

THE MASSGENERAL HOSPITAL FOR CHILDREN AND CHILDREN'S HOSPITAL BOSTON  
CONGENITAL DIAPHRAGMATIC HERNIA STUDY  
NEWSLETTER

*A group of doctors and scientists at MassGeneral Hospital for Children and Children's Hospital Boston are working together to identify genes that cause Congenital Diaphragmatic Hernia (CDH) and abnormal lung development*

CDH  News

**VISION behind the STUDY**

This study, **Gene Mutation and Rescue in Human Congenital Diaphragmatic Hernia**, tries to identify some of the causes of this common and serious birth defect. We believe that CDH is caused by different factors, many of which could be genetic. There is growing evidence that in some cases, CDH, along with co-existing lung underdevelopment, can be traced to a non-working gene in one or more pathways important for normal diaphragm and lung formation.

We try to identify these pathways by comparing the DNA (the genetic blueprint) in the person with CDH to his/her parents and siblings. Once these pathways have been identified, then treatments may follow that will be less invasive and less stressful to patients with CDH and their families. For example, one long-term hope is to identify therapies that can be used prenatally to improve the lungs of CDH patients before they are born and thus simplify their care after delivery.

We are currently looking for DNA changes in several different genes that might be responsible for CDH. In these particular genes, we compare the DNA patterns between individuals with CDH to the patterns in their healthy parents and siblings. Some of the DNA changes we find may be just normal variations of the genetic material while others may actually contribute to CDH. The challenge for us as researchers is to figure out which changes are normal, versus which might cause CDH.

**Our study is funded by the National Institute of Child Health and Human Development.**



Schuyler and Dalton Jones and cousin Sophia LeBrun take a break from carving pumpkins and making cookies

Our study incorporates a variety of “cutting-edge” genetic tools, such as “FISH”, “CGH”, and “SNP chips” that can detect small DNA changes that typically are not apparent in standard analysis.

The number of parents and families joining this effort has been phenomenal, making it one of the largest studies of the genetics of CDH in the world. We are grateful that your contribution to our research may help us open the door for future remedies for CDH and lung abnormalities.

Thanks to all of you for your generous participation!

**Patricia K. Donahoe, MD** (Program Project Director)

**Jay Wilson, MD** (Principal Investigator)

**IN THIS ISSUE:**

<i>Vision Behind the Study</i>	<i>p.1</i>
<i>Genetics 101;What is CDH?</i>	<i>p.2</i>
<i>Types of CDH; Is CDH genetic?</i>	<i>p.3</i>
<i>Exiting New CDH Research</i>	<i>p.4-5</i>
<i>A Mother's Story</i>	<i>p.6</i>
<i>Resources on CDH and Related Topics</i>	<i>p.7</i>
<i>Kid's Corner</i>	<i>p.8</i>

Issue 1

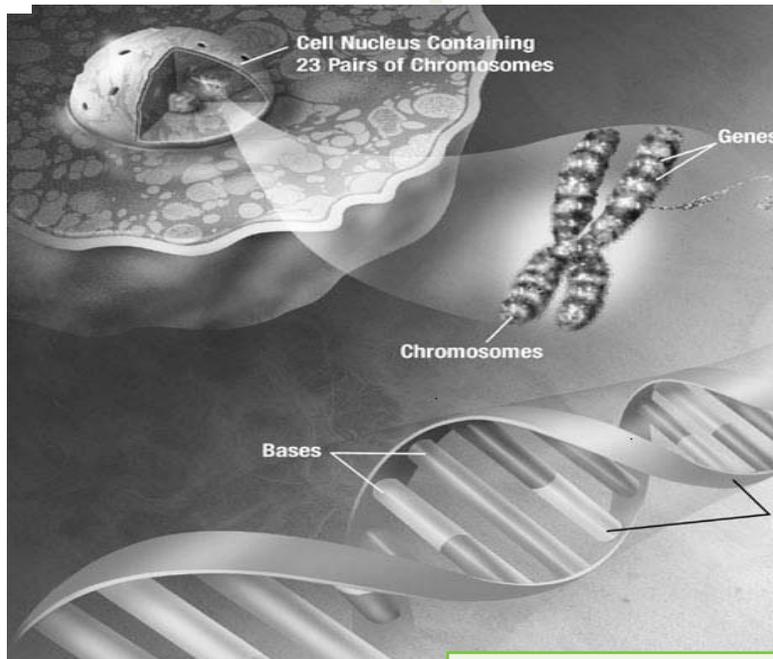
1

February 2006



## DNA:

What is it and why is it important for our study?



Issue 1

2

February 2006

Living organisms are made of cells that contain **DNA (deoxyribonucleic acid)**. DNA is the molecule that encodes genetic information carrying the instructions for making all the structures and materials the body needs to function. Found within the nucleus of a cell, DNA consists of two spiraling strands of chemical building blocks known as bases. DNA is tightly packed into structures called **chromosomes**. Humans have 23 pairs of chromosomes, one member of each pair inherited from the mother, and the other from the father. Chromosomes contain **genes**, our units of hereditary information. Our bodies house 25,000-30,000 genes which compose our genetic blueprint. This blueprint determines features such as body height, eye color and allows the transmission of different kinds of genetic information from one generation to the next.

### What is CDH?

Congenital diaphragmatic hernia (CDH) is a very common birth defect. CDH refers to an abnormality that can either be a **“hole”** (diaphragm hernia) which then allows the contents of the abdomen to enter into the chest, or a **“thinning”** (diaphragm eventration). Most babies have underdevelopment of the lungs along with the diaphragm abnormality and, in fact, lung problems are often the most severe medical problem facing the baby. In 85-90% of the cases, the defect appears on the left side of the diaphragm, and the remainder are on the right or both sides of the diaphragm. About half the time, CDH is the only abnormality. However, the other half of babies have CDH along with additional birth defects or syndromes.

## Common Types of Congenital Diaphragmatic Hernia:

There are several types of diaphragmatic defects based on the location of the "hole" in the diaphragm:

**Bochdalek:** the most common type (90% of all cases); the opening is in the back or side of the diaphragm

- stomach, intestines, liver, spleen might move into the chest cavity

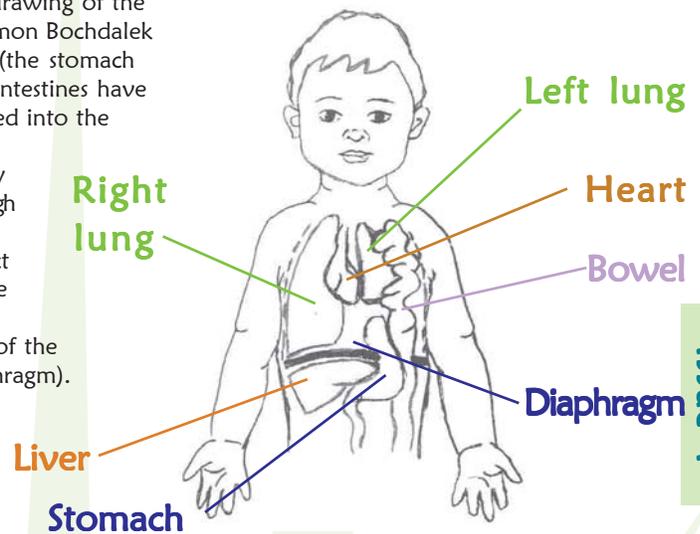
**Morgagni:** relatively rare; the hole is in the front, behind the breastbone

- liver and intestine might move into the chest cavity

**Central:** rare (1-2% of CDH cases); occurs in the non-muscular part of the diaphragm.

**Eventration:** diaphragm thinning, not an actual "hole"

Shown on the right is a drawing of the common Bochdalek CDH (the stomach and intestines have moved into the chest cavity through the defect in the left side of the diaphragm).



### CDH Study Statistics:

As of November 2005, we have a total of **536** study participants of which

- ◆ 179 are individuals with CDH
- ◆ 357 are parents, siblings and other family members

Let us know how YOU're doing!  
Please Send us Your Pictures and Updates at  
[lina.mitova@childrens.harvard.edu](mailto:lina.mitova@childrens.harvard.edu)

## SPECIFIC EVIDENCE THAT CDH MIGHT BE GENETIC

You kindly participated in our study "Gene Mutations and Rescue in Human Congenital Diaphragmatic Hernia" which aims to identify underlying genetic causes of CDH. We believe this research offers great hope for improving the outlook of babies with CDH. Described below is our current understanding about why genetic factors may cause **CDH**.

Several findings suggest that CDH is caused by changes in one or more genes:

- 1) Although in most families, only one person is ever affected with CDH, some families have been found where CDH occurs in two or more persons indicating that it is "running in the family".
- 2) About 10% of CDH cases occur in babies with chromosome abnormalities (chromosome abnormalities are genetic changes). Depending on the specific chromosome change, there can be an increase in the number of genes, a decrease in the number of genes, or a gene may actually be "disrupted" or broken.



## Exciting New CDH Research



In the accompanying article, Dr Kate Ackerman tells you about her important finding, recently published under the title "Fog2 Is Required for Normal Diaphragm and Lung Development in Mice and Humans":

- ◆ Dr. Ackerman's finding of a genetic change in *FOG2* is the 1<sup>st</sup> discovery of a genetic basis for *de novo* CDH that occurs in the child without being evident in the parents.

The scientific paper describing Dr. Ackerman's work was published in PLoS Genetics, July 2005 and is available free online at [www.plosgenetics.org](http://www.plosgenetics.org).

- ◆ We are now looking for mutations in the *FOG2* gene in 100 other children with CDH.
- ◆ In addition, we are searching for genetic changes over a dozen other genes that we think may contribute to CDH.
- ◆ We are using the latest DNA technology (Comparative genomic hybridization, CGH, and SNP chips) to detect subtle genetic changes to pinpoint a region or gene that could cause CDH. We believe that more genes responsible for CDH are likely to be identified through genetic research.

During my training as a pediatric intensivist, I took care of many babies with CDH. I was bothered by the fact that we have little understanding about why diaphragmatic defects occur. Some babies did very well while others died, and it was often difficult to predict. It seemed that some patients had pulmonary hypoplasia (small lungs) that were much smaller than expected, and I wondered whether some babies with CDH might have a genetic abnormality that was causing both the diaphragmatic defect as well as underdevelopment of the lungs.

I set out to answer this question in the laboratories of the Division of Genetics at Brigham and Women's Hospital.

(Article continues on next page)



Dr. Kate Ackerman at her research laboratory bench, Brigham and Women's Hospital in Boston

There, I was able to take advantage of an ongoing program aimed at discovering the genetic cause of birth defects by using mouse models. In the laboratory headed by Dr. David Beier, I started to work on a line of mice that had offspring with diaphragm and lung defects.

After identifying that the gene causing these defects was a gene called *Fog2* ("Friend of GATA 2"), I looked for human patients that might have changes in the same gene (which in humans is known as the *FOG2* gene). I was able to look at samples from children who had died with diaphragmatic defects and had autopsies. In one baby, we identified a mutation in the *FOG2* gene that looked very significant.

When we find a genetic change, it is often very difficult to determine whether or not that genetic change actually causes the defect. In this case, it was essential for us to compare the change in the baby to the DNA patterns in the parents. Luckily, we were given permission to contact the parents and they were happy to participate in our study. We found that the genetic change did not exist in the parents which proved that it was a new genetic change in the baby likely responsible for the diaphragm defect and small lungs. This finding also proves that one genetic mutation can cause both lung and diaphragm defects.

We are currently examining the DNA in all our study participants looking for changes in this gene as well as other related genes. Although it is exciting to find a first cause of a congenital diaphragmatic defect, we do not yet know how often genetic changes or mutations in the *FOG2* gene will be the culprit. We expect that changes in many different genes may contribute to congenital

defects of the diaphragm. Work is ongoing to look at more mouse models and to learn more about the function of the *Fog2* gene. This will allow us to understand better how the lung and the diaphragm develop in normal children and in children with CDH.

**WE BELIEVE**  
**that understanding the genetic causes of this common and often devastating birth defect will provide the foundation for developing MORE EFFECTIVE therapies.**

**Microscope view of normal mouse lung in culture (in a petri-dish)**



**Underdeveloped lung (decreased airway branching) in culture from a mouse with non-working *Fog2* genes. Note that this underdevelopment occurs in the petri-dish without the presence of a diaphragm defect.**



These figures were reprinted from:  
 Ackerman KG, Herron BJ, Vargas SO, Huang H, Tevosian SG, et al. (2005) *Fog2* Is Required for Normal Diaphragm and Lung Development in Mice and Humans. *PLoS Genet* 1(1):e10

# CDH News

## CDH STUDY STAFF:

### **Program Project Director**

Patricia K. Donahoe, M..D.

### **Principal Investigator Children's Hospital, Boston**

Jay Wilson, M.D.

### **Geneticists**

Barbara Pober, M.D.

Lewis Holmes, M.D.

### **Clinical Coordinators**

Meaghan Russell, M.P.H.

Phone: 617-726-0828

Email: [mrussell@partners.org](mailto:mrussell@partners.org)

Lina Mitova, M.A.

Phone: 617-355-2555

Email:

[lina.mitova@childrens.harvard.edu](mailto:lina.mitova@childrens.harvard.edu)

We're on the Web!

See us at:

<http://www.mgh.harvard.edu/deps/mghfc/>

## HOW TO REACH THE CDH STUDY STAFF:

### CHILDREN'S HOSPITAL BOSTON

300 Longwood Ave  
Fegan 3  
Boston, MA 02115

PHONE:  
617-355-2555

FAX:  
617-730-0173

EMAIL:  
[lina.mitova@childrens.harvard.edu](mailto:lina.mitova@childrens.harvard.edu)

### MASS GENERAL HOSPITAL

Charles River Plaza  
185 Cambridge St.  
6th floor, Room 214  
Boston, MA 02114

PHONE:  
617-726-0828

FAX:  
617-716-5057

EMAIL:  
[mrussell@partners.org](mailto:mrussell@partners.org)

## CDH WEBSITES:

The Association of Congenital Diaphragmatic Hernia Research, Advocacy, and Support (CHERUBS) is a support group for families of children with CDH.

**Website:** [www.cherubs-cdh.org](http://www.cherubs-cdh.org)

The International Birth Defects Information Systems website with links to articles on CDH.

**Website:** <http://ibis-birthdefects.org/start/diaphern.htm>



One of our favorite 4 year olds with CDH

## OTHER USEFUL WEBSITES:

The Nutrition.gov website has access to health and nutrition related web pages.

**Website:** [www.nutrition.gov](http://www.nutrition.gov)

Kidshealth.org is a website with health information about children of all ages (prenatally through adolescence).

**Website:** <http://www.kidshealth.org>

MUMS National Parent to Parent Network matches parents who have a child with a disorder, medical condition or rare diagnosis with other parents whose children have the same or similar condition.

**Phone:** (877)336-5333 or (920)336-5333

**Email:** [mums@netnet.net](mailto:mums@netnet.net)

**Website:** [www.netnet.net/mums](http://www.netnet.net/mums)

Dear participants,

CDH



News

We hope that you have enjoyed reading the first issue of CDH News, and found it helpful in answering some of your questions. However, we realize that not all of you are interested in receiving future issues of our newsletter. Please take this opportunity to let us know if this is your preference by completing the enclosed reply card and mailing it back to us. We will make sure to take you off our newsletter mailing list, so you do not receive any more materials. Also, please kindly inform us if this newsletter has reached you in error.

If you don't indicate on the reply card that you wish to be taken off the mailing list, we will send you the next issue of CDH News. We would greatly appreciate your feedback on the current issue, and any suggestions you might have for upcoming issues. Don't hesitate to let us know what you would like to see in future CDH News! Please use the card and envelope provided below to communicate with us. You are also welcome to contact us via email ([lina.mitova@childrens.harvard.edu](mailto:lina.mitova@childrens.harvard.edu)) or over the phone (617-355-2555). We also encourage you to ask questions about the study, or your participation.

Thank you for reading CDH News! We look forward to hearing from you!  
~ From the CDH study staff

In future issues, we plan to have a PARENT'S CORNER. Parents will share, in their own words, what it was like to learn their child had CDH and their experiences following the diagnosis. Some of the children in these stories will be doing well, while others unfortunately may have multiple medical and/or developmental problems, or have even died of complications from their CDH. Outcomes for children with CDH continue to improve! However, our PARENT'S CORNER will reflect the highly variable impact this defect has both on the individual with CDH and their families.

Issue 1

7

February 2006

**Please Use The Enclosed Reply Card And Pre-Paid Self-Addressed Envelope On This Page To:**

- 1) Let us know you if you would like to be taken off our mailing list and **NOT receive** any future issues of the CDH Study Newsletter
- 2) Provide us with feedback on the current issue of the newsletter
- 3) Tell us what you would like to see in future issues of the newsletter
- 4) Update your mailing address or other contact information
- 5) Update us on how you or your child with CDH is doing, send us your pictures, stories, etc.

6) Request a copy of the newsletter to be mailed to others who are not on our mailing list (a family member, another family with CDH, your physician, etc.)

My name is: \_\_\_\_\_ My child's name is: \_\_\_\_\_  
(please PRINT) (please PRINT)

**Please mark this section if you do NOT wish to receive the next issue of our newsletter.**  
 Please sign here:  
 Feel free to use this section if you:

- have comments regarding the current issue \_\_\_\_\_
- would like to make the following suggestions/recommendations for future issues \_\_\_\_\_
- would like to send us your CDH story, or update us on how your child with CDH is doing \_\_\_\_\_
- OTHER: \_\_\_\_\_

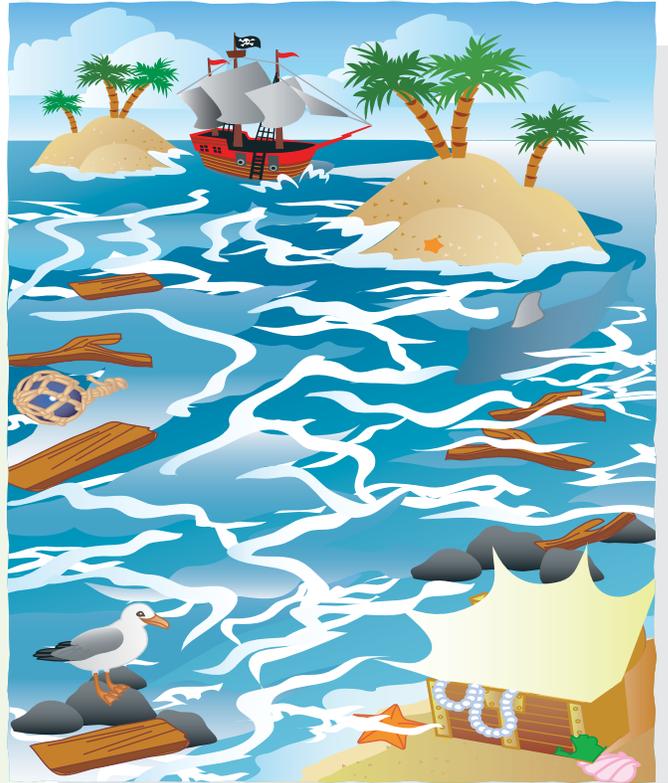
If you have a change in address, please provide us with your new contact information.  
 \_\_\_\_\_

~ Thank you!

# Kids Corner

## Trip to the Treasure Maze

Steer your ship through the white waves to reach the treasure chest you'll find on shore.



© FamilyFun

### Sweet Little Scrambler

Care to take a peek at our candy cart? Unscramble the words below to see what you'll find!

1. LIOLPLOP \_\_\_\_\_
2. RILCEOICI \_\_\_\_\_
3. MUGMY RASBE \_\_\_\_\_
4. BLEBUB MUG \_\_\_\_\_
5. RAWKSARJEBE \_\_\_\_\_
6. LUGMLASB \_\_\_\_\_
7. TONOCY NAYDC \_\_\_\_\_
8. MEPPINSERTP \_\_\_\_\_
9. LATM SLABL \_\_\_\_\_
10. OAHOTCELC \_\_\_\_\_
11. SPORUDMG \_\_\_\_\_
12. FAYFT \_\_\_\_\_

ANSWERS: 1. LOLIPOP 2. LICORICE 3. GUARANT BEANS 4. BUBBLE GUM  
5. MINT BUBBLES 6. CHOCOLATE 7. COOKING CUPCAKE 8. PEPPERMINT  
9. MINT BUBBLES 10. CHOCOLATE 11. GUARANT BEANS 12. TART

© FamilyFun

Issue 1

8

February 2006

## CHILDREN'S HOSPITAL BOSTON

300 Longwood Ave  
Fegan 3  
Boston, MA 02115

John Q. Public  
123 Address  
City, ST 01234

