Happy New Year!

Members of the DHREAMS team at the 2013 American Pediatric Surgery Association. L-R: Dr. David Bliss, University of California, San Diego; Julia Wynn and Dr. Wendy Chung, Columbia University; Sheila Horak, Nebraska Children's Hospital; Dr. Samuel Soffer, North Shore University Hospital; Dr. Casey Calkins, Children's Hospital of Wisconsin; Dr. Foong-Yen Lim, Cincinnati Children's Hospital.

Inside this edition

Happy New Year to all of the DHREAMS families! We now have over 500 participating families from all across the nation and the world. Thank you to all of you who educate the CDH community about our study. Nearly a quarter of the participating families find us through CDH support groups and/or other families who are enrolled in the study.

The DHREAMS study has had a busy year with some exciting findings.

GATA6: A new genetic cause of CDH

We recently identified mutations in a gene called GATA6 that cause congenital diaphragmatic hernia. Some of the children with mutation in the GATA6 gene also had congenital heart defects.

Recall that genes are the blue print or instructions for how our body grows and develops. We have a complete copy of our genes in nearly all of our cells (Figure 1). We have two copies of most of our 20,000 genes in each cell, one copy comes from mom and one copy comes from dad. If a change occurs in the gene that affects the function, this is called a gene mutation. 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.

Each gene has a specific function but some genes work together. Just like members of a family work together to complete a task, there are genes that are part of a family that work together in the development of the body. Last year, we identified mutations in a gene called GATA4 that cause CDH. The genes GATA4 and GATA6 are part of a family of genes that

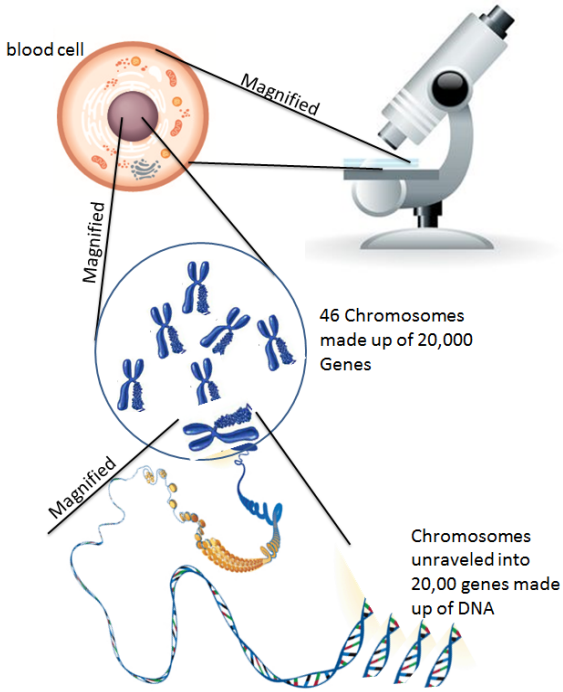


Figure 1: A complete set of our 20,000 genes are inside nearly every cell. Our genes are made up of DNA.

GATA6: A new genetic cause of CDH (continued)

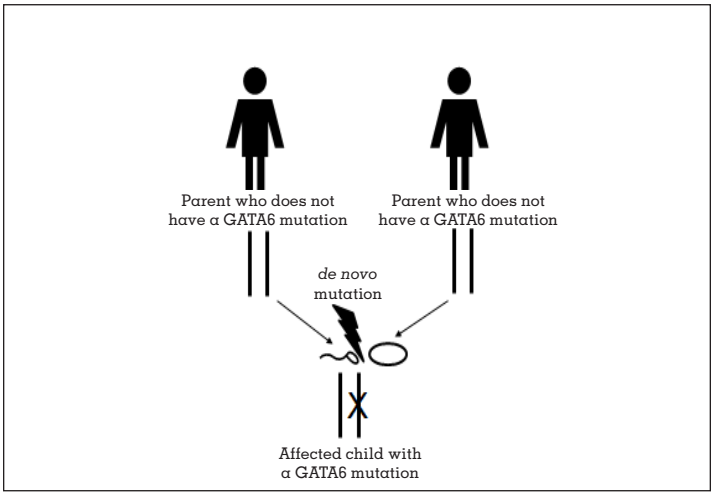


Figure 2: ***De novo* GATA6 mutation.** Neither parent has a GATA6 mutation. The GATA6 mutation happened new in the child. The risk for the parents to have another child with the GATA6 mutations is 1%.

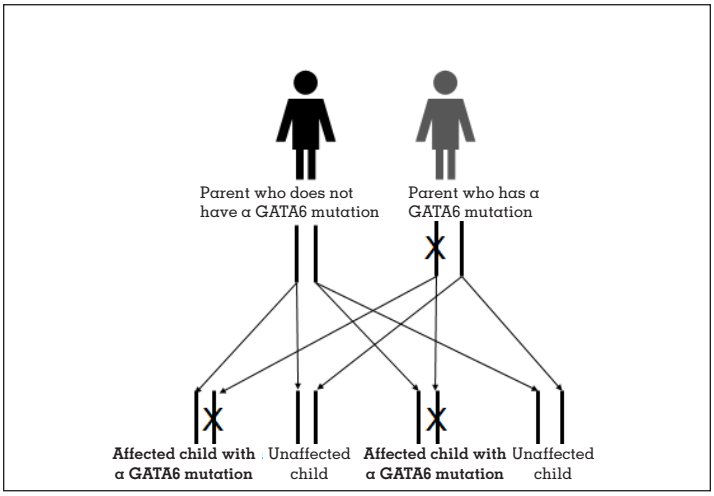


Figure 3: **Inherited GATA6 mutation.** One parents has the GATA6 mutation. Each time they have a child there is a 2 in 4 chance (50%) chance of passing the mutation onto the child and having a child at risk for a CDH and/or heart defect.

are important in diaphragm and heart development. If one of the genes in this family has a mutation that causes it not to work, it can lead to problems with the development of different organs, leading to a birth defect.

We identified a mutation in the GATA6 gene in three different children. Two of the children were born with a left CDH and a congenital heart defect. Both of these children had a new GATA6 mutation that was not inherited their mother or their father (Figure 2). In the third family, the child was born with a left CDH and a heart defect. In this third family, the child inherited the GATA6 mutation from the mother, who also was born with a heart defect, but did not have a diaphragmatic hernia.

We looked for GATA6 mutations in over 100 other DHREAMS participants who had both a CDH and a heart defect and did not find any other children with a GATA6 mutation. This means that while GATA6 mutations are the cause of CDH in some individuals, it is not a very a common genetic cause.

Most genetic causes of CDH are not common and only a small percentage of all of the individuals with a CDH share the same genetic cause. This makes studying the genetic causes of CDH very complex and requires us to study many individuals with CDH before we can understand all of the genetic causes of CDH.

Now that we know of two genes in the GATA family that cause CDH, we will use this information to look for genetic mutations in genes that are related to the GATA6 and GATA4 family.

The results of this study were published in the *American Journal of Medical Genetics*.

Developmental outcomes in two-year-old children with CDH

Children born and enrolled in the DHREAMS study at the study sites have formal developmental assessment at two years of age. We recently published our findings on the development of 49 children with CDH in the Journal of Pediatric Surgery. Prior to our study, there was very little information known about the development of children with CDH.

All children in the study had a Bayley Scales of Infant Development III (BSID-III) evaluation. The BSID-III measures a child's language, motor and cognitive skills through a series of games and questions with a developmental specialist. In the general population, the average score is 100 and development is considered normal with a score above 85 for each domain (language, motor, cognitive), borderline with a score of 70-85, and delayed if the score is below 70. In our study, we found that the majority of children scored within the normal range (figure 4). Overall, the average language, motor, and cognitive scores of the children we studied were 5-7 points below the normal score of 100.

Developmental outcomes in two-year-old children with CDH (continued)

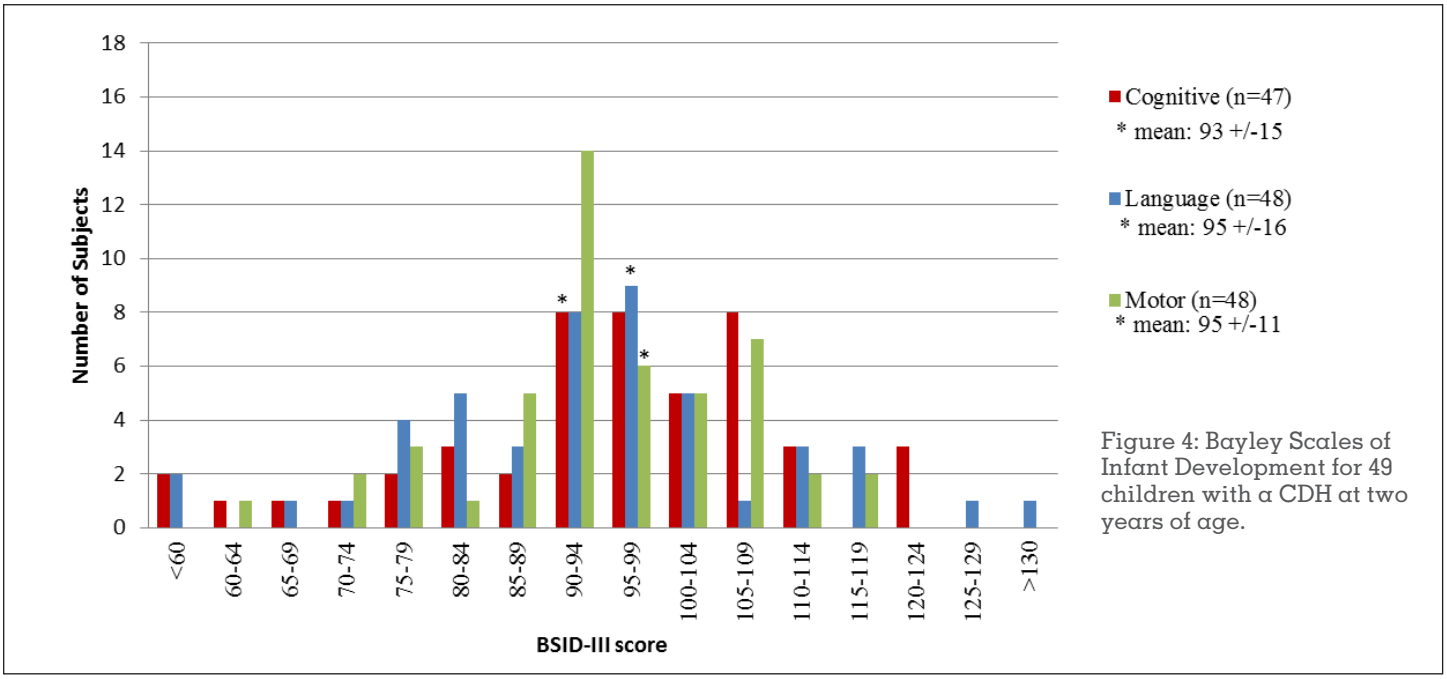


Figure 4: Bayley Scales of Infant Development for 49 children with a CDH at two years of age.

We found that children who had more medical complications, including needing oxygen past 1 month of age, needing ECMO, needing feeding assistance through a tube in the nose or in the stomach after they went home from the hospital, tended to have more developmental challenges than children who did not need these interventions. Over half of the children received interventional therapies such as physical, occupation or speech therapy.

Our study of the developmental outcomes in children with CDH is ongoing and we are now assessing children at 5 years of age. We hope to learn about specific learning disabilities associated with CDH and the best therapies to treat and prevent developmental delays.

What about my family's research results?

We are hard at work trying to identify if there is a genetic cause of the CDH in all families enrolled in DHREAMS. Presently we have an answer for approximately 10% of the families participating in the study, and all of these families have been contacted with their results if they indicated at the time they enrolled in the study that they wanted to receive results. For the remaining 90% of families in our study, our genetic research has not yet been able to identify the cause. This could be due to several reasons: scientists do not yet know all of the genes involved in CDH, genetic analyses are not yet sensitive enough to detect all genetic causes, and the CDH in a particular family is not caused by a genetic mutation.

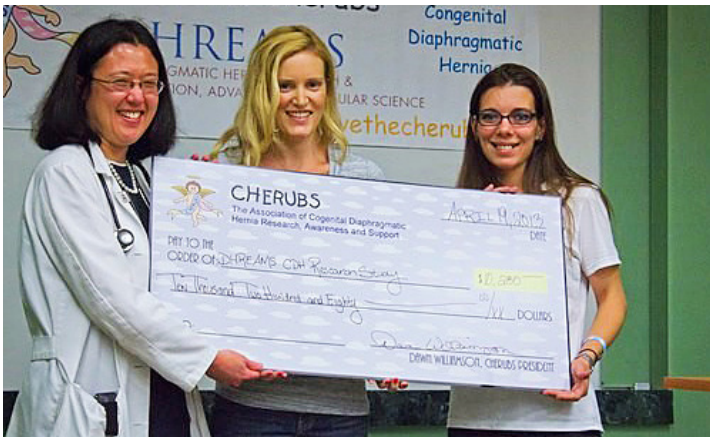
Sometimes we find a genetic change that we think might be the cause of the CDH in the family but we need to do further studies to better understand the genetic change. We may need to collect additional blood samples to complete these studies. We will contact your family if we need additional samples and explain why we need them.

When our study first began, some participants provided saliva samples for the study. Unfortunately, we have not been able to obtain the quality and amount of DNA we need from these samples to complete the sensitive genetic studies. If your family provided a saliva sample and you would like to now provide a blood sample, please contact us. We can arrange for a certified phlebotomist to come to your home to complete the blood draw at your convenience, free of charge.

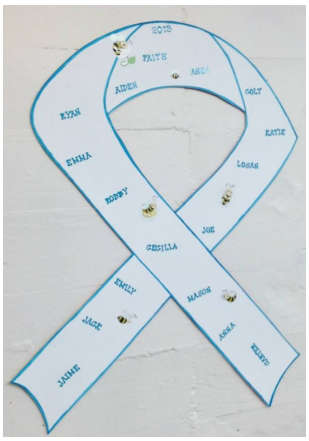
We are very appreciative of each and every family that participates in our study and are dedicated to finding an answer for everyone. Unfortunately we are not able to call everyone to provide individual updates. We encourage you to contact us if you have questions. We can update you on the studies that 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.

CDH Events

The DHREAMS study group co-hosted CDH Awareness Day at New York Presbyterian Hospital with the New York Chapter of CHERUBS. We also attended The CHERUBS International CDH Conference in Boston and The Breath of Hopes CDH Summit in Cincinnati. 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.



CDH Awareness Day at New York Presbyterian Hospital with Dr. Wendy Chung, Erica Larsen and Noel Williams.



Breath of Hope CDH Summit 2013 with Elizabeth Doyle-Propst and Sheryl Trost.

If you have any questions about the information in this newsletter, please call (212) 305-6987.

DHREAMS Participating Hospitals

The Children's Hospital of Wisconsin joined the DHREAMS team this year. We now have 8 Hospitals participating in the DHREAMS study. At each of these hospitals all families affected by CDH are invited to be part of the study.

- Columbia University Medical Center/ Children's Hospital of New York
- University of Nebraska/ Children's Hospital & Medical Center
- Vanderbilt University/ Monroe Carell Jr. Children's Hospital
- 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
- Children's Hospital of Wisconsin

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Columbia University IRB
IRB-AAAB2063
IRB Approval Date: 12/04/2013
for use until: 10/01/2014