

## **Summary – Genetic Inheritance in Mitochondrial Disease Fact vs. Fiction**

**Dr. Katherine Sims**

Dr. Sims is the director of the Developmental Neurogenetics Clinic at MGH in Boston, MA and is a member of the MitoAction Medical Advisory Committee. Dr. Sims is a practicing clinician and researcher with interests in mitochondrial and energy metabolism disorders as well as genetic counseling for neurogenetic disorders.

### **What are mitochondria, and mitochondrial disease?**

Mitochondria are complicated organelles involved in the complex cellular activities of multiple proteins whose end product is ATP. **They are, therefore, essential in the production of energy for the human body to function.**

The electron transport chain is an important part of mitochondrial function. There are five (5) multi-protein complexes that are part of this chain, and each has multiple protein parts. These use oxygen, take protons, transfer electrons, and otherwise provide energy to ATP to be stored. Again, this gives the cell the energy it needs to accomplish that particular cell's function.

It is important to note that today's discussion is about **Primary Mitochondrial Disease**; that is disease caused directly by mutated, damaged or deleted mitochondria. Secondary Mitochondrial Disease can occur when these organelles are damaged or under stress due to other diseases like Parkinson's or Alzheimer's. The connection between other diseases and Mitochondrial Disease is being studied. Primary Mitochondrial Disease can be due to mutated genes that are passed on or inherited or can be sporadic; that is, the disease occurs for the first time in a family or is an isolated episode due to an unknown cause (also called spontaneous mutation). Sporadic occurrences are less common than inherited and are often correlated with an actual deletion of the mitochondria. Less is known about this form of primary disease.

### **Is mitochondrial disease always inherited?**

Mitochondria can be divided into two main genomes: **Mitochondrial DNA Genome** and **Nuclear DNA Genome**.

Mitochondrial DNA Genomes appear as double stranded organelles and make only a few proteins. Nuclear DNA, which we generally refer to as chromosomes, is what we commonly associate with most inherited diseases. **Mitochondrial disease may be inherited from the mitochondrial DNA, from the nuclear DNA, or can occur as a spontaneous mutation.**

### **Mitochondrial DNA Disease**

This is a very small piece of DNA and makes only 13 proteins which are part of the electron transport chain. In the 1980's these were the first Mitochondrial Diseases identified based on a single change in one of these 13 proteins and how this one change could cause certain specific symptoms. Over time more changes have been recognized, symptoms and syndromes identified and then named. We actually have

lists of nucleotide changes in mitochondrial DNA and the human function affected by this change.

From an inheritance standpoint, these syndromes/changes are transferred only in the eggs and, therefore, are transmitted from the mother. When the egg is fertilized, the mitochondrial DNA is duplicated and will get passed on to the next generation. ALL mitochondrial DNA (mtDNA) comes from the egg, including any mutations in the mtDNA. However, not all the DNA is mutated, so as the egg duplicates and multiplies, there is a mix of both normal and mutated DNA. This will continue to mix in an almost mosaic-like pattern as the egg combines with the sperm. The percent of mutated mitochondrial DNA versus unaffected DNA will vary, and as cells differentiate and develop, the cells affected (i.e., GI, cardiac, central nervous system, etc.) will determine the extent and kind of disease symptoms an individual will inherit.

It is also possible for Mitochondrial DNA to sustain a deletion (for example, due to injury/trauma/physiologic stress). This type of disease is not familial and would not be inherited. The loss of specific Mitochondrial DNA could result in very specific problems/symptoms.

### **Nuclear DNA Disease**

There are many more proteins encoded in the Nuclear DNA (the number is estimated to be anywhere from a low of 100 to a high of 1200), and they occur primarily in electron transport chains. The proteins have complex functions, and scientists are just beginning to understand them. If problems occur in the Nuclear DNA, the transference to the next generation would not be just through the mother (egg) but would follow standard Mendelian Laws of Inheritance. Those that are Autosomal Recessive would have a 25% risk of inheritance (in this case both parents would appear normal or without disease). Autosomal Dominant disease would have a 50% risk of inheritance. Under these laws there is also the possibility for the disease to be X linked, meaning the defect is carried on the X chromosome so the female is the carrier and males would be more likely to inherit the disease. This appears to be a rarer form of Nuclear DNA Disease at this time. It is now understood that many of the mitochondrial disorders which appear in infancy are autosomal recessive.

Currently there are 40 identified Nuclear Genes which cause Nuclear DNA Mitochondrial Disease (there may be as many as 1200). These account for the majority of Mitochondrial Diseases identified in children. They can be very complex, onset is usually in infancy or childhood, and may be severe. Since these are encoded in the nuclear genes, this type of mitochondrial disease can be inherited from either parent.

### **How do we Diagnose Mitochondrial Disease?**

There are several means to detect and diagnose Mitochondrial Disease. Gathering as much data as possible through histories and extensive physical exam begins the process. Blood (serum), skin, cerebral spinal fluid (CSF), urine and muscle may be tested. Genetic tests allow the DNA to be sequenced to identify the exact location of the mutation or deletion; however, Nuclear DNA is much more difficult to pinpoint than mtDNA. Clinical manifestations are often difficult to distinguish from other diseases, so symptoms and family history are usually considered as well. However, the diagnostic

process remains difficult. Since most inherited mitochondrial diseases are autosomal recessive, neither parent has symptoms. With dominant inheritance patterns the disease occurs in each generation and is passed on. Nonetheless, the variability of symptoms, severity and expression patterns make even these cases difficult to diagnose. Muscle biopsy is used in order to narrow down the precise nature of the disease, but has a potential for false results as well, again due to the complexity of the disease and the diagnostic process.

All diagnostic methods can be useful, yet Dr. Sims continues to attempt to consider the extent of how aggressive diagnostic procedures should be. Clinicians can usually distinguish between Mitochondrial DNA and Nuclear DNA (but not always). In addition, today there is no direct way to treat or correct these diseases. The treatment modalities for all forms of the disease is to decrease mitochondrial stress and to use vitamin/mineral supplements (see the "Mito Cocktail"). Some researchers are focusing on compounds which boost mitochondrial function and would therefore have a direct therapeutic effect for people with a mitochondrial dysfunction or disease. Aggressive diagnostic procedures may not change the management of the disease, but some would advocate for the clearest diagnosis possible.

*Special thanks to Joanne Turco, PhD RN for assistance in compiling this summary*