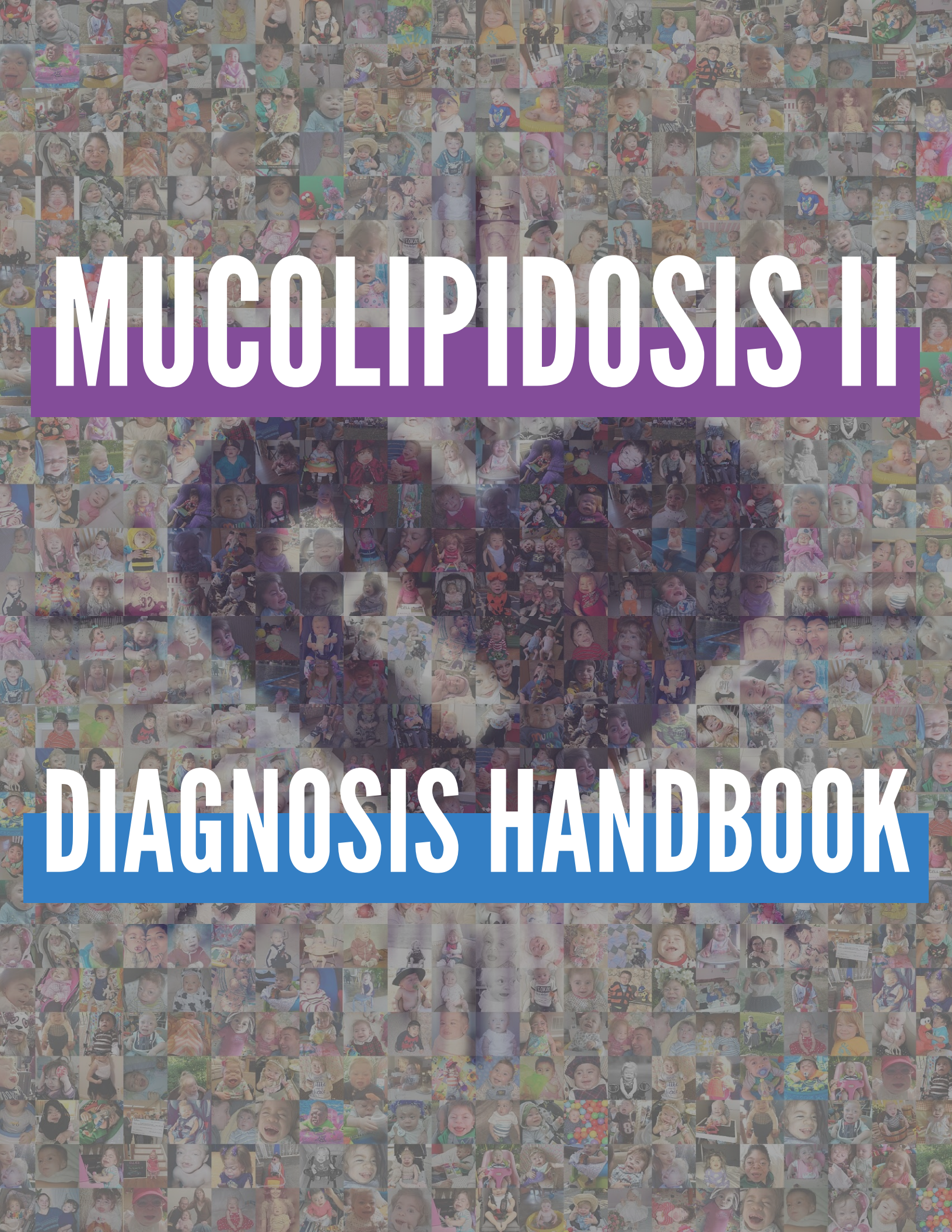


MUCOLIPIDOSIS II

DIAGNOSIS HANDBOOK

INTRODUCTION

My parents recount the moment in a way that shatters my heart.

"It's a day etched in our memory forever. Our firstborn son Yash was eleven months old when we were told that he had a terminal rare disease. He wasn't expected to live for more than four to five years and we were told there was nothing we could do apart from loving him to the fullest."

To introduce myself, my name is Kavi Gandhi. I am eighteen years old, I am from the suburbs of Philadelphia, and perhaps most importantly to those of you reading this handbook, my older brother Yash had Mucolipidosis II, also known as I-Cell Disease.

To you, reading these words, I want you to know that you are not alone. Whether you are a parent, grandparent, sibling, aunt or uncle, you are not alone. I was not there when my parents received Yash's diagnosis, but I know what you are feeling. I know and have experienced the feelings of uncertainty, hopelessness, and fear. There are so many other people who have been in the same shoes as you are in right now, and they are on standby to help you. There is a fierce community of I-Cell families across the world who will not let anything stand in their way of supporting another family.

What I can also tell you is that your I-Cell baby is a miracle baby. Those feelings of hopelessness will quickly be usurped by happiness and joy. Your I-Cell child will show you the limitless beauty of smiling, laughing, and loving. They will inspire you and every person they ever meet. You will create memories that last a lifetime. My memories with Yash, albeit from over ten years ago, are still some of the fondest memories I hold in my heart.

As you read through these pages, I hope it also brings you a sense of peace and comfort, knowing there are others out there who have traversed the same journey as you. As we like to say in the rare disease community: Alone, we are rare. But together, we are strong.

With love,

Kavi Gandhi
Development & Communications Coordinator, Yash Gandhi Foundation

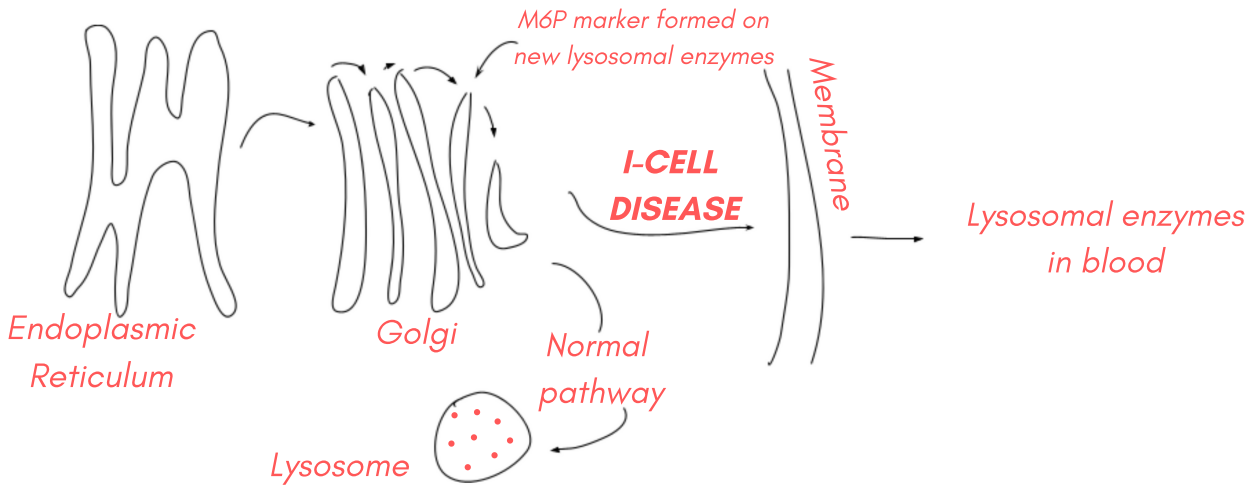
WHAT IS MUCOLIPIDOSIS II?

Mucolipidosis II, also known as I-Cell Disease is an inherited (or genetic) disease, meaning it is passed down from one generation to the next. It follows an autosomal recessive pattern of inheritance, meaning that both parents carry one copy of the mutated gene. Since they only carry one copy, the parents are not clinically affected by the disorder and are known as carriers. In order for a child to have Mucolipidosis II, they must inherit both copies of the mutated gene - one from each parent.

AUTOSOMAL RECESSIVE INHERITANCE - *Both parents carry one copy of the mutated gene. A child must inherit the mutated gene from both parents in order to have the disease.*

So, what is the mutated gene anyway? Let's begin with some basic biology.In every cell, there are organelles called lysosomes, whose function is to break down and dispose of waste that comes from the cell. To do that, the lysosomes have the assistance of proteins called enzymes, molecules that catalyze the degradation of waste material. Lysosomal enzymes are synthesized in another cellular organelle known as the endoplasmic reticulum. After synthesis, they then travel to the golgi apparatus, where lysosomal enzymes are tagged with a marker called mannose-6-phosphate. This marker is what directs lysosomal enzymes to travel to the lysosome, where they carry out their intended function.

Now, to return to our original question - what is the mutated gene with Mucolipidosis II? In simple terms, when this gene is mutated, the mannose phosphorylation of enzymes is impaired. In other words, lysosomes never have the directions to get to the lysosome and since there are limited enzymes in the lysosome, that means waste material will accumulate in the lysosome. This ultimately causes Mucolipidosis II. Because of this, the Mucolipidoses (yes, there are different types) are classified as lysosomal storage disorders.



HISTORY OF RESEARCH

I-Cell was first described by researchers Jules Leroy and Robert DeMars in 1967. Over the next five years, findings from multiple research teams allowed for the fundamental characterization of Mucolipidosis II. Some of these discoveries included the dense inclusions that arise in cells because of lysosomal waste storage, the deficiency of lysosomal enzymes in the lysosome, and a pedigree analysis that confirmed the autosomal recessive mode of inheritance.

As shown in the work pioneered by Dr. Jules Leroy and others, many significant findings were made in the late 1960s and early 1970s, but much about this newly discovered disease remained unknown. In the late 1970s and early 1980s, strides were made to define the mutation that prevents the uptake of lysosomal enzymes by lysosomes in ML II cells. Dr. Stuart Kornfeld of the Washington University in St. Louis School of Medicine pioneered much of that work that allowed researchers to identify the specific mutation that caused ML II (and more details about the gene) as well as the role of the mannose-6-phosphate marker.

When it comes to disease research, understanding the biology and pathogenesis of the disease is just as important as having a clinical understanding of the condition. In 2010, researchers executed a robust natural history study that allowed for the clinical understanding of how the disease manifests itself in different individuals.

Of course, much of the work to understand the biology of Mucolipidosis was done in a controlled laboratory setting. In addition to using cell lines derived from various sources, mice and zebrafish have been invaluable model organisms that have contributed to the advancement of research.

RESOURCES

YASH GANDHI FOUNDATION

The Yash Gandhi Foundation is a family-run 501(c)(3) organization with the mission of raising awareness, building patient advocacy, and sustaining research efforts into finding a cure for I-Cell Disease. YGF is the only organization with this specific focus on ML II, and since 2014, the Foundation has awarded nearly $800K in research grants to prominent researchers and institutions investigating ML II. In addition to fundraising and raising awareness, supporting and advocating for I-Cell families is an integral part of our mission. **Find out more at ygf4icell.org**

SUPPORT GROUPS

Like I mentioned previously, the community of I-Cell families is an incredibly supportive group of people. One of the most powerful resources for I-Cell families is the online support group we have, with over 900 members from across the world. This is a space to ask questions, air grievances, and most importantly, share photos of your I-Cell children! Email ygf4icell@gmail.com to introduce yourself and to receive the link to the support group.

FUTURE OF RESEARCH

In recent years, researchers have recognized that the basic biology, pathogenesis, and clinical manifestations of ML II are comprehensively understood. Therefore, there has been a shift towards developing viable treatment or therapy options. The following are two currently anticipated efforts for treatment:

FELINE MODEL

GENE THERAPY

Feline model - Interestingly, in cats, Mucolipidosis II is naturally occurring and they share many of the same clinical features as humans, making them a valuable model organism. Efforts are currently underway to expand the ML II cat colony at the University of Pennsylvania and treat the cats with various molecules that have been shown to remediate phenotypes in the zebrafish model.

Gene therapy - Developing viable gene therapy will require the collaboration of many seasoned experts from various institutions. Current ideas for gene therapy include the use of mRNA to rescue phenotypes and the administration of other nanoparticles with therapeutic properties.

MUCOLIPIDOSIS COLLABORATIVE RESEARCH NETWORK (MCRN)

Along with this new drive for treatment came the creation of MCRN, a global coalition of researchers and advocates from institutions like the Greenwood Genetic Center, University Medical Center Hamburg-Eppendorf, and Nationwide Children's Hospital as well as patient organizations like the Yash Gandhi Foundation, MPS Society, and ISMRD. This group allows for the exchange of ideas and resources across institutions, an ability to provide comprehensive status updates on various research projects, discussion of new discoveries and publications, and an opportunity to creatively brainstorm new paths forward. The group meets regularly once a month.

REFERENCES

Cathey, S. S., Leroy, J. G., Wood, T., Eaves, K., Simensen, R. J., Kudo, M., Stevenson, R. E., & Friez, M. J. (2010). Phenotype and genotype in Mucolipidoses II and III alpha/beta: A study of 61 probands. Journal of Medical Genetics, 47(1), 38-48. doi: 10.1136/jmg.2009.067736

Hickman, N., & Neufeld, E. F. (1972). A hypothesis for I-cell Disease: Defective hydrolases that do not enter lysosomes. Biochemical and Biophysical Research Communications, 49(4), 992-999. https://doi.org/10.1016/0006-291X(72)90310-5

Leroy, J.G., & DeMars R.I. (1967). Mutant enzymatic and cytological phenotypes in cultured human fibroblasts. Science, 157(3790), 804-806. doi: 10.1126/science.157.3790.804

Leroy, J. G., Ho, M., MacBrinn, M. C., Zielke, K., Jacob, J., & O'Brien, J. S. (1972). I-Cell Disease: Biochemical studies. Pediatric Research, 6, 732-757. https://doi.org/10.1203/00006450-197210000-00002

Leroy, J. G., Spranger, J. W., Feingold, M., Opitz, J. M., & Crocker, A. C. (1971). I-cell disease: A clinical picture. The Journal of Pediatrics, 79(3), 360-365. https://doi.org/10.1016/S0022-3476(71)80142-7

Qian, Y., Flanagan-Steet, H., van Meel, E. Steet, R., Kornfeld, S.A. (2013). The DMAP interaction domain of UDP-GlcNAc:lysosomal enzyme N-acetylglucosamine-1-phosphotransferase is a substrate recognition module. PNAS, 110(25), 10246-10251. 10.1073.pnas.1308453110

Reitman, M. L., & Kornfeld, S. (1981a). UDP-N-Acetylglucosamine:Glycoprotein N-Acetylglucosamine-1-phosphotransferase. The Journal of Biological Chemistry, 256(9), 4275-4281.

Reitman, M. L. & Kornfeld, S. (1981b). Lysosomal enzyme targeting. The Journal of Biological Chemistry, 256(23), 11977-11980.