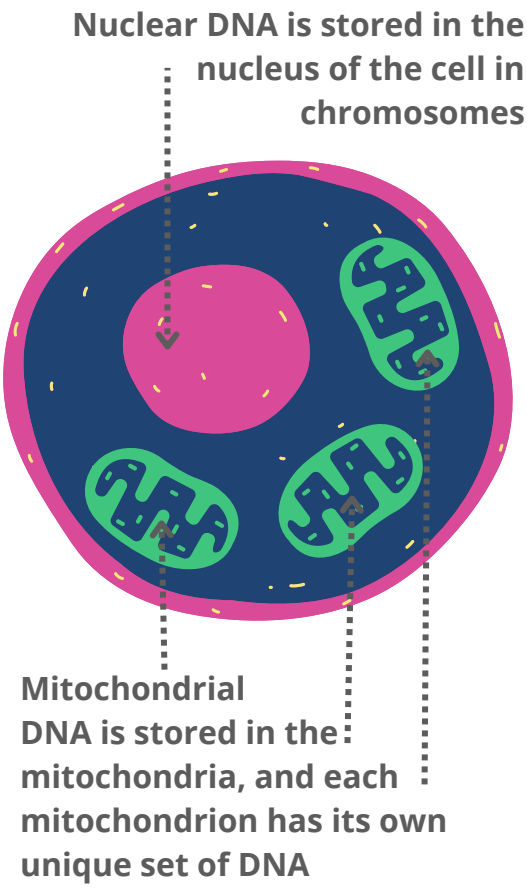
FAMILY PLANNING

CURE MITO FOUNDATION

INTRODUCTION

Family planning for Leigh syndrome, similar to other mitochondrial conditions, is further complicated by the existence of several types of inheritance. Some forms of assisted reproductive technologies (ART) may only be available to families with certain inheritance patterns. This guide aims to summarize the different types of inheritance observed in Leigh Syndrome as well as available ART options.

This guide is not meant to provide medical advice but is rather a resource of information. Additionally, different countries have different regulations regarding ART, meaning that certain ART options outlined in this guide may not be available to you. If you have a family history of Leigh Syndrome, or another mitochondrial condition, and are looking to move forward with family planning, you should consult a healthcare provider.



Types of Inheritance

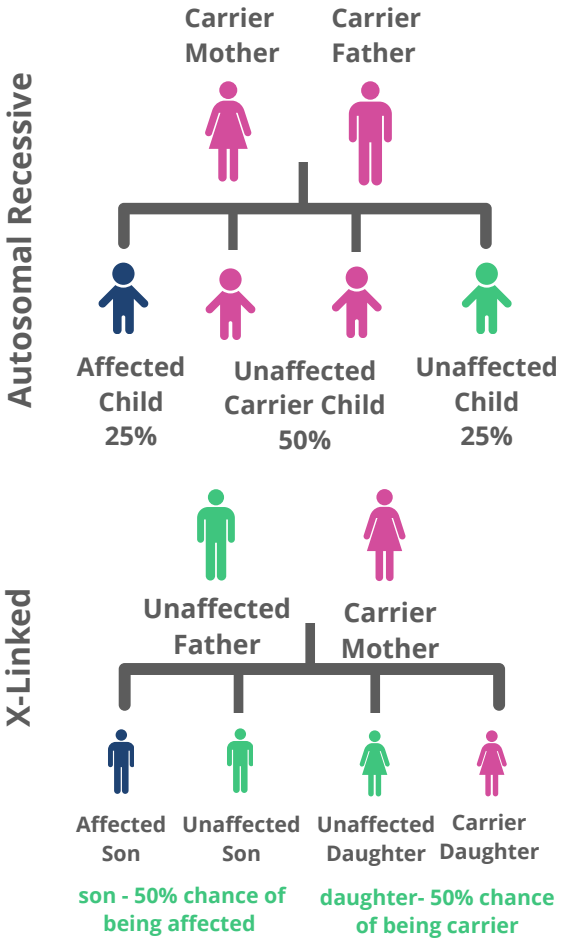
Genetic traits and conditions are passed down through families through DNA. DNA is stored in every cell in the human body and provides instructions for the body to function. Most DNA is stored in the nucleus of the cell. The nucleus functions as the control center of the cell, guarding the instructions (the DNA) and using them to guide the cell's function. Another part of the cell, the mitochondrion (plural: mitochondria), has its own unique DNA. This mitochondrial DNA is much smaller and assists the mitochondria in their function (energy production).

There are two major divisions of genetic inheritance: **nuclear** and **mitochondrial**. Nuclear inheritance indicates that a trait is passed down by DNA in the cell nucleus while mitochondrial inheritance indicates that a trait is passed down by DNA in the mitochondria of the cell.

Nuclear Inheritance

DNA is organized in pairs of chromosomes, one from each parent. Sometimes, for a disease to occur, both copies of a gene need to be affected. This is called **autosomal recessive inheritance**. In recessive inheritance, having one unaffected copy of a gene is enough to prevent disease. Someone who has one affected and one unaffected copy of a gene is called a **carrier**. Two people who are carriers of a certain condition have a 25% chance of having an affected child.

Another type of inheritance, called **X-linked inheritance**, is passed through the X chromosome. Most biological females are born with two X chromosomes, while most biological males are born with one X and one Y chromosome. Typically, X-linked inheritance disproportionately affects males as they only have one copy of the X chromosome. Conditions are often passed from an unaffected (carrier) mother to an affected son.

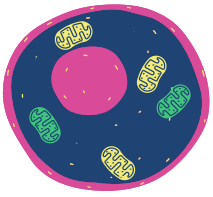


Mitochondrial Inheritance

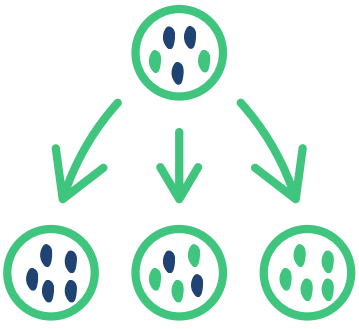
Mitochondrial DNA is passed maternally (mother to children) and is often harder to predict. In each cell, there are many mitochondria, each with their own set of DNA which can differ, called **heteroplasmy**. Most people with Leigh Syndrome have affected and unaffected mitochondrial DNA. Typically, the higher the proportion of affected mitochondrial DNA, the more severe the symptoms.

During conception, egg cells receive a random assortment of mitochondria. The mitochondria in sperm cells is lost during fertilization of the egg, meaning that affected men cannot pass mitochondrial DNA variants to children. Maternal inheritance is more complicated because of the random nature of the mitochondrial DNA assortment in each egg cell. For instance, a mother with 40% affected mitochondrial DNA could produce egg cells with anywhere from 0% to 100% affected mitochondrial DNA, completely by chance.

Heteroplasmy: Different mitochondria in the cell have different DNA



Homoplasmy: All of the cell's mitochondria have the same DNA



When mitochondria are passed down, they sort randomly. This means children can be less, equally, more severely affected, or even completely unaffected.

Leigh syndrome can also be caused by a *de novo* mutation, which is a type of mutation in either nuclear or mitochondrial DNA that occurs spontaneously in the affected individual and is not inherited from either parent.

ASSISTIVE REPRODUCTIVE TECHNOLOGIES

Prenatal Diagnosis (PND)

Prenatal diagnosis is offered for most pregnancies and is the only available option for pregnancies that are already in progress. Chorionic villous sampling is offered between 11- and 12-weeks' gestation and tests placental cells, while amniocentesis is offered between 15–17 weeks' gestation and tests fetal cells in the amniotic fluid. PND can detect the presence of nuclear DNA variants in the pregnancy and help inform pregnancy decisions or early interventions. PND can also detect presence of mitochondrial DNA variants, however testing for mitochondrial DNA variants is not as precise because the correlation between fraction of affected mitochondria and severity of symptoms is not confidently known for all variants. Additionally, PND for mitochondrial DNA variants is not available for all variants or in all countries.

Preimplantation Genetic Diagnosis (PGD)

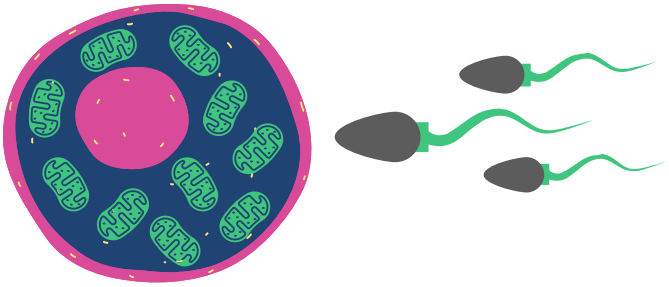
Preimplantation genetic diagnosis is an in-vitro fertilization technique in which eggs and sperm are collected from prospective parents, the eggs are fertilized in the lab to create embryos, and then the embryos are screened for genetic variants prior to transfer to the uterus. PGD is used for nuclear DNA variants for a variety of conditions but testing for mitochondrial DNA variants is new and not performed in all countries. PGD for mitochondrial DNA variants is a risk-reducing but not risk-avoiding procedure as it allows couples to select for embryos with lower fractions of affected mitochondria but the embryo distributions occur by chance. PGD may not find any embryos with low fractions of affected mitochondria and is often not helpful for women with high affected fractions. Moreover, as a reminder, the correlation between fraction of affected mitochondria and severity of symptoms is not confidently known for all variants.

Mitochondrial Donation

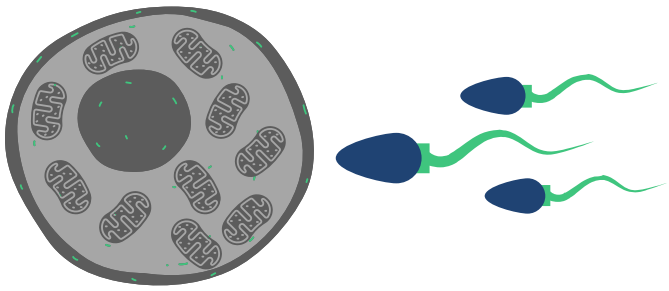
Women with affected mitochondria may be interested in an intervention called Mitochondrial Replacement Therapy (MRT). MRT is a form of in-vitro fertilization in which a woman’s eggs are collected and their affected mitochondria is replaced with healthy mitochondria from a donor. This is achieved by a couple different techniques, but MRT is not currently available in the United States. MRT differs from egg donation in that the nuclear DNA passed on to the child comes from the mother, only the mitochondrial DNA is from the donor.

OTHER FAMILY PLANNING OPTIONS

Sperm Donation
As mentioned above, men with mitochondrial DNA variants cannot pass them on to their children. However, men with nuclear DNA variants can and may choose to use a sperm donor to avoid this.



Egg Donation
Women with either nuclear or mitochondrial DNA variants may choose to use an egg donor. Utilization of an egg donor allows affected women to carry their child but the nuclear DNA that contributes to the child will consist of the father and the egg donor.



Adoption
Adoption remains a family planning option for all individuals, whether affected with nuclear or mitochondrial DNA variants.

Acknowledgements
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