DHREAMS | DIAPHRAGMATIC HERNIA RESEARCH & EXPLORATION; ADVANCING MOLECULAR SCIENCE

Winter 2014-2015 Newsletter
www.cdhgenetics.com

DHREAMS Team at our annual meeting. Left to Right: Julia Wynn, MS; Wendy Chung, MD, PhD; Anthony Hesketh, MD,;Robert Cusick, MD; Tim Crombleholm, MS, MD; Foong-Yen Lim, MD; Ken Azarow, MD; Brad Warner, MD; George Mychaliska, MD; Amy Wagner, MD; David Schindel, MD

Inside this edition

Happy New Year!

We hope 2015 finds all of our DHREAMS families happy and healthy. We have had a productive year in the DHREAMS study with many new families, new participating centers, and new discoveries about CDH.

Thanks to our dedicated clinicians and families spreading the word about the DHREAMS study, we now have over 1700 DHREAMS participants composed of over 600 participating families from all across the nation and around the world.

DHREAMS Goes International

We are excited to announce our collaboration with Dr. Mahmoud ElFiky, a pediatric surgeon who cares for infants and children with diaphragm defects at the University of Cairo. Dr. ElFiky and his colleagues in the Department of Pediatric Surgery are enrolling families at the University of Cairo Hospital in the DHREAMS study and providing biological specimens for genetic analyses.

Dr. Mahmoud ElFiky

DHREAMS also had the opportunity to attend the first meeting of the Alliance of Congenital Diaphragmatic Hernia in Dublin, Ireland in August of 2014. We were able to meet some of our existing DHREAMS families and enroll many new families. It was a wonderful experience to share our research with these generous families as well as learn about the care of CDH infants in Dublin and across the United Kingdom.

Photo Courtesy of Cherubs

Enrollment of families from all around the world is critical to one day understanding the full spectrum of the genetic causes of CDH. We know that CDH is a birth defect that occurs in all ethnicities. While everyone has the same 20,000 genes, we know that there are some genetic variants or mutations that occur more frequently in people of specific ancestry. Therefore it is important that we include individuals of all ethnicities in the DHREAMS study.

Photo Courtesy of Cherubs

MYH10 A New Genetic Cause of CDH

We recently identified a mutation in the *MYH10* gene that causes congenital diaphragmatic hernia and other birth defects.

To understand how mutations in the *MYH10* gene can cause CDH it is helpful to review information about our genes. We each have approximately 20,000 genes that are important in the development and function of our bodies. A complete set of our genes is located in nearly every single one of our cells. Genes are packaged onto chromosomes and are made up of DNA. The DNA "spells" our genes using the "letters" A, C, T, and G. Just like spelling mistakes can make a word unreadable, a mistake or a mutation can occur in the "spelling" of a gene making the gene unreadable. A gene that cannot be "read" does not function or does not function properly, and this can lead to a birth defect or genetic disease.

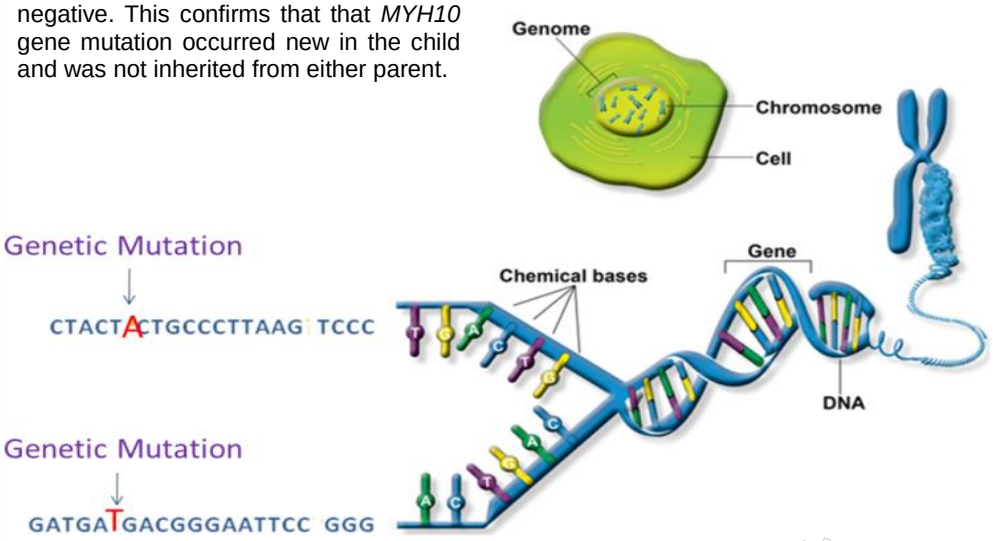
Most of our genes come in pairs, one copy we receive from our mother and one copy we receive from our father. Some genetic mutations are passed down or inherited from our parents and some genetic mutations occur new in the child and are not passed down from either parent. We encourage you to visit our website, www.cdhgenetics.com, where a more complete review of genes and genetic mutations can be found in the "genetic overview" tab.

We identified a mutation in the *MYH10* gene in a child with a CDH, as well as many other birth defects including growth restriction during the pregnancy, a small head with cerebral and cerebellar atrophy, developmental delay, low weight and congenital bilateral hip dysplasia. The number of medical problems that this child has suggests that the *MYH10* gene is important in the development of many parts of the body. The exact function of the *MYH10* gene is not completely known. Studies in mice have shown that it plays an important role in the development of the heart, brain and hernia.

We examined the parents for the *MYH10* gene mutation and both of them were negative. This confirms that that *MYH10* gene mutation occurred new in the child and was not inherited from either parent.

This is important information for the family. When a mutation occurs that is new in a child, there is a less than 1% chance for the parents to have another child with the same genetic mutation. Additionally, the other family members are not at risk to have a child with the same genetic mutation.

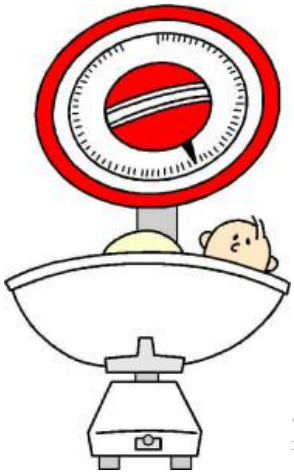
This is the first time the mutations in the *MYH10* gene have been identified in a human and more research is needed to fully understand the function of the *MYH10* gene in diaphragm development. We are also in the process of screening the other children in our study with CDH and additional birth defects for mutations in the *MYH10* gene.



ECMO and Pulmonary Hypertension are Associated with Low Weight in CDH Children

We recently analyzed the risk factors for low weight in children with CDH at 1 year of age. We followed 72 infants with CDH born at New York Presbyterian/Morgan Stanley Children's Hospital for one year. At one year of age, 35% of the infants were less than the 5th percentile for weight. This means that at one year of age, 35% of the children weighed less than 95% of all other one year olds. Additionally, 18% of the children had difficulty eating enough calories by mouth and were receiving feeding assistance by a gastrostomy tube (G-tube) or nasogastric tube (NG-tube).

All of these children were also on medication for reflux. Examining the risk factors for low weight, we found that infants who required extracorporeal membrane oxygenations (ECMO) and/or had pulmonary hypertension in the neonatal period were at greater risk to have low weight at 1 year of age. This is important information that will be used to guide nutritional monitoring and counseling in CDH children. These findings were published in the October issue of the Journal of Pediatric Gastroenterology and Nutrition.



Columbia University IRB
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Undescended Testis Occurs Frequently in Males with CDH

Undescended testis (UDT) occurs when one or both testicles are not present in the scrotum at birth. The undescended testicle may move into the correct place but in some cases surgery is required to move the testis into the scrotum. UDT occurs in approximately 1-2% of all males in the general population. There have been several studies that suggested that UDT occurs more frequently in males with CDH.

We studied 65 males with CDH at two years of age. We found that 18% required surgical repair for UDT. Two males had both testes undescended and 10 had one testis undescended. Interestingly, all 10 of the boys with one testis undescended had it on the same side as their CDH. Our study confirmed that UDT is significantly more frequent in males with CDH than in the general population.

We also found that the side of the UDT correlates with the side of the CDH. One hypothesis for this correlation is that the absence or deficiency of diaphragm tissue may affect the normal descent of the testis when a baby is developing. Evaluation for UDTs is already part of the standard pediatric care for all males, but this research underlines the importance of this screening for males with CDH. Our study also demonstrates that more research is needed to understand why the side of the UDT correlates with the side of the CDH. These findings were presented at the 2014 Canadian Association of Pediatric Surgeons Meeting.

DHREAMS Events

The DHREAMS study group had an eventful year attending and virtually attending many different CDH events. Washington University Medical Center and St. Louis Children's Hospital hosted a Family Meeting Day in April and DHREAMS was able to present information on the DHREAMS study. We attended the 2014 International CDH Conference in Washington, DC in July and the first meeting of the Alliance of Congenital Diaphragmatic Hernia in Dublin, Ireland in August.

On August 29, 2014 we rang the NY Stock Exchange Closing Bell with the Scelfo family and CHERUBS.

We especially enjoy these opportunities to update DHREAMS families on our research, meet new families and catch up with those already enrolled. Please contact us if you would like us to speak at your CDH event. We enjoy all opportunities to share information on CDH and the DHREAMS study.

Photo Courtesy of NY Stock Exchange

Questions about the status of research for your family

We are very appreciative of each and every family that participates in our study and are dedicated to finding an answer for everyone. Unfortunately, we are not able to call everyone to provide individual updates. If your child was born at one of the DHREAMS hospitals, we encourage you to contact them for follow up information. If you enrolled directly in the DHREAMS study, we encourage you to contact us at **(212) 305-6987** or **jw2500@columbia.edu** with any questions. We can update you on the studies that have been completed on your family and plans for future studies. We also want to learn about any updates in your family. More information will help us to better target possible genetic causes.

DHREAMS Funding

DHREAMS was funded for five years by a grant from the National Institute of Health (NIH), an agency of the U.S. Department of Health and Human Services that funds many different types of research. Due to budget cuts, NIH funding has been reduced across the board. As a result, many great research studies including the DHREAMS study did not continue to receive funding from the NIH. We will continue to apply for NIH funding and are hopeful that we will be successful in the future. We are fortunate to have alternate funds to help keep the DHREAMS active, but additional donations are critical. It costs approximately $150 to enroll a family in the study and $1000 to complete comprehensive genetic analysis on one individual. We are appreciative of all donations of all sizes.

If you are interested in making a donation to the DHREAMS study, please contact us at (212) 305-6987.

Many thanks to everyone who makes the DHREAMS Research Possible!

The DHREAMS families
ACDHO
Breath of Hope
Brountzas/Kostaridis Family
The Vanech Foundation
CHERUBS
Global CDH
The Larsen Family
The Wheeler Foundation
National Greek Orthodox Ladies Philoptochos Society, Inc.

DHREAMS Centers

New York Presbyterian/ Morgan Stanley Children's Hospital
Wendy Chung, MD, PhD
Gudrun Aspelund, MS, MD
Julia Wynn, MS

Medical College of Wisconsin/ Children's Hospital of Wisconsin
Amy Wagner, MD

Children's Hospital of Omaha/ University of Nebraska
Robert Cusick, MD

CS Mott Children's Hospital/ University of Michigan
George Mychaliska, MD

Children's Hospital of Pittsburgh/ University of Pittsburg
Douglas Potoka, MD

Cincinnati Children's Hospital Medical Center/ University of Cincinnati
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North Shore Long Island Jewish Hospital, Children's Hospital
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