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## Three-Parent Baby: Mitochondrial Diseases and Gene Therapy

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# Three-Parent Baby

## Mitochondrial Diseases and Gene Therapy

ALEXA ARAKAKI



Honors 491 (Junior Seminar)  
Mentor: Dr. Zoia Stoytcheva

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*Mitochondria provides energy to sustain life and is inherited by the mother. If a female is diagnosed with mitochondrial disease, if trying to get pregnant, her fetus will inherit her damaged or mutated mitochondria. This results in babies who develop mitochondrial disorders, resulting in life-threatening diseases such as MELAS, LHON, Leigh's Disease, and Barth Syndrome. One of the methods to solve this maternal issue is for the woman to undergo mitochondrial replacement therapy. This treatment involves replacing the diseased mitochondria in the mother's egg with the healthy mitochondria from a donor egg, then fertilizing the reconstructed embryo with the father's sperm. As this is a novel treatment, long-term effects of embryonic manipulation are still unknown.*

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“He was our eighth... Gone too soon.” Jen curled up into a ball, urging the wave of deep sorrow to subside. The emotions were too strong. Eight babies, she and her husband have lost to mitochondrial disease. A part of her blames herself because the disease was passed from her to her babies. They keep trying. What can she do to earn just one angel here on Earth? On the stormy night of her eighth child's death, she decided to research the mitochondrial disease thoroughly. She would find any scientific advances to find a way to have a healthy child.

Jen took out her laptop and searched “Mitochondrial Disease Patients.” Thousands of children popped up. These children had breathing tubes, were confined to wheelchairs, and were very sick. Children's Miracle Network Hospitals had an

exceptional patient named Nathan. He was born with mitochondrial disease and visited the hospital frequently for blood work, to check on his breathing tube, therapy appointments, and to get his medication. Despite all his hardships, he had a positive attitude and a caring outlook on life: he was a happy boy. Many patients visited Cleveland Clinic Children's Hospital due to mitochondrial disease conditions. They suffer the consequences of a faulty gene. Their parents, who like Jen and her husband, were strong people who support and care for their children. To lose a child to disease is devastating, but to keep trying and learning is a strength, Jen did not know she had. She sat at her desk night after night, pulling up article after article. Here is the information she found...

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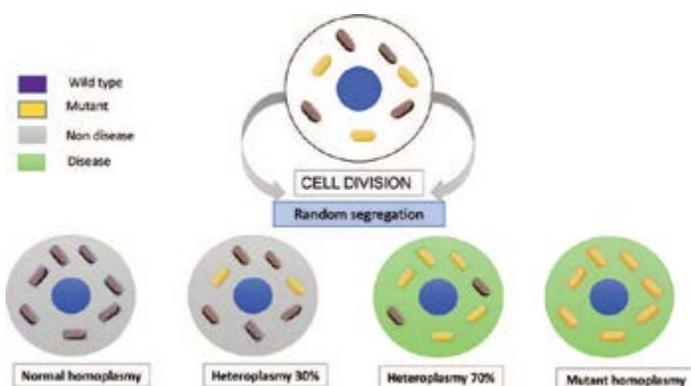
This paper was written for the Honors 491 class, instructed by Dr. Zoia Stoytcheva. I am a University of Hawai'i at Mānoa junior majoring in biology with the aim of pursuing a career in the medical field. I have always looked up to mothers and found it fascinating that the human body can create and shelter life. I discovered my passion for reproductive biology because I was interested in how humans form cellularly in an embryo. I wanted to research more about what takes place in embryos and mothers to birth children who are genetically sick. One of the diseases I found had to do with the mitochondria, which is maternally passed down. I did literature and narrative review, hoping to intertwine a relatable storyline with cellular knowledge. In doing so, I am hoping that my writing connects with all audience members and hope that it raises awareness about the emotional and physical trials that mothers face when trying to get pregnant, in the hopes of giving birth to healthy children.

## Mitochondria

The mitochondria are the energy plants of the cell, providing energy to sustain life. They are cell organelles found in the cytoplasm and are 0.75 to 3.0 micrometers long. Mitochondria have their own DNA, called mitochondrial DNA, or mtDNA for short. A few facts about the mtDNA is that they contain 16,500 base pairs and 37 genes (Genetics Home Reference, n.d.). Out of those 37 genes, 13 encode enzymes that are involved in oxidative phosphorylation (Genetics Home Reference, n.d.). The other 24 genes encode for tRNA and rRNA. There are ~ 1,000 copies of mtDNA per cell (Genetics Home Reference, n.d.).

Mitochondria are inherited by the mother. Oocyte, the biggest cell in the human body, contains from 100,000 to 600,000 mitochondria per cell. Contrary to that, sperm cells are the smallest and consist of a head, neck, and tail. The nuclear DNA is tightly packed into the sperms' head, while the mitochondria are localized in the neck of the sperm cell. During fertilization, only the head of the sperm passes the zona pellucida (the outer layer of the oocyte) while the neck of the sperm is cut out and dissolved. Thus, mitochondria are only from the mother and therefore transmitted through the maternal line. In terms of nuclear DNA, half comes from the father and the other half from the mother.

Mitochondrial diseases are disorders caused by damaged or mutated mitochondrial DNA. More than 60% of mtDNA molecules need to be mutated for a disease to emerge (Haskett, 2014). Jen found out that 1 in 5,000 people have a mitochondrial disease (Haskett, 2014). There are homoplasmic mtDNA and heteroplasmic mtDNA (Haskett, 2014). Homoplasmic mtDNA is when the daughter cell receives mitochondria with either purely healthy mtDNA or purely mutant mtDNA. Heteroplasmic mtDNA is when the daughter cell receives mitochondria as a mixture of normal and mutant mtDNA.



**Figure 1** Homoplasmic vs. Heteroplasmic mtDNA (11)

## How Can We Detect the Defects in the mtDNA?

A procedure that can detect genetic defects within embryos is called Preimplantation Genetic Diagnosis (PGD). This is an assisted reproductive technology technique used to scan embryos in Fertility clinics. After the egg is fertilized by the sperm, an embryo is created. PGD is done when the embryos are 5 days old. One or two cells are removed from the embryo and placed in a tube; then are analyzed and screened by a technique called FISH to check for genetic disorders (Fernandez, 2019). If any defects are found, the embryo will not be transferred. The embryos free from genetic abnormalities are transferred back to the mother's womb.

The most common mitochondrial disorders are Mitochondrial Encephalopathy, Lactic acidosis, and Stroke (MELAS), Leber Hereditary Optic Neuropathy (LHON), Leigh's Disease, and Barth Syndrome.

MELAS disease symptoms appear in humans before 20 years old. They include stroke (paralysis), dementia (memory disorders, personality changes, impaired reasoning), brain dysfunction (encephalopathy) with seizures & headaches, and muscle disease (Shiel, 2016). The most serious symptom of MELAS is the build-up of lactic acid in the blood (lactic acidosis) which leads to vomiting, abdominal pain, fatigue, muscle weakness, loss of bowel control, difficulty breathing, muscle spasms, and diabetes (Shiel, 2016). This disease is diagnosed with a muscle biopsy, which would show ragged red fibers and a brain biopsy, which would show stroke-like images (Shiel, 2016).

Another common disease called LHON's disease affects 1 in 50,000 people (NORD, n.d.). It is denoted with visual loss of the central vision, blurring, and reduced perception of color beginning in young adulthood (NORD, n.d.). The disease is caused by degeneration of the optic nerves and retina. Patients usually lose vision in one eye first, then lose vision in the other eye (NORD, n.d.). To continue, Leigh's Disease is caused by 26 mutations (Genetics Home Reference, n.d.). Symptoms appear within a few months and include the inability to suck, to control head motions, to walk, and to talk (Genetics Home Reference, n.d.). There is also irritability, loss of appetite, vomiting, seizures, heart, kidney, vision, and breathing complications (Genetics Home Reference, n.d.). This disease is found in the brain by an MRI and is denoted by dying tissue or lesions (Genetics Home Reference, n.d.).

The last disease Jen discovered is called Barth Syndrome. This disease is present at birth or within the first few months (ITV, 2012). Its symptoms include heart failure, growth delay, weakness in muscles, and a weak immune system (ITV, 2012).

## Current Treatments for Mitochondrial Diseases

Mitochondrial disease, treatments come in the form of vitamins and supplements such as CoQ10, vitamin K, vitamin C,

L-carnitine, exercising, conserving energy, and speech, physical, respiratory, or occupational therapy. There is also a method called mitochondrial replacement therapy (or three-parent baby). It gives women with mitochondrial DNA mutations a high chance of having a child-free of mitochondrial disease. This treatment involves a third parent with healthy mtDNA. The child would still have the two parent's nuclear DNA, but also possess the female third parent's healthy mtDNA. In vitro fertilization produces an embryo with nuclear DNA from the father and mother along with healthy mtDNA from the female donor (Cree and Loi, 2014). It utilizes two techniques: the maternal spindle method and the pro-nuclear (PN) injection method. The spindle method involves the mother's egg and a healthy donor's egg. Chromosomes are removed from the mother's egg (Mitochondrial Replacement, 2014). The mother's egg, which contains the unhealthy mtDNA, is then discarded. Separately, a donated egg with healthy mitochondria has its chromosomes removed and discarded, leaving behind healthy mtDNA (Mitochondrial Replacement, 2014). The spindle-like chromosomes taken from the mother's egg are inserted into the donor's egg. The new, reconstructed egg now contains nuclear DNA from the mother and healthy mitochondria from the donor. The resulting egg is ready to be fertilized by the intended father's sperm, and the resulting embryo will be implanted into the mother (Mitochondrial Replacement, 2014).

The PN injection method, on the other hand, uses unfertilized eggs instead of early embryos. This method involves the removal of the two pronuclei (Mitochondrial Replacement, 2014). This technique leaves behind the mother's unhealthy nuclei. The cell without nuclei is discarded. Separately, a second embryo is created from a female donor with healthy mtDNA and the intended father's sperm (Mitochondrial Replacement, 2014). The second embryo is also enucleated at day one. The pronuclei of the intending parents are then inserted into the second enucleated embryo. The new embryo now has the DNA of the intended parents and the healthy mitochondria from the female donor's egg (Mitochondrial Replacement, 2014). The reconstructed embryo can be transferred back into the mother to develop healthily.

### Mitochondrial Gene Therapies/ Mitochondrial Donation

This gene therapy treatment has only been tested in human cells grown in Petri dishes. Gene therapy recognizes then eliminates the mutant mtDNA with mitochondrially targeted zinc finger-nuclease (mtZFN) or mtTALEN (Drug Target, 2018). MtZFN recognizes then eliminates mutant mtDNA, leaving healthy copies. This gene therapy method is meant to destroy the mutated DNA, which allows healthy DNA to take its place. This could be an alternative to mitochondrial replacement therapy.

Mitochondrial Donation (MTD) is a recently developed technique, where a donor egg containing the healthy mitochondria is enucleated and then substituted with the mother's nuclear DNA (Sharpe, 2019). This hybrid oocyte is then fertilized and transplanted. This procedure is preceded by the genome analysis of the donor and recipient (the mother) to assure a good match.

### Successful and Unsuccessful Gene Therapy Trials for Mitochondrial Disease

RAAV2-ND4 (recombinant Adeno-Associated Virus-NADH dehydrogenase, subunit 4) gene therapy was successfully used in clinical trials to treat Leber's Hereditary Optic Neuropathy (LHON) (U.S. National Library, 2010). This study included 9 participants. It started in 2011 and ended in 2015. Patients were administered an injection of the rAAV2-ND4 drug, through the right or left eye. The region of enrollment was in China and consisted of an Asian patient population. The outcome of this experiment was that visual acuity and enlargement of the visual field improved (U.S. National Library, 2010).

An unsuccessful clinical trial of mitochondrial disease treatment tested the effects of the dichloroacetate drug to treat MELAS syndrome (Eunice Kennedy, 2003). Dichloroacetate is from the chlorine disinfection of water and is salts of dichloroacetic acid. This study included 35 participants. It started in March 2000 but was terminated. The outcome of this trial was that the drug caused peripheral nerve toxicity, or damage to the nerves outside the brain and spinal cord, in patients (Eunice Kennedy, 2003). It caused weakness, numbness, and pain in their hands and feet.

### Ethics

There are many ethical dilemmas when dealing with genetic manipulation. Firstly, the U.S. government does not allow federal funds to be used for research on gene therapy on embryos. This means that no technological improvements can be made legally. Change is always something humans fear. Engineering embryos means changing the genes of future generations. Mitochondrial replacement therapy is controversial because the mitochondrial DNA of an embryo is being tampered with. The goal is to prevent "the birth of children who would be wheelchair-bound and oxygen-starved and are doomed to a slow, painful death, and whose parents must be going through hell," said reproductive biology Professor Eli Adashi of Brown University (Viswanathan, 2018). However, when defining mitochondrial replacement therapy, there is the question of it being just another form of in vitro fertilization or an early form of gene editing that could lead to riskier methods of human enhancement (Viswanathan, 2018).

## Costs of the Mitochondrial Replacement Therapy

The procedure is also costly, at \$15,000. The long-term effects of embryonic manipulation is still unknown because only a handful of babies have been born using mitochondrial replacement therapy. The ethical question is: should scientists be given the power to alter future generations of humans? There are also concerns about eugenics, which is the idea of breeding humans to be a perfect species. There is another argument that asks why women should do mitochondrial replacement therapy if in vitro fertilization or adoption exists. In the U.K., regulations exist where mitochondrial replacement therapy is only available to those who have mitochondrial DNA mutations in the egg and if the embryo will develop the mitochondrial disease. There is a lot to mitochondrial replacement therapy that we do not know. Long-term effects are unknown, which may be a risk in itself. If humans could get over the fear of the unknown, we could progress rapidly with genetic technology.

## Conclusion

If people can understand the reasons why mitochondrial replacement therapy should be researched with regulations, dramatic technological improvements can be made. Families like Jen's, affected with mitochondrial mutations, have the potential to give birth to babies free from mitochondrial disease.

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Jen took out her phone and searched up the nearest embryologist. She dialed the number given, ready, and excited to make her first appointment. "Why didn't I think of this before?" she asked herself. She found mitochondrial replacement therapy appealing—a gift from heaven. She would not mind having a healthy donor's mitochondria in her future child. As her phone rang, she started to daydream about her future baby... Her own healthy baby. A baby who can breathe without a tube, walk and run properly, not go to the hospital for a disease they had no control over. "If any parent could choose whether they could have a healthy baby or a disease-stricken baby, they would choose a healthy baby," Jen thought to herself.

To put it simply, the option is there to give her babies a chance at a disease-free life. Why would she not take it? The ringing stopped, "Hello, Fertility Institute of Hawaii, this is Gwen speaking, how may I help you?" Jen sat up straight in her chair, and her anticipation barely contained, "Hi, this is Jen! I would like to make an appointment, please?" Gwen replied kindly, "Of course! We have an opening for tomorrow at 8 am if you are available?" Jen rushed over to her husband, Mark, "Honey, are we available tomorrow morning to see a fertility doctor?" She took Mark by surprise. He was enjoying a nice bowl of chocolate ice cream and was so startled that it ended up

all over the floor. He laughed and said, "Yes, of course, we can. I am glad you're feeling better." Jen beamed up at him, and he looked at her with newfound hope in his eyes.

Jen and Mark opened the fertility clinic to pastel pink walls and a friendly receptionist. "Aloha, how can I help you?" she greeted them with a welcoming smile. Jen walked up to the desk, "Yes, we have an 8 am appointment with Dr. Kami." The receptionist checked her computer, stood up, and said, "Right this way. Dr. Kami will see you both in this room." She directed Jen and Mark to a room with a white couch and beige walls. They took a seat and waited for Dr. Kami to enter the room. Jen looked over to Mark, "I am nervous, but I have a good feeling about this one." Mark reassured her, "This will be our ninth child. However, it will be our first healthy child if this therapy works. To give our future baby a life he or she can fully enjoy. A life where our baby is not born into a crippling disease. A life where we can show our baby the world and where our baby can learn and grow well into 90 years old. I pray this therapy works. I have hope for us both." Dr. Kami walked into the room, introduced himself warmly, and sat in front of Jen and Mark. After they told Dr. Kami of their fertility struggles, of their eight past babies, and Jen's mitochondrial disorder, he sat back in his chair and looked at them both with love. He was caring, compassionate, kind, empathetic, and he would do what he could to help this inspiring couple. They set up an appointment for the next day to meet the third parent.

Jen was a bit apprehensive at first, but as soon as she met the donor, a flood of gratitude overcame her. Tears filled her eyes as she hugged her donor—Kori was her name. A sweet, soft-spoken lady who would donate her healthy mitochondria to Jen. Kori greeted her with, "How blessed am I to have this opportunity to help you have a healthy child?" Jen and Mark wept with happiness. Jen and Kori entered a small white room and met with Dr. Kami. The procedure was over in 10 minutes. Jen thought that it would take much longer. Five days later, the reconstructed embryo was re-implanted into Jen. She was overcome with joy after finding out that the fertilization was successful. She was officially pregnant.

Nine months have gone by... Nine months of ups and downs. Of doubts and praying and nesting. Jen and Mark worked together to create their future baby's room. They painted a blue sky on the ceiling and a field of sunflowers on the walls. The sky was to remind them that there are brighter days ahead. That if they keep their faith that everything would work out, they would be forever blessed. The sunflowers were there to remind them to always grow towards the light and to stand tall, even the stormiest of days. The day came when Mark rushed Jen to the hospital. Her baby was on its way. Twenty-four hours later, Jen was holding a healthy baby girl of 6 ounces. Jen and Mark could barely believe it. They were overwhelmed with love and felt so blessed to have her in their life. They named their baby girl Angel because she was their angel here on Earth.

A year later, Jen and Mark stood on a stage before 3,000

parents facing fertility problems. She spoke of her struggles to conceive and of her discovery of mitochondrial replacement therapy. She spoke of its benefits and the ethical dilemmas surrounding it. She spoke of how it had changed her life for the better and blessed her with a baby girl. She spoke of its risks and how it is not guaranteed, but how the risks are worth taking.

Jen and Mark now travel the world talking to fertility specialists and those struggling to have healthy children. They now research mitochondrial replacement therapy and are trying to discover new techniques to treat mitochondrial disease. "Ah, another successful day," Jen exclaims as she exits New York's Ted Talk building. Mark looks from his daughter to his beautiful wife, "Yes, it indeed was." Giving hope to families through the advancements of technology is something the human race should take advantage of. To have the ability to learn more about science in medicine is a passion people pour their lives into. How does it feel to know that you had a hand in creating healthy children? That you gave that lost hope back to parents in despair. Mitochondrial replacement therapy is one method to improve future generations' lives. Yes, it is scary and still developing. But it has the ability to impact and change lives for the better.

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