genes that makes it not work properly, 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 mitochondrion in an egg cell has a variant where the gene product is not made properly, the impact on how the body makes energy may be so severe that the developing baby may not survive to birth.

This may not always hold true. For example, the genes in the nucleus and the genes in the mitochondria may work together in a complex way that makes it sometimes difficult to predict how this will impact on a person's health and development.

In each cell, there may be a mixture of mitochondria. Some may have a non-working copy of a mitochondrial gene and others may have a working copy of the gene.

Even if there is a working copy of the mitochondrial gene that sends the right instructions, the total amount of energy produced may be affected and may result in a mitochondrial condition.

On the other hand, having some mitochondria with a non-working gene copy may not cause a problem at all as described next.

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.

This is a **new** or **spontaneous** variant that has happened and the mitochondrial gene does not work. In this case the affected person is the first in the family to have the condition and the condition is described as **sporadic**. If the affected person is female, she may pass on the mitochondrial gene variant to her children.

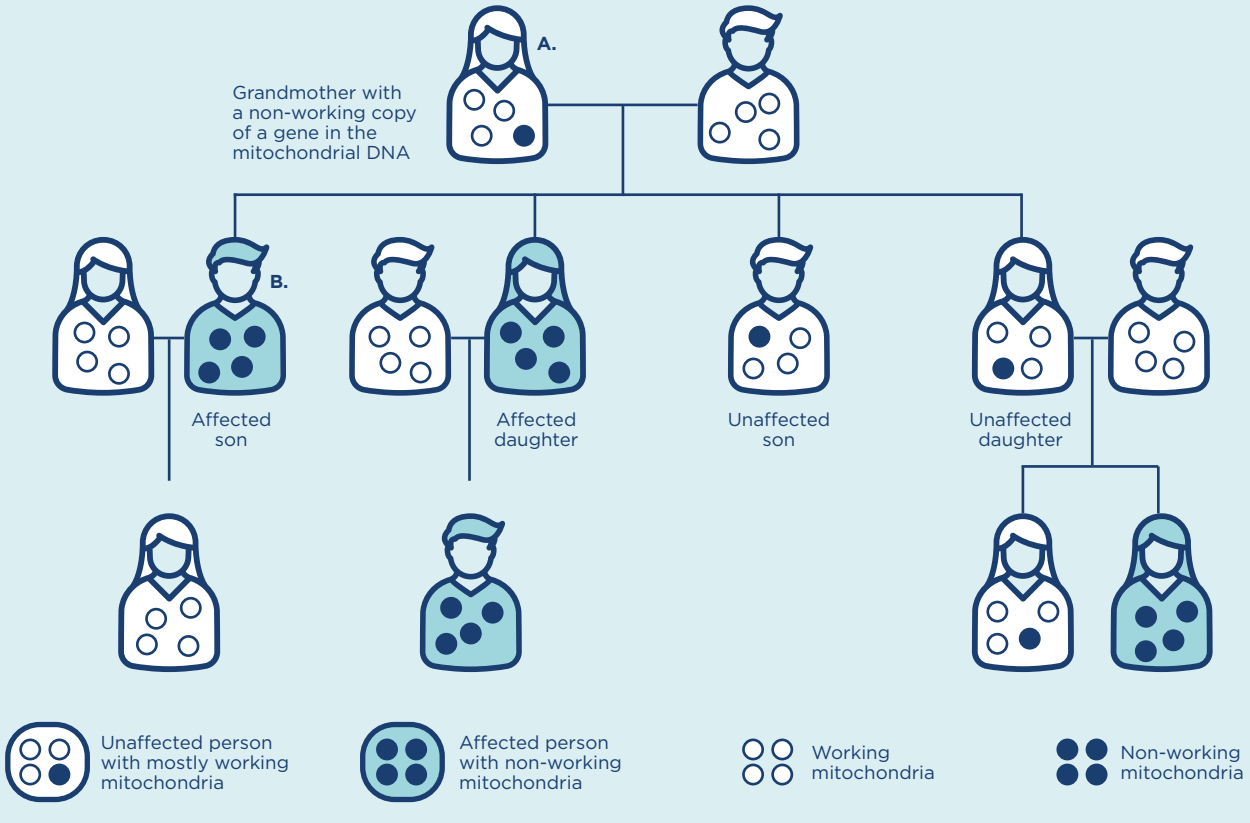
Usually, however, the mitochondrial variant is inherited from a mother whose own cells, including her egg cells, contain both working and non-working copies of this mitochondrial gene. *Figure 12.2* is an example of a family tree with a pattern of inheritance of a genetic condition caused by a non-working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

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

- While the grandmother passed on these non-working mitochondrial genes to her children, through her egg, not all necessarily have the condition
- One of the reasons for this is thought to be the **threshold effect** of non-working mitochondrial genes.

Mitochondria are randomly distributed into the egg cells when the eggs are first forming. Therefore each person's egg cell's mitochondrial make-up may vary from mostly working to mostly non-working.

Figure 12.2:
Mitochondrial inheritance in a family with a non-working copy of a gene in the mitochondrial DNA



- Therefore, all of this grandmother's children, regardless of their sex, would inherit some non-working mitochondria
- A child would only develop symptoms if:

  (a) the proportion and number of mitochondria with the non-working gene copy reaches a critical level

  (b) this happens in enough cells of the body so that the ability to make energy is affected enough to cause the condition.

So, even though two of the grandmother's unaffected children in *Figure 12.2* have inherited the gene variant, they have enough working copies compared with non-working copies.

- While the **father (B)** in the family shown in *Figure 12.2* has the health condition, his children should not inherit the condition as this is mostly passed on by the mother in the eggs
- The **grandmother's daughters**, however, have a chance of having a child with the mitochondrial genetic condition, regardless of whether they themselves have it. It is difficult to give an exact estimate of this chance. It will depend on how many non-working mitochondria are in the egg at conception, which tissues and organs will have enough cells with non-working mitochondria over the critical threshold for the condition to occur, and any impact of genes in the nucleus.