



Complex Child E-Magazine

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Diagnosing Mitochondrial Disorder: Our Journey through the Genetic Jungle by Melody Pohla

Mitochondrial Disorder? Respiratory chain deficiency? These words were as foreign to me the first time I heard them as if the doctor who suggested them was speaking another language. This was a diagnosis the neurologist mentioned as a possibility for my then ten-month-old son. My mind was spinning as I went home to do what I always do to be an informed parent...research. The things I read were frightening and bleak. I could not believe this could be true! But, the more I read, the more I realized that many of the symptoms not only fit my baby to a tee, but they also explained so much of what we were seeing in my then two-year-old son. They just made sense. This was strangely a relief to me as we had been struggling with trying to figure out my older son's issues for years before my second son was even born. It was then that our journey with Mitochondrial Disorder began.

My boys had always been a puzzle from the moment they were born. Each was affected with symptoms that were different, yet so much the same. Not one of their doctors had any idea what to make of them or how to get to the bottom of what was going on with them medically. We had a list of specialists a mile long who were treating every symptom they had in isolation. What we really needed was someone who could look at the "big picture" and painstakingly piece together a diagnosis from all the seemingly unrelated issues. When Mitochondrial Disorder was first mentioned, it seemed to explain everything my boys were dealing with, but finding out if this was truly what was affecting my sons proved to be an exceptionally difficult task. It was a long journey through a number of doctors, countless tests and procedures, and even out-of-state travels in pursuit of ever-elusive answers.

Mitochondrial Disorders are believed to affect 40,000-70,000 people in the United States. Researchers are discovering that this disease, formerly thought to be rare, affects many more people than originally believed. Mitochondrial Disorder is a relatively new diagnosis and is still poorly understood by most medical professionals due to the lack of research and information available. Because this disease is so newly recognized, it is difficult to diagnose and even more difficult to determine how each individual became affected with it in the first place.

Our Journey through the Genetic Jungle

For two years, we have been searching for answers that would explain my two oldest children's constellation of symptoms, which include fatigue, poor stamina, exercise intolerance, low muscle tone, poor growth, short stature, inability to gain weight, GI issues, poor suck/swallow reflexes, heat/cold intolerance, enlarged liver, reactive airway disease, myopia (nearsightedness), slow speech development, immune deficiency, heart murmur, and developmental delays. After extensive labwork, diagnostic procedures, and a muscle biopsy result positive for Mitochondrial Disorder in my middle son, our new doctor recommended pursuing further testing to discover more specific information on the exact type of Mitochondrial Disorder the boys have.



Medical science is moving very quickly with new discoveries being made every day in regards to the diagnosis and treatment of Mitochondrial Disorders. In the two short years that we have been on this journey, a number of new tests have been developed or existing tests have been improved to include more and more diagnostic information. Mapping of both nuclear DNA and mitochondrial DNA (mtDNA) is being expanded to include more and more genes all the time.

Even with all the advances being made every day in this field, our neurologist cautioned us that we might never find the genetic cause behind our boys' Mitochondrial Disorder. There is still much to be learned, studied and discovered. We accepted this in stride, and

as long as we had a general diagnosis and knew how to effectively treat our children, knowing the exact genetic cause was not our priority. We knew that looking for the genetic cause would be like looking for a needle in a haystack and would not change much as far as their treatment was concerned. We came to terms with this and were OK with the possibility that we may never know the exact cause.

First we had to determine whether the Mitochondrial Disorder was primary, meaning it was the main disorder, or whether it was secondary to something else, meaning the malfunction of the mitochondria was caused by another disorder. My middle son, because he was the one who had the muscle biopsy performed, was then tested for several other genetic disorders commonly associated with Mito, including Prader-Willi and Fragile X. Once we were able to eliminate another primary diagnosis, we began testing to look for their specific type of Mitochondrial Disorder, first testing for types that fit most closely. One of these was a simple blood test for MNGIE (MyoNeuroGastroIntestinal Encephalopathy), because of their gut issues.

We also ran the newest version of the mtDNA blood test, even though it had turned up nothing during previous rounds of testing. Both boys have had several blood tests in the past 18 months and each time, the results came back negative for all known mutations. Even as recently as fall, 2007, a newer mtDNA test was run on my son's muscle tissue and it came back with no abnormalities. Just this year we were told about the most updated version of the mtDNA blood testing, a more complete version, and we were urged by our doctor to retest. We readily agreed, even though we knew the chances were slim to none that it would show anything different than any of the other previous testing. To our utter surprise and shock, this latest round of testing did come back with a genetic mutation and several polymorphisms.

Even more surprising than the discovery of a mutation was the fact that this same mutation and every single polymorphism was present not only in one son's testing, but in both of theirs. In other words, the boys' testing came back identical. Our neurologist took several weeks researching and comparing our children's results to the literature that was available and realized that this mutation was one that was not previously recorded in anything she found. The mutation and every polymorphism were all located on one specific mtDNA gene. It is called the ND1 gene and governs the complex 1 function of the respiratory chain (Krebs cycle). Because my middle son's muscle biopsy showed moderately reduced function in complex 1, it was determined that this was indeed the cause of the Mitochondrial Disorder in both of my boys, and that it was maternally inherited because it was found on the mtDNA that is inherited from the mother. Their final diagnosis is Mitochondrial Cytopathy with a Complex I deficiency, the most common diagnosis out of the respiratory chain deficiencies. We had found our needle in a haystack.

How Mitochondrial Disorders May be Inherited

While my sons' Mito is maternally inherited, according to the United Mitochondrial Disease Foundation (UMDF), nearly all models of inheritance from parent to child are demonstrated with Mitochondrial Disorder.¹ Inheritance modes include autosomal recessive, maternally inherited, X-linked recessive, autosomal dominant, and sporadic or spontaneous mutations. Please see Table 1 for a description of these different models of inheritance. The majority of Mitochondrial Disorders discovered thus far are found within the autosomal recessive or maternally inherited models.

Autosomal recessive inheritance is demonstrated in many forms of Mitochondrial Disorder including defects within the respiration chain, also known as the Krebs cycle (complex deficiencies), disorders of fatty oxidation (FODs), and transporter disorders. This form of inheritance is characterized by the affected individual receiving one faulty gene from each parent. These genes are located within the nuclear DNA found inside each cell of the body and contain genetic information that affects the mitochondria. Each parent must be a carrier of the disorder, meaning they carry only one faulty gene and are unaffected with symptoms of the disorder. The chance of two carrier parents having an affected child is 25% and the chance of having a child who is a carrier is 50%. Affected siblings with this form of inheritance usually present with symptoms very similarly. This group includes the most severe forms of the disorder.

Maternally inherited Mitochondrial Disorders, like the one affecting my children, characterize a completely different type of inheritance pattern as the DNA involved is not nuclear DNA like in all other forms of inheritance. This defect is located within the mitochondrial DNA (mtDNA) inside each cell, which is a completely different set of DNA than the nuclear DNA and is received from the mother. The mtDNA do not divide equally as the nuclear DNA do, so the individuals affected with this form can have markedly different degrees of involvement, depending on the amount of the affected mtDNA received from the mother. Different body systems may also be involved, depending on where the affected mtDNA is located within the body. The mother is usually affected in this form of inheritance. Siblings with this form of inheritance are not necessarily affected in the same ways. Boys who are affected will not pass this disorder to their children, but girls will. Some examples of maternally inherited Mitochondrial Disorders are MELAS, MERFF, LHON, NARP, and some forms of respiratory chain deficiencies.

Mitochondrial Disorders that are inherited in other ways include Pyruvate Dehydrogenase Complex deficiency, which is an X-linked recessive Mitochondrial Disorder, and a rare form of Kearns-Sayre syndrome that is an Autosomal dominant Mitochondrial Disorder.

Table 1: Models of Inheritance

Autosomal Recessive	Both parents are carriers of the genetic disorder, which appears on any of the 22 chromosome pairs other than the sex chromosomes. In other words, each parent has one affected chromosome and one unaffected in his/her individual pair. Because each parent contributes only one chromosome to the child, only some children are affected. In recessive disorders, both parents must contribute the affected chromosome for the disorder to be present.
Maternally Inherited	Mitochondria and mitochondrial DNA (mtDNA) are typically inherited from the mother. If a mother is a carrier of a gene that presents in the mitochondria or mtDNA, she will pass it on to her children, who are usually affected.
X-linked Recessive	The disorder is found on the sex chromosome, which is typically XX for females and XY for males. X-linked recessive disorders are inherited through the X chromosome and usually only affect males since males receive only one X chromosome. If it is a faulty X chromosome, there is no normal copy and thus, they will be affected. Females are usually carriers since they receive two X chromosomes. The unaffected X chromosome is the dominant one and therefore there is no expression of disease characteristics due to the presence of the normal X copy. Boys have a 50% chance of inheritance with this type and girls have a 50% chance of becoming a carrier and passing the faulty gene to future children.
Autosomal Dominant	At least one parent is a carrier of the disorder, which appears on any of the 22 chromosomes other than the sex chromosomes. Since it is a dominant trait, a child only needs to receive one copy of the affected chromosome to have the genetic trait.
Sporadic/Spontaneous Mutations	Neither parent carries the disorder. A random gene mutation occurs for unknown reasons.

There is not much information known about sporadic or spontaneous inheritance as it pertains to Mitochondrial Disorders, since they can be caused by any number of contributing factors, including genetic and environmental causes. It is thought that as many as 75% of cases of Mitochondrial Disorder are the result of spontaneous mutations.²

The Importance of Getting a Genetic Diagnosis

Our genetic diagnosis was an especially important discovery to our family because, at the time of discovery, we were expecting a new baby any day and we had been worried about if and how this baby would be affected. Knowing that now there is a specific gene mutation to test for means that our new baby will not have to undergo the extensive testing our older boys did. He will need only one simple blood test to look for this mutation. It also means that we can begin to look back within the maternal line of my own family to see who else may be affected. We realize just how lucky our family is to have been able to find an identified genetic mutation so soon after diagnosis.



Not only has this discovery meant a lot to my own family, but it will also mean a lot to medical science. The vast majority of individuals diagnosed with Mitochondrial Disorder have yet to discover what is causing their disorder because either their genetic mutation has not yet been identified or the current testing is not sophisticated enough at this time to determine where their mutation lies. With the advent of new and improved for this

disorder and the discovery of new mutations as well, researchers can use all this information to make diagnosis easier for everyone who will be diagnosed in the future.

For us, finding our genetic “needle in a haystack” was made possible by the fact that we had chosen to take our boys to see one of the top Mitochondrial Disorder specialists in the country. We have a long history of well meaning but inexperienced doctors who did not know enough about Mitochondrial Disorders to diagnose the boys. Because Mitochondrial Disorders were originally thought to only be present in severe forms, many doctors are currently unaware that medical research has now discovered Mito comes in milder forms that may or may not be progressive and degenerative. These milder forms are not easily recognized or diagnosed. Because of this, we ran into the roadblock of, “But they look too good to have Mito!” many times on our journey, which made the doctors unsure of how to effectively treat the boys. This is likely the biggest issue Mito families have with pursuing a diagnosis for their loved one.



After running into this same problem with two different local doctors, we chose to travel to a doctor specializing in Mitochondrial Disorders to seek help. Upon returning, we discovered another Mito specialist right in the town where we live, and her extensive knowledge and research of Mitochondrial Disorders enabled us to finally reach a diagnosis. Without having seen someone specializing in diagnosing and treating Mitochondrial Disorder, we may have never reached a diagnosis at all.³

Thanks to the extensive knowledge of a doctor who specializes in the diagnosis and treatment of Mitochondrial Disorder, we now know what is affecting our boys. They now receive specialized treatment, take their own version of the Mito Cocktail, have written protocols for illness and hospitalizations, know what precautions to take for anesthesia, and have annual testing to monitor for disease progression. We are watching them thrive under the care of our wonderful doctor. Because we now know our diagnosis and what we need to do to treat it, we can ensure they have the brightest future possible.

Melody Pohla lives outside of Houston, Texas and is a stay at home mom to three wonderful little boys: Nicholas who is 5, Nathan who is 3, and Daniel who just turned 8 weeks old. In her former life, she was a teacher of 3rd and 4th grade students for six years. Since early on in her oldest son's life, she has researched and educated herself about everything dealing with her children's medical diagnoses as she feels the best advocate for her kids is an informed parent. Living daily with Mito has not been easy, but her boys are amazingly resilient and live life to the fullest without regard to any of their medical diagnoses. She and her husband have been active in promoting Mitochondrial Disorder awareness in their community and their boys have just taken part in an ad campaign for the hospital that treats their Mito. She is also active on a support board [<http://www.parent-2-parent.com/forum/>] for parents of children facing Mito or related metabolic disorders and those on the journey to a diagnosis for one of these disorders. Please visit the boys' Caringbridge site [<http://www.caringbridge.org/tx/nicholasp/>] or check out their story on the CMHH website [http://www.memorialhermann.org/services/PS_Pediatric_CH_NichNath.html].

¹ See the UMDF's section on genetics at <http://www.umdff.org/site/c.dnJEKLNqFoG/b.3042179/>

² See the UMDF's section on sporadic cases at

<http://www.umdff.org/site/c.dnJEKLNqFoG/b.3042179/#SporadicCases>

³ A new article provides in depth information on diagnosis. See The Mitochondrial Medicine Society's Committee on Diagnosis, Richard H. Haas, *et al.* "The in-depth evaluation of suspected mitochondrial disease." *Molecular Genetics and Metabolism* 2008;94(1):16-37. For an overview of useful tests to diagnose Mito, please see <http://www.umdff.org/site/c.dnJEKLNqFoG/b.3752521/>