

Important points

- Some of the estimated 20,000 genes in the human genome are located in small compartments in the cell called the **mitochondria**, rather than on chromosomes in the cell's nucleus. Some cells contain many hundreds of mitochondria
- The genes found within the mitochondria contain the information that codes for the production of many of the important enzymes that drive the biochemical reactions to produce the body's source of energy: a chemical called ATP (*adenosine triphosphate*). 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 (ATP)
- Faulty mitochondrial genes can result in absence of these enzymes, 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
- The pattern of inheritance of conditions due to faulty mitochondrial genes is often called **maternal inheritance**. This is because a child inherits the great majority of their mitochondria from their mother through the egg
- Usually a mother will have a mixture of mitochondria containing the working gene copy and others containing the faulty gene. For a condition to develop, the number of mitochondria with the faulty gene must be above a critical level (the threshold)
- The cells of different tissues and organs can have varying amounts of mitochondria containing a faulty gene, and the number of cells with the faulty mitochondria in each tissue or organ may also vary
- Conditions due to having faulty mitochondrial genes create complexities when assessing the risk the mother has for passing on the faulty mitochondrial genes to a child and if, or how severely, the child would be affected
- While it is possible to test for the presence or absence of some faulty mitochondrial genes and their products during pregnancy, the result may be difficult to interpret
- Whether symptoms of the condition will occur or not depends on whether the numbers of mitochondria with the faulty genes is above the critical threshold in enough cells to interfere with energy production
- Genetic counselling can provide the most current information on the availability and appropriateness of testing for mitochondrial conditions, either in an affected person or during pregnancy (see Genetics Fact Sheet 3)

Understanding the patterns of inheritance of genetic conditions in families is becoming increasingly complex (See Genetics Fact Sheet 2).

Complex patterns of inheritance

The cells of the body contain the genes or set of instructions for the cell to make all the necessary proteins (chemicals) for our bodies to grow and work normally (see Genetics Fact Sheet 1).

If there is a variation in the information in a gene so that it does not work properly, the gene is described as being faulty (i.e. there is a *gene mutation* present). The product of the faulty gene is impaired, or is not produced in the right amounts (see Genetics Fact Sheets 4 & 5).

The traditional patterns of inheritance apply to the inheritance of conditions due to changes in a single gene, located on the chromosomes in the nucleus (see Genetics Fact Sheets 8, 9 & 10). Estimating the chance of developing a genetic condition when someone carries a faulty gene is generally straightforward in these individuals.

In some cases, interactions between a person's genetic make-up and the environment means that despite the presence of a faulty gene, the condition does not always develop.

For example, not all women with a faulty breast ovarian cancer gene will develop breast or ovarian cancer (see Genetics Fact Sheet 48). This is described as incomplete penetrance of the faulty gene: the gene is present but will not be expressed unless other environmental factors, or variations in other genes, are also present (see Genetics Fact Sheet 11). It is therefore more complex to determine the pattern of inheritance and to estimate the chance for a genetic condition to occur, if a faulty gene was present.

Another example of complex inheritance patterns is the situation where the faulty gene(s) is located on a chromosome is/are not present in all of the mother's egg cells or the father's sperm cells. Egg cells and sperm cells are also called 'germ' cells. The parent therefore has a mixture of faulty and working gene copies in their germ cells. This situation is described as *mosaicism* and is discussed in Genetics Fact Sheet 13.

This Fact Sheet discusses the complex pattern of inheritance where the faulty gene(s) is/are located in the mitochondria rather than on chromosomes in the cell's nucleus. This pattern of mitochondrial inheritance is also known as **maternal inheritance**.

The mitochondrial genes

As shown in *Figure 12.1* and described in Genetics Fact Sheet 1, genes are located on the chromosomes, within the nucleus of every cell. The chromosomes (and therefore genes) are made up of the chemical called DNA.

Another place in the cell where DNA is found is in very small compartments called **mitochondria** (plural), that are found randomly scattered in the cytoplasm of the cell outside the nucleus. So, mitochondria contain genes too, although the mitochondrial DNA is one long string of genes and is not arranged as chromosomes. The genes in bacterial DNA are also arranged in a long string, giving rise to the theory that the mitochondria originated from bacteria that invaded a cell early in evolution.

Mitochondria are like little 'factories' in each of the cells of the body that are responsible for making most of the body's source of energy.

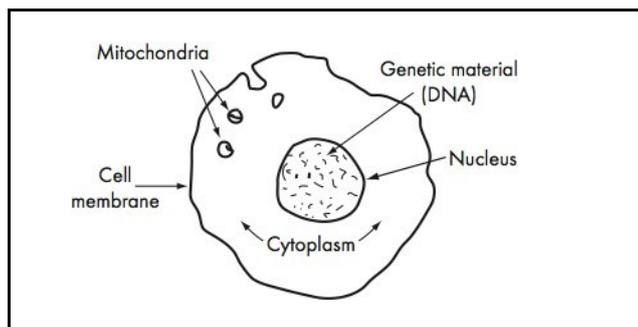


Figure 12.1: Diagram of a cell showing the mitochondria that are present in the cell's cytoplasm.

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.

What are the biochemical reactions that occur in the mitochondria?

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 over 80 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.

Variations in any of these mitochondrial genes that make them faulty 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.

Some of these problems include any of those listed in *Table 12.1*, and can occur either in isolation or in various combinations.

Inheritance of faulty mitochondrial genes (maternal inheritance)

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

Organ or tissue	Impact
General	Small stature and poor appetite
Central nervous system	Developmental delay/intellectual disability, progressive neurological deterioration (dementia such as the late-onset form of Alzheimer disease), seizures, stroke-like episodes (often reversible), difficulty swallowing, visual difficulties and deafness
Skeletal and muscle	Floppiness, weakness and exercise intolerance
Heart	Heart failure (cardiomyopathy) and cardiac rhythm conditions
Kidney	Problems in kidney function

Table 12.1 Examples of the impact of faulty mitochondrial genes

- 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 in 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 is faulty 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 faulty gene. 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 faulty gene may cause no 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. 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*.

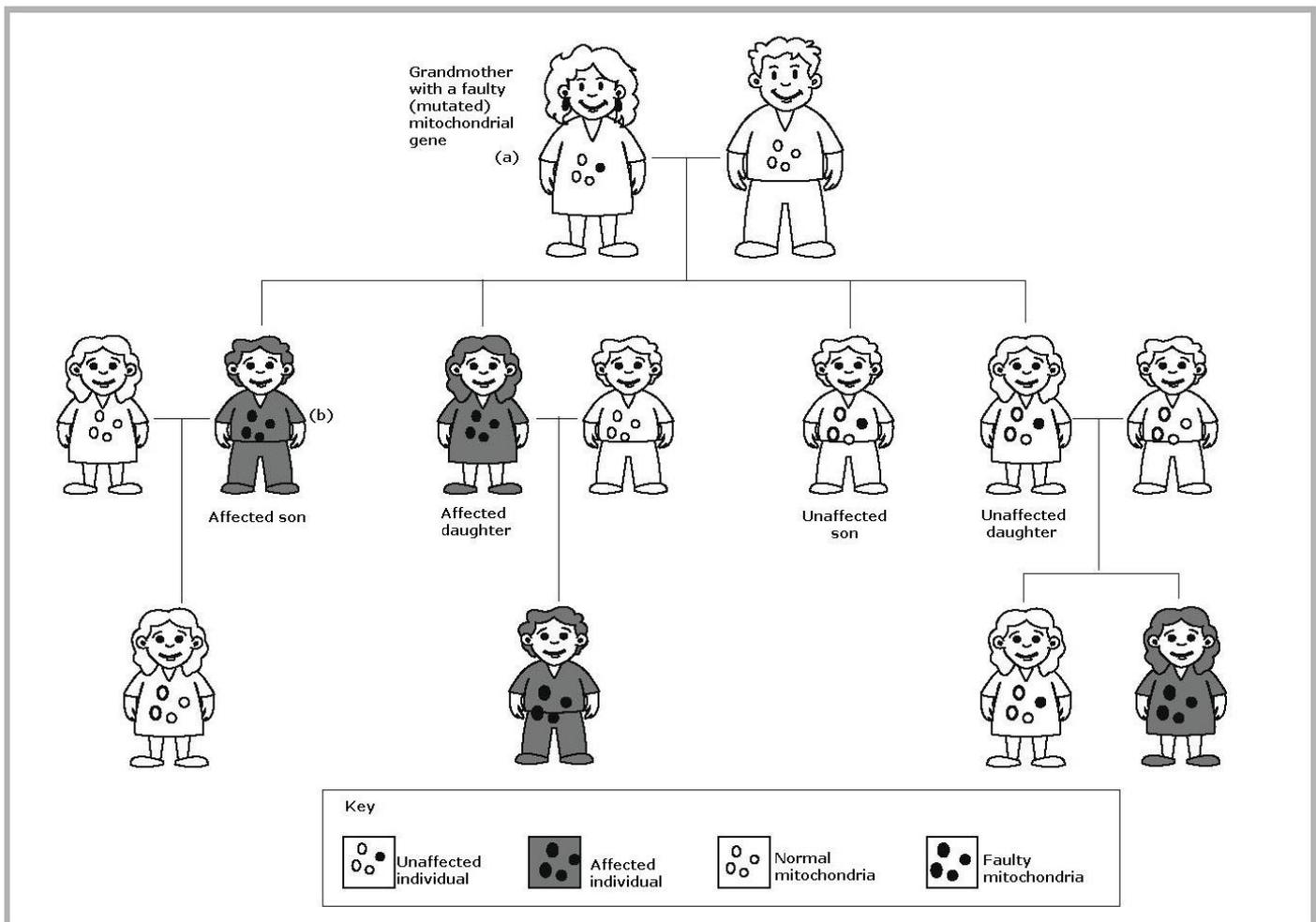


Figure 12.2: Example of a family tree showing members of a family in which runs an inheritance of a mitochondrial condition (Adapted from: Greenwood Genetic Centre (1995): *Counselling Aids for geneticists*. Greenwood Genetic Centre, USA)

Usually, however, the mitochondrial variation 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.

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 (ie. exceed the critical level)

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

- 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.
- If the testing showed that the baby had the faulty mitochondrial gene or its product, it may not be possible to reliably predict how severely the baby would be affected, or even if the baby was affected at all
- The cells of different tissues and organs can have varying amounts of mitochondria with a faulty gene, and the number of cells with the faulty mitochondria in each tissue or organ may vary
- Whether symptoms of the condition will occur or not depends whether the number of mitochondria with the faulty gene(s) is above the critical threshold in enough cells so as to interfere with energy production

Prenatal diagnosis for mitochondrial conditions

Conditions due to having faulty mitochondrial genes create complexities when assessing the risk that the mother has for passing on the faulty mitochondrial genes to a child and how severely, or even if the child would be affected.

While it is possible to test for the presence or absence of some faulty mitochondrial genes and their products during pregnancy (see Genetics Fact Sheet 17C), the interpretation of the result can be difficult and complex:

Genetic counselling can provide the most current information on the availability and appropriateness of testing for mitochondrial conditions, either in an affected person or during pregnancy (see Genetics Fact Sheet 3).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 8, 9, 10, 11, 13, 17C, 48

Information in this Fact Sheet is sourced from:

Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) [online]. Available from: <http://www.ncbi.nlm.nih.gov/omim/>. [Accessed April 2012]

Read A and Donnai D. (2010). *New Clinical Genetics (2nd edition)*. Bloxham, Oxfordshire: Scion Publishing Ltd

Naviaux R. (2006). The Spectrum of Mitochondrial Disease [online]: Available from: <http://biochemgen.ucsd.edu/mmdc/ep-3-10.pdf> [Accessed April 2012]

Edit history

April 2012

Author/s: A/Prof Kristine Barlow-Stewart

Previous editions: 2007, 2004, 2002, 2000, 1998, 1996

Acknowledgements previous editions: Bronwyn Butler; Prof John Christodoulou; Prof Graeme Morgan; Gayathri Parasivam; Mona Saleh; Prof Ron Trent