mito FOUNDATION
Hope for mitochondrial disease

THE GENETICS OF MITOCHONDRIAL DISEASES

We often hear phrases such as ‘You have your mother’s eyes’ or ‘You have your father’s hair’. These physical features are the result of your genes.

Genes are pieces of DNA in our cells that pass our physical features through generations. Genes also tell our body how to function, and problems in genes can lead to diseases, like mitochondrial disease.

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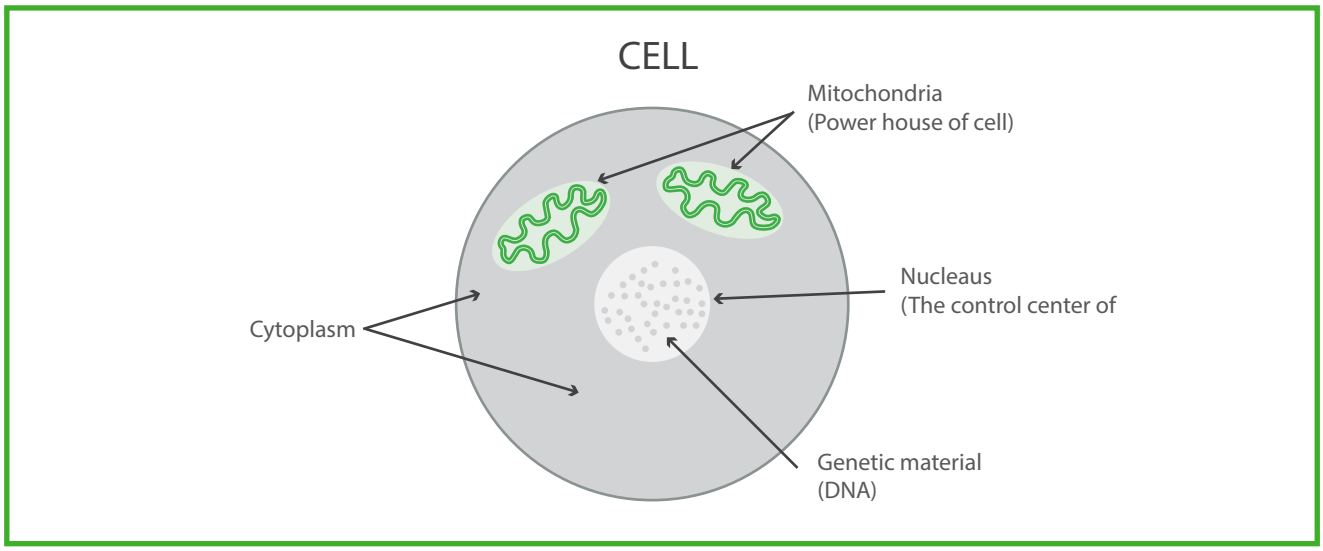
CELLS, GENES, PROTEINS AND DNA

Genes are the stored in cells. Your body is composed of 40 trillion cells. Each serves a specialised role that allows your body to function. For example, neurons are the cells in nerves that transmit electrical signals that coordinate your movement. White blood cells fight disease and respond to infection.

Each cell contains a complete bluprint of our genetic plan, packaged in the form of genes.

All cells contain organelles (tiny organs) that perform tasks like transporting nutrients and breaking down waste products. Only two of these organelles contain genes. These are:

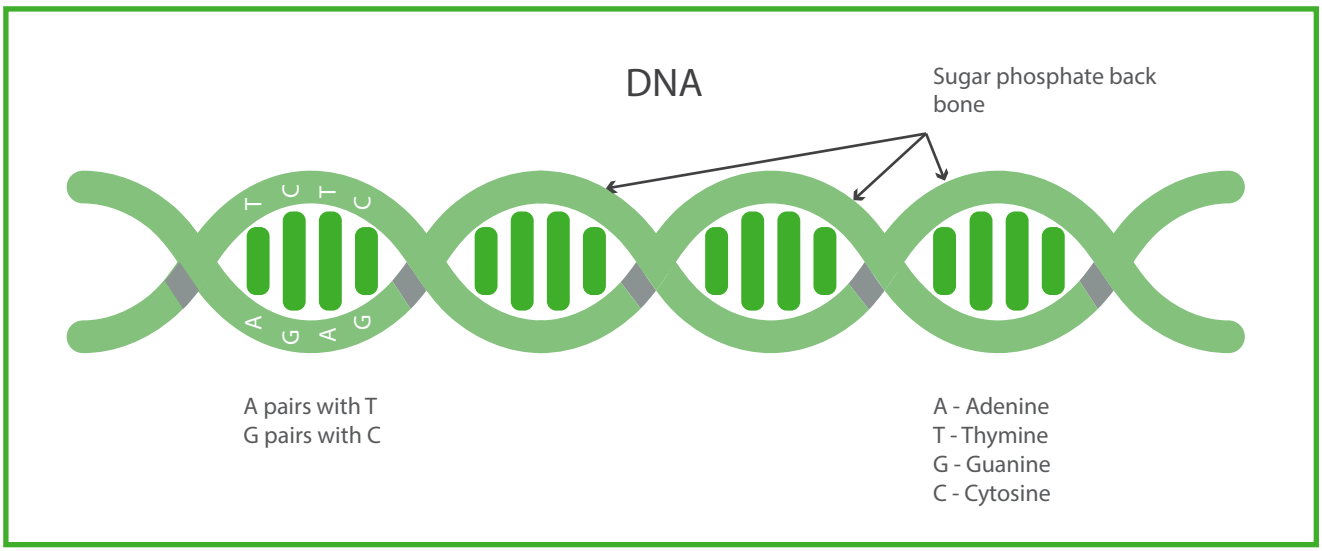
- **Nucleus** - This is control centre of the cell where nearly all genes are stored. It contains over 20,000 genes.
- **Mitochondria** - This is the powerhouse of the cell that converts food into energy. Contains a very small number of genes, just 37.



Genes are the basic units of inheritance. They pass physical features from parents to children. The combination of your parent's genetic codes results in an entirely new and unique individual- you. Genes not only influence our outward appearance, like eye colour, but also control how our body works from the inside.

Genes contain the information our body needs to make chemicals called proteins. Each gene corresponds with a protein. Proteins are the building blocks of our body and make up our muscles, our connective tissues, our organs and our skin. They build bones, control digestion, and keep your heart beating. They carry out all the chemical reactions around our body that keep us alive. The structure and function of the body is controlled by different types of proteins which are created within the cell. The body is therefore regulated by our genes.

Each of your cells contains two sets of genes: one from each parent. Each gene is therefore is one of a pair. There is variation between these genes pairs which contributes to your unique nature. The term for different versions of the same gene is allele. For example, in the region of DNA that codes for eye colour, you have two alleles, one from your mother and one from your father. These may be the same, or different.



Genes are made up of a chemical called Deoxyribonucleic acid (DNA). DNA is shaped like a double helix. It has two long, thin strands twisted around each other like a spiral staircase. The steps of this staircase are composed of special molecules, called "bases. There are four types of bases: Adenine (A), Thymine (T), Guanine (G), Cytosine (C). Your genetic code is determined by the sequence of these four bases; it consists of about 3 billion A, T, G and C bases in a unique combination.

DNA has 2 important properties:

- It can make copies of itself. If two strands are pulled apart, each can be used to make a new DNA strand.
- DNA can carry information. The order of the bases along a strand is written in code - a "genetic code" for making proteins

If we were to take DNA from all the cells of our body and line it up, end to end, it would form a very thin strand which would be 9,656,064,000 kilometers long!

MITOCHONDRIA AND THE CELL

Mitochondria are the powerhouses of the cell. They contain a sequence of proteins and enzymes that convert food and oxygen into usable energy for the body. This conversion process produces adenosine triphosphate (ATP), the body's power source. Organs like the heart, the muscles, and the brain cannot function normally if this supply of ATP is low.

Mitochondria have their own DNA and genes. Although most of a cell's DNA is in the nucleus, the mitochondria have a small but crucial piece of DNA. Mitochondrial DNA (mtDNA) codes for 13 mitochondrial proteins. Approximately 1500 mitochondrial proteins are coded by nuclear DNA, and transported into the mitochondria.

Mitochondrial DNA is only passed down from the mother. During conception, when the sperm fuses with the egg, the sperm's mitochondria, and its mtDNA, are destroyed. Hence, all of the embryo's mitochondria (and mtDNA) come from the mother. Mitochondria are very important to fuel the growth of a fertilised egg.

Nuclear DNA passed down from both the mother and the father.

MITOCHONDRIAL DNA (MTDNA) AND NUCLEAR DNA (NDNA)

Most of your genes are stored in the nucleus, but a small number are stored in small circular genome (called mtDNA) in the mitochondria. Each cell has many mitochondria, and each mitochondrion is estimated to contain 2–10 mtDNA copies.

Only a small number of the mitochondria's proteins are encoded by mtDNA. The remainder originate from the nucleus as nDNA.

GENETIC VARIATION AND MITOCHONDRIAL DISEASE

Certain variations in the genetic code can lead to disease. We all have variations in the genetic code that is why despite being very similar we still are unique. Most variations are harmless, but some can lead to disease. A genetic variation can lead to a particular type of protein not being produced in the body, or it can cause too much or too little production of that particular protein, affecting growth, development and functioning of the body. Changes in the genetic code can make us more prone to developing a genetically inherited condition.

Mitochondrial disease (mito) arises from genetic changes that lead to incomplete proteins, or even completely missing proteins, in the mitochondria. These genetic variations prevent the mitochondria from producing enough ATP (energy) for the body, leading to the symptoms of mitochondrial disease.

TYPES OF INHERITANCE FOR MITOCHONDIRAL DISEASE

Mito arises from variations in genetic code which can be passed down from parents to children. Understanding the basic types of genetic inheritance is very important. It helps you communicate with your doctor and genetic counsellor, who can assess the risk of passing mito to your children, or determine of other people in your family carry mito genes.

There are fundamental different patterns by which mito may be passed from parents to children.

- **Mito genes may be either dominant or recessive.** The dominant form will always overrule the non-dominant (recessive) form. Returning to the example of eye colour: brown eyes are more common than blue eyes because the gene for brown eyes is dominant over the gene for blue. This means that whenever the brown eye gene is present, it will overrule the recessive blue eye gene. The same applies to dominant and recessive mito genes.

- **Mito genes may be linked to the genes that determine gender.** These mito genes affect one gender more often than another. In the case of X-linked mitochondrial disease, the harmful genetic variation exists on the X chromosome and affects males more often than females.

- **Mito genes may be passed down only from the mother.** A number of genes crucial to mitochondrial function are passed down exclusively from the mother in the form of mtDNA. In cases where the mother's mtDNA has harmful changes, her children will inherit them as well.

- **Genetic variations that cause mito may occur spontaneously.** Certain genetic changes occur on their own during the formation of eggs and sperm. These are sometimes referred to as spontaneous mutations. In these cases, the mito gene is not present in the parents.

OTHER FACTORS OF MITO INHERITANCE

- **An individual may carry a recessive mito gene but show no sign of disease. This is because this person carries only one recessive copy of the gene. If this person has a child with another person with a recessive copy of the same mito gene, their child will have a significant chance of developing the disease.**

- **The level of harmful mtDNA can vary in a person due to heteroplasmy – The mitochondria have many copies of their own DNA, and some of them may have harmful variations and others may not. The ratio of harmful to normal mtDNA is called heteroplasmy, and affects the severity of mito. Levels of heteroplasmy may change over time, leading to disease onset later in life.**

UNDERSTANDING YOUR FAMILY'S HEALTH HISTORY IS EXTREMELY IMPORTANT DURING MITO DIAGNOSIS

Gather as much information about your family's health history as possible before an evaluation for mito. If you have relatives with premature deafness, blindness, seizures, or other signs of mito, this information is very important to doctors. It can help determine what type of mito may run in your family.

Doctors and genetic counsellors will use this information to develop a **family pedigree**, which is a graph of your family tree. It can illustrate which individuals carry disease genes and which do not.

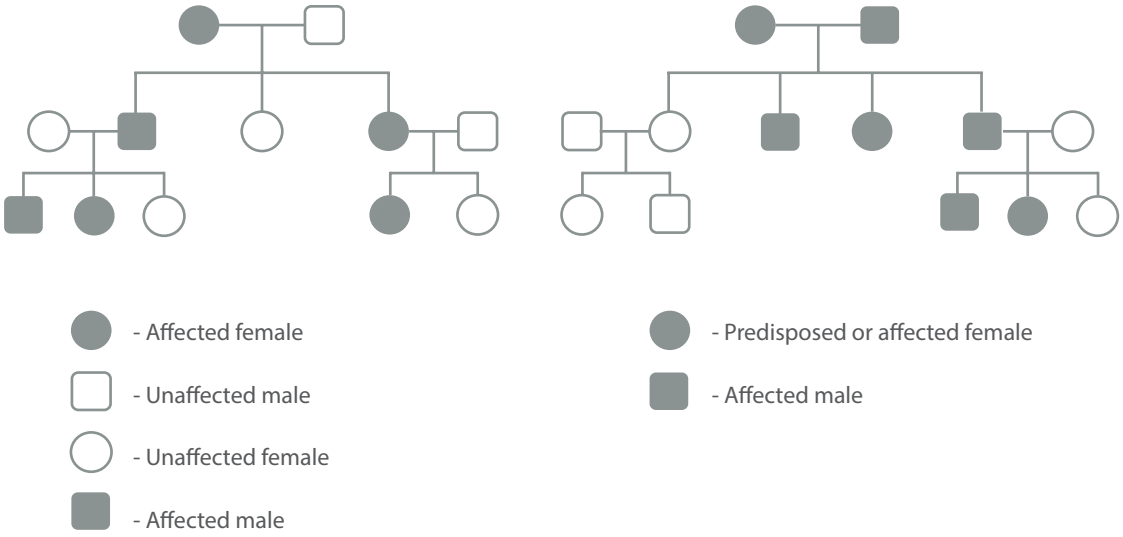
FORMS OF INHERITANCE

Mito may be passed from parents to children through a number of different ways. The most common forms of inheritance are described below. Family pedigrees and specific types of mito are given for each form of inheritance.

The most common patterns of inheritance of genetic conditions due to change in a single gene are:

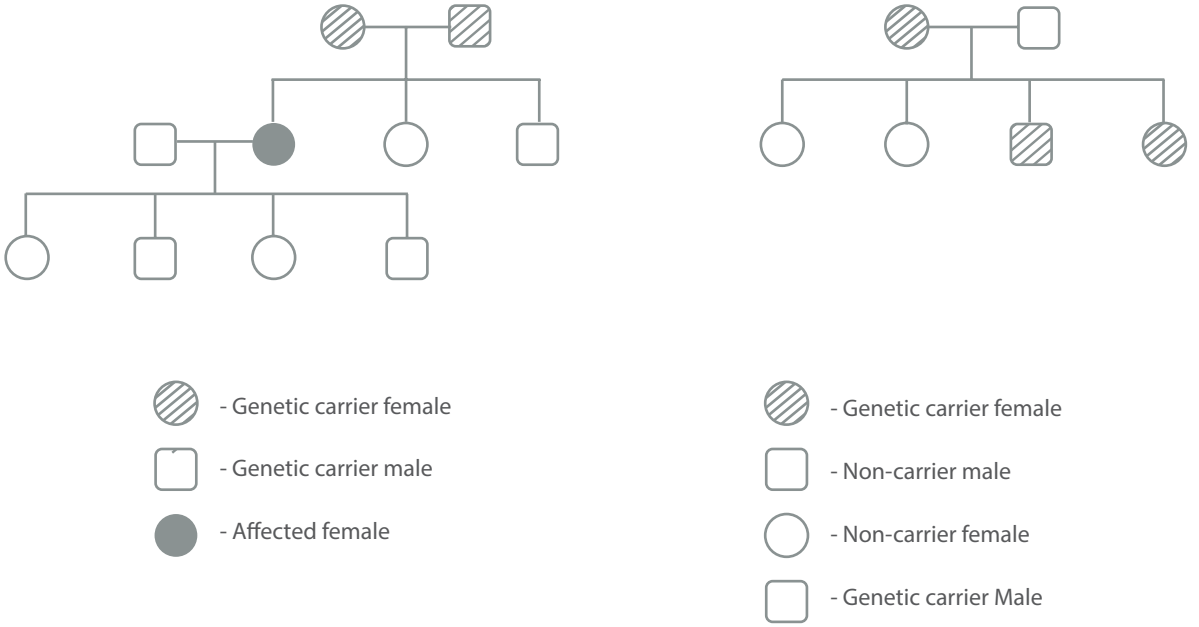
- Autosomal dominant
- Autosomal recessive
- Mitochondrial inheritance
- X-linked recessive

Autosomal Dominant Inheritance



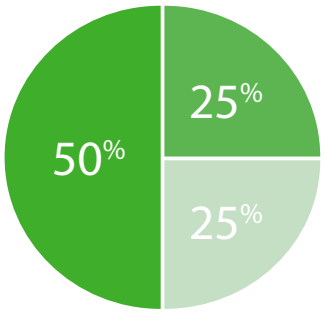
- In an **autosomal dominant disease**, if you inherit the abnormal gene from only one parent, you can get the disease.
- Often, one of the parents may have the disorder
- When one parent has the disorder and other parent does not, each offspring has 50% chance of inheriting the disorder.
- People who do not carry the disorder, usually do not carry the faulty gene and so do not pass the trait to their offspring.
- In many generations both the male and female are affected.
- In most of the cases, clinical manifestation starts after puberty.
- Family history is crucial for diagnosis.

Autosomal Recessive Inheritance



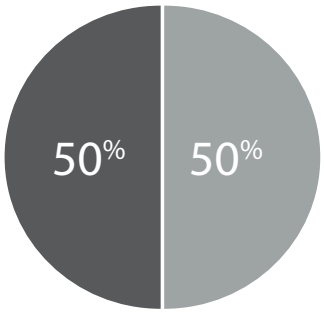
- In autosomal recessive mito, two copies of the abnormal gene (one from mum and one from dad) must be present for mito to develop
- Parents may not necessarily have the disease, but may be carriers

Autosomal Recessive Liklihood of Inheritance



IN THE OFFSPRING OF TWO UNAFFECTED GENETIC CARRIERS:

- 25% will be affected
- 50% will be unaffected carriers
- 25% will be non-carriers



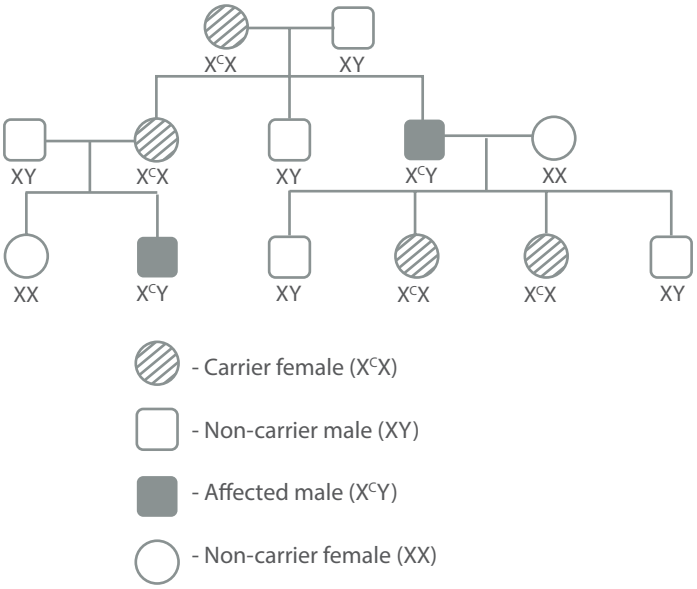
WHEN ONLY ONE PARENT IS AN UNAFFECTED GENETIC CARRIER FOR THE CONDITION:

- 50% of offspring can be unaffected carriers
- 50% will be non-carriers of the genetic disease

Some examples of autosomal (both dominant and recessive) mitochondrial diseases are:

- Alper's Syndrome (autosomal recessive, caused by POLG defects)
- Leigh disease (may be due to a number of autosomal recessively inherited nuclear gene defects eg SURF1, NDUFS1, GFM1etc
- Co-Enzyme Q10 Deficiency
- GRACILE: *Growth Retardation, Amino aciduria, Cholestasis, Iron overload, Lactic acidosis, Early death*
- MAD: *Multiple Acyl-CoA Dehydrogenase Deficiency / Glutaric Aciduria Type II*
- MCAD: *Medium-Chain Acyl-CoA Dehydrongenase Deficiency*
- Miller Syndrome
- MNGIE: *Mitochondrial Neuro-Gastrointestinal Encephalopathy*
- Pyruvate Carboxylase Deficiency

X-linked Recessive Inheritance

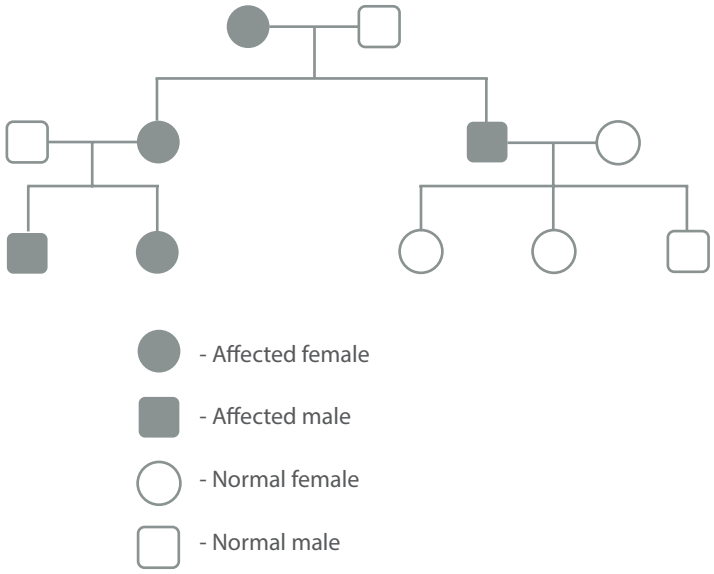


- Nearly everyone affected is male.
- All daughters of an affected male are carriers of the abnormal gene.
- An affected male does not transmit the disorder to his sons.
- Females who carry the faulty gene do not have the disorder (unless both X carry faulty gene) Daughters of such mothers will be carriers and 50% of her sons will have the disorder.

Some examples of x-linked recessive mitochondrial disorders are:

- Barth Syndrome: *X-linked Cardiomyopathy, Mitochondrial Myopathy, Cyclic Neutropenia (caused by TAZ gene)*
- LIC: *Lethal Infantile Cardiomyopathy*

Mitochondrial Inheritance



In these cases, if the mother has mito, all of her children will have the mito genes.

However, if the father has mito, the children will not inherit the mito genes

Some examples of mitochondrial diseases that are inherited through the mitochondria include:

- Aminoglycoside-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 Fibres
- MIDD: Maternally Inherited Diabetes and Deafness
- NARP: Neuropathy, Ataxia and Retinitis Pigmentosa