Bench to Bassinet: Pediatric Cardiac Genomics Consortium

CHD GENES Newsletter

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Welcome! This is the 2nd newsletter for the CHD GENES Study, a multicenter research study investigating the genetic causes of congenital heart disease (CHD). Since the study began in November 2010, 9,559 individuals with CHD have been enrolled in the study along with 12,672 relatives. To our knowledge, this is the largest set of samples assembled to study CHD. Articles in this newsletter include a summary of some of what we have learned from the samples donated thus far as well as some of what can be gained from understanding the genetic cause(s) of CHD.

From the Study Investigators and Coordinators – *thank you for helping to advance our understanding of what causes congenital heart disease.*

Enrollment Update

Subjects Enrolled
12,672 Relatives Enrolled

New Genetic Discoveries - An Update

By Dr. Wendy Chung

The goal of the CHD GENES Study is to determine the causes of congenital heart disease (CHD) and to determine the role of genes in causing congenital heart disease. Genetic differences come in many sizes. Our genetic blueprint is like a set of encyclopedias with 46 volumes. The genetic differences leading to congenital heart disease in some cases is like having an extra volume in the encyclopedia set as seen in conditions like Down syndrome that are due to having an extra copy of chromosome 21. In other individuals, the difference is more subtle and similar to having a chapter missing from a single volume as is the case with conditions like DiGeorge syndrome that are associated with missing a portion of chromosome 22. Smaller differences include missing a single paragraph, missing a single word, or even a subtle alteration in just a single letter.

Some individuals with congenital heart disease have no one else in their family with this condition. You might think that the CHD can't be genetic when it doesn't run in families. However, we now realize that

New Genetic Discoveries - An Update cont.

some genetic changes are NEW genetic changes that start for the first time in the individual with CHD. We call these *de novo* genetic changes. Even though these new genetic changes weren't inherited from either parent, they can be passed down from the person who has them to the next generation.

We recently completed a large study of 538 individuals with CHD (including hypoplastic left heart, tetralogy of Fallot, and heterotaxy) and their parents to try to determine how frequently *de novo* or new genetic changes (similar to a missing chapter or missing paragraph of an encyclopedia volume) lead to CHD and to try to determine which genes are responsible. By using the parents in comparison to the child with congenital heart disease, we were able to determine what genetic information in the child was different than either parent and therefore new. We determined that 9.8% of the individuals with CHD in our study have missing or extra genetic material that is different from their parents, often a major contributing cause to the CHD. Some of these genetic changes have been previously associated with CHD, but many of them have not been previously reported. We identified new genetic causes of CHD including the genes *ETS1*, which is associated with Jacobsen syndrome, and *CTBP2*, as the CHD gene involved in deletions at the end of chromosome 10. This study, in addition to our prior study that used the exome sequencing method to detect single letter changes, now suggest that 20% of severe CHD is due to new genetic changes in the child that are not inherited from the parents. This information will ultimately prove helpful for families to determine the risk of congenital heart disease for future children and to provide better predictive information for individuals with CHD.

Photo Credit: iStockphoto

One Family's Heartwarming Gift

By Nancy Cross

I have been in the position of the Bench to Bassinet Research Coordinator at Yale University for the last four years. As nursing is my background, accepting this position was very exciting to me realizing the limitless opportunities for learning and professional growth. Additionally, through my role, I have had the good fortune to meet some truly exceptional individuals and families affected with congenital heart disease (CHD). Spending time with CHD GENES participants has been very special to me as I am repeatedly amazed with how sincerely kind, caring, and generous these families are, and I have had many wonderful experiences as a result.

One such family has created a memory I will treasure forever. This family of three became a family of five in December of 2011 when they welcomed the birth of their beautiful twin boys Riley and Marcus. Riley was much smaller than his brother and was facing many additional health challenges. CHD was one of his challenges and Riley had to undergo two heart operations in the first several months of his life. Supported and

nurtured by his loving family, Riley did very well and after many months in the hospital was able to go home and join his family. I am pleased to say Riley is now three years old, happy and healthy and starting pre-school.

Photo Credit: Bummer Bears

Riley's parents, Leanne and Colin, contacted me in January of 2014 as Congenital Heart Disease Awareness Week was approaching. They were grateful Riley did so well and wanted to find a way to give back. They purchased twelve *Mended Heart Bummer Bears* which are beautiful teddy bears with a plastic zipper located on the chest (much like an incision) with an embroidered heart revealed beneath the zipper. They attached their personal story and honored me with the pleasure of gifting these bears to children undergoing heart surgery during the awareness week. This generous and thoughtful act of kindness touched the hearts of the families receiving the bears, helping them realize they are not alone and inspired hope for their child's recovery. This created so many beautiful experiences and memories- a ripple effect of kindness. This family's commitment to CHD and generosity was truly impactful to many children and families, I am so honored they allowed me to be part of their dream. With the success of their effort, they plan to repeat the Bummer Bear gifting in February 2015 as well.

THANK YOU Leanne and Colin; you are truly a beautiful family!

The Benefits of Understanding the Genetic Causes of Congenital Heart Disease (CHD)

By Dr. Amy Roberts

There are many potential benefits of understanding the genetic cause(s) of CHD for an affected individual and his or her family.

1. COMPLETE THE DIAGNOSTIC ODYSSEY

Many children with CHD have undergone extensive genetic and other testing to try to determine why they were born with their special heart. Because our current understanding of the cause(s) of CHD is incomplete, these tests often do not provide a complete answer. Continued research to find the genes that direct the normal development of the heart will lead to discoveries about new genes that can then be tested for the presence of a causative mutation in individuals. If a mutation in a gene is found, the family has an answer and no longer has to wonder "why?".

2. ADDITIONAL GUIDANCE/PREVENTION

It is not uncommon for a child with CHD to have other medical problems and/or developmental challenges. Once the genetic cause is understood, we can look to other children with the same or similar mutations to see if there are additional issues commonly reported for which a child should be followed. For example, a common cause of pulmonary valve stenosis is a mutation in a gene that also causes Noonan syndrome, PTPN11. Children with Noonan syndrome are monitored for delayed growth, bleeding problems, and learning issues which

can accompany the pulmonary stenosis. By knowing the genetic mutation, other potential complications can either be prevented or detected and treated early.

3. RECURRENCE RISKS & FAMILY PLANNING

Discovering the genetic cause of CHD in a child may lead to testing of a parent. This can help to determine the likelihood of having a second child with CHD. For an adult with CHD and a known genetic cause, he or she can meet with his or her obstetrician prior to a pregnancy to understand the likelihood of having a child with CHD and to discuss his or her pregnancy options.

4. TREATMENT

Understanding the genes that regulate normal heart development is a window to understanding how changes in complex biochemical pathways lead to heart malformations. Drugs that target these pathways can then be tested in the laboratory to see if they might be helpful in slowing progression (for forms of CHD that get worse over time) or preventing the development of CHD (for example in an at-risk pregnancy). This is an active area of research with promise for drug research trials in the not too distant future.

Thank you for your continued support.

Enrolling both parents of an individual with congenital heart disease is very important to understanding the genetic causes of CHD. It is not too late if you have not yet enrolled.

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