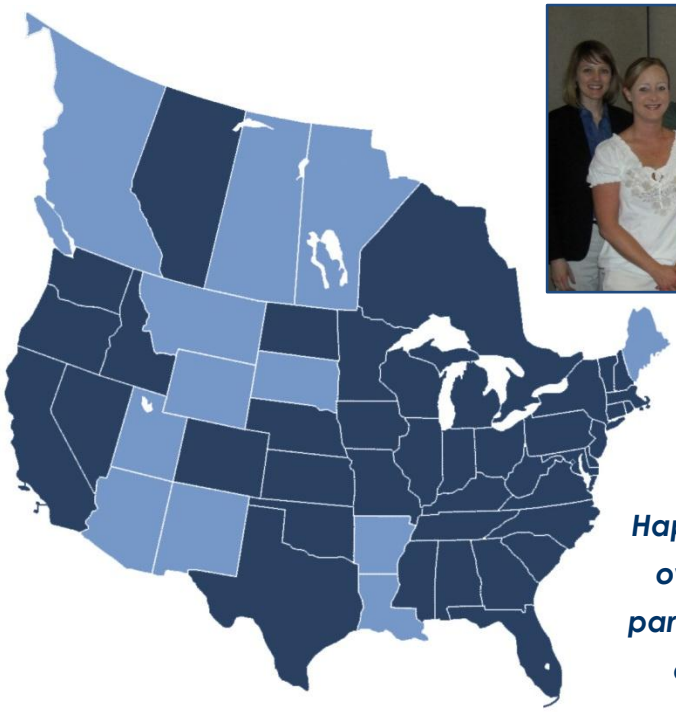
DHREAMS

DIAPHRAGMATIC HERNIA RESEARCH & EXPLORATION; ADVANCING MOLECULAR SCIENCE



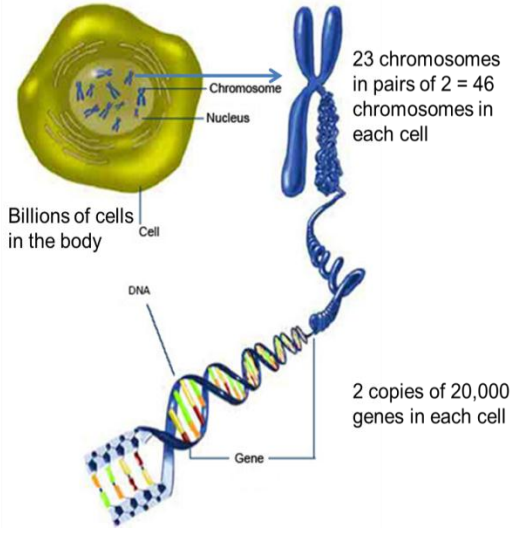
Happy New Year to the over 1200 DHREAMS participants from nearly every state and 7 countries

Inside This Edition

Happy New Year!

We hope the New Year finds our over 450 participating CDH families happy and healthy. We would like to begin by thanking all of you. Without your participation, this research would not be possible.

This was an exciting year with the discovery of new genetic causes of CDH and publications on the outcomes and development of CDH children.



GATA4: A New Genetic Cause of CDH

Your participation in our research helped us to identify mutations in the GATA4 gene as the genetic cause of CDH in two families. The results of this study were published in the journal *Human Genetics*. Mutations in the GATA4 gene have previously been identified as the genetic cause of congenital heart disease in some individuals but this is the first time the gene has been associated with CDH.

The GATA4 gene is part of the body's instruction manual that tells it how to form the heart and diaphragm.

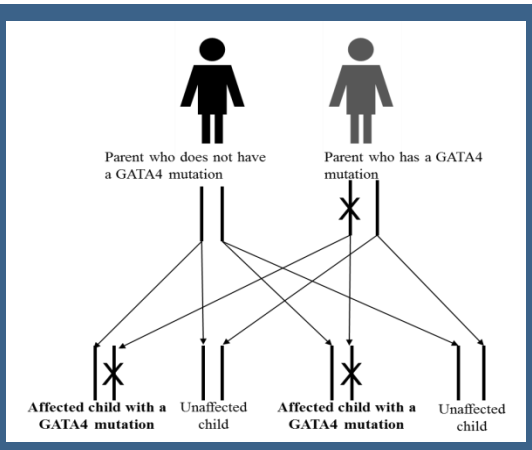
Like almost all of our genes, we have two copies of the GATA4 gene; one we get from our mother and one we get from our father. If a mutation occurs in one copy of the gene, this can cause a child to be born with a birth defect.

We found that GATA4 mutations cause a CDH with varying degrees of severity. We found a GATA4 mutation in an infant with an isolated CDH that required surgery shortly after birth (continues on the next page).

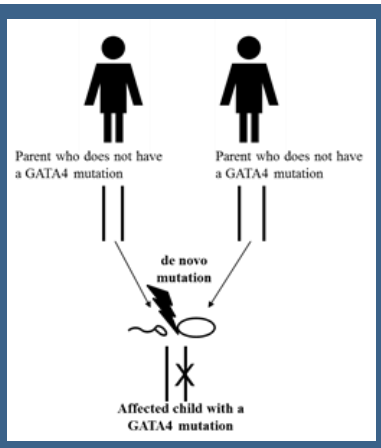
Columbia University IRB
IRB-AAAB2063
IRB Approval Date: 12/17/2012
for use until: 10/29/2013

GATA4: A New Genetic Cause of CDH (continued)

We also found a GATA4 mutation in adult individuals with a very mild CDH that did not cause any symptoms and was only detected after an MRI was done to examine the diaphragm. These individuals never required surgery to fix the diaphragm. We also found a GATA4 mutation in an infant with a CDH and congenital heart defect. The identification of a GATA4 mutation in these individuals demonstrates that a GATA4 mutation affects individuals with different degrees of severity.



Inherited GATA4 mutation. There are 4 possible combinations of the GATA4 genes that parents can pass on each time they have a child. In 2 of these 4 (50%) combinations the child inherits the GATA4 gene with the mutation.



De novo GATA4 mutation. Neither parent has the GATA4 mutation. The GATA4 mutation happened new when the sperm and egg came together.

A GATA4 mutation may be inherited from one parent (the mother or the father) with no symptoms or it may occur new in a child at the time the egg and the sperm come together. If a GATA4 mutation is inherited from a parent, each time the parent has a child, there is a 50% chance the child will inherit the GATA4 mutation and be at risk to have a CDH and/or congenital heart defect. If the GATA4 mutation occurs new in the child, there is a very low chance that the parent will have another child with the GATA4 mutation. When the genetic cause of a CDH is known, a family can pursue reproductive options to prevent their children from inheriting the GATA4 mutation

DHREAMS |
DIAPHRAGMATIC HERNIA RESEARCH & EXPLORATION; ADVANCING MOLECULAR SCIENCE

Current Neonatal Outcomes

We completed the largest prospective study of children with CDH. This study will be published in the *Journal of Pediatrics*.

We collected over 1000 pieces of information about the children's hospital stay. We had an equal number of boys and girls in our study. 84% had a left sided CDH and 16% had a right sided CDH. Approximately 40% had another birth defect in addition to their CDH. The most common additional birth defect was a heart defect. 32% of the children in the study required extracorporeal membrane oxygenation (ECMO). Interestingly, we found that the side of the CDH (right or left) was NOT associated with survival. This is different than past studies that have found a higher mortality in children with right side CDH compared to children with a left sided CDH.

We also completed a detailed analysis of pulmonary hypertension in this group of children. Pulmonary hypertension is a common complication of CDH. Nearly 50% of the children in the study had pulmonary hypertension at 1 month of age while only 25% had pulmonary hypertension at 3 months of age.

Future studies will focus on understanding why pulmonary hypertension continues to be a complication in some children, but resolves or improves in other children.

Chromosome Microduplications and Microdeletions in CDH

We recently published one of the largest studies of the genetic causes of CDH in the *Journal of Medical Genetics*. We completed genetic analysis on 256 study participants and their parents. The specific genetic analysis we completed is called chromosome microarray analysis or CMA. A CMA examines all 23 pair of chromosomes for missing or extra pieces of genetic information called microdeletions and microduplications. Sixteen (6%) of the 256 study participants were found to have a large chromosome abnormality or a chromosome microdeletion or duplication that was determined to be the genetic cause of the CDH. All of these chromosomes abnormalities occurred new in the child and were not inherited from the mother or father.

Some of the microdeletions /duplications were the same as those previously found in other children with CDH, while others had never been identified before. We also found that children with a CDH and a second birth defect, such as a heart defect, were more likely to have a microdeletion /duplication than children with only a CDH. These children were also more likely to pass away than children who were not found to have a microdeletion /duplication.

A cartoon drawing of our chromosomes 1-22, X, Y showing Microduplications (dark red) and microdeletions (dark green) that were identified in our study and those that have been identified in previous studies (light red, green, and blue)

The results of this study are very important for healthcare providers caring for families with CDH, as well as future studies of the genetic causes of CDH. Our next step is to examine the genes that are located in the microdeletions /duplications in more detail to try to identify other genetic causes of CDH.

Support Groups

We had the opportunity to attend several CDH patient support group meetings this summer where we saw old friends and met new families. We were also able to virtually attend several meetings by video conference

If you would like DHREAMS to attend your support group, fund raiser or other CDH event, please contact our research coordinator Julia Wynn:
jw2500@columbia.edu
(212) 305-6987

DHREAMS Participating Hospitals

Columbia University Medical Center/ Children's Hospital of NY
University of Nebraska/ Children's Hospital & Medical Center
Vanderbilt University/ Monroe Carell Jr. Children's Hospital
University of Texas Southwestern, Children's Medical Center
University of Cincinnati/ Cincinnati Children's Hospital
University of Michigan/ CS Mott Children's Hospital
University of Pittsburgh/ Children's Hospital of Pittsburgh
Washington University/ St. Louis Children's Hospital

DHREAMS | DIAPHRAGMATIC HERNIA RESEARCH & EXPLORATION; ADVANCING MOLECULAR SCIENCE

Please contact us if you have any questions about the articles in this newsletter.

Phone: (212) 305-6987

Email: jw2500@columbia.edu

Website: www.cdhgenetics.com

Columbia University Medical Center

1150 St. Nicholas Ave, Russ Berrie Pavilion, 6th Fl

New York, NY 10032