Bench to Bassinet: Pediatric Cardiac Genomics Consortium

CHD GENES Newsletter

Welcome!

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Welcome to the first CHD GENES Newsletter.
Halfway through the enrollment period, we are at more than 60% of the goal of enrolling 10,000 individuals with congenital heart disease. This Newsletter summarizes some of what we have learned to date and some of our plans for the near future. Enrolling both parents of a proband is very important to our work. If a parent has yet to enroll, it's not too late. Please see the article about a new way to link data across many studies by using a new ID system. If you have not provided the information for us to assign this new ID, please contact the study coordinator at your site (see the last page). From the study Investigators and Coordinators - **thank you** for helping us in our search for the causes of congenital heart disease.

Enrollment Update

Subjects Enrolled
8,084 Relatives Enrolled

New Genetic Discoveries

A common question many families ask us is ***"What caused my child's congenital heart disease?"*** This question has been difficult to answer because the cause is likely to be different in different individuals, and we therefore need large numbers of individuals with congenital heart disease to answer the question. One of the main goals of the Pediatric Cardiac Genomics Consortium (PCGC) has been to enroll enough individual with congenital heart disease to tackle this question. We have already enrolled over 6000 individuals with congenital heart disease, and in many cases we have enrolled their parents as well.
Our ultimate goal will be to enroll over 10,000 individuals with congenital heart disease.

New Genetic Discoveries

One possible cause of congenital heart disease is a change (or mutation) in genes that shape the heart. Although we inherit our genes from our parents, there are some genetic mutations that start in the child with congenital heart disease and are not passed down from either the mother or father. These are called de novo or new mutations. We wondered how frequently such new mutations might be seen in individuals with congenital heart disease when there was no family history of congenital heart disease.

We used a method called exome sequencing to analyze the genetic code of almost all of the 20,000 genes in the body in trios of mothers, fathers, and the individuals with congenital heart disease. The exome represents about 2% of the genetic code that directly provides the instructions to make all the proteins in the body. We believe that the majority of highly impactful mutations are in the exome. By comparing the genetic code of the mother, father, and child, we were able to easily determine the small number of new genetic changes that were present in the child and absent from both parents. This is the reason having blood samples on both parents is important to our study.

We studied 362 families with severe types of congenital heart disease that required surgery in infancy. In ~10% of the families, we identified mutations that we think are responsible for the congenital heart disease. In some cases we identified mutations in genes that were previously known to cause congenital heart disease.

More importantly, in most cases we identified brand new genes for congenital heart disease. Many of the genes we identified seem to work together to modify a protein called histones that interacts with DNA to turn on and off genes that are important in heart development. Based upon our study, we believe there are likely at least 400 genes in which new mutations in the child can cause congenital heart disease. Thus, we still have a lot more work to do.

This study has important implications for our research and tell us what cellular processes and which genes are important for heart development. This study also has important implications for families. If a child's congenital heart disease was the result of a de novo mutation, the child's parents have only a 1% chance of having another child with the same genetic problem. However, that child with the de novo mutation will have a 50% chance of passing the mutation onto a child if he/she has children in the future.

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Global Unique Identifiers for Congenital Heart Disease Patients

We are introducing a new ID system into CHD Genes called global unique identifiers or GUIDS. GUIDs are unique identification numbers that can be used to track patients with congenital heart disease through multiple studies and over time and link the information about a single person across research studies. The GUID will allow researchers to increase the amount and types of clinical information and avoid duplicating efforts to collect the same information from patients multiple times.

Right now, various types of information are being collected on patients with CHD in separate studies. For instance, the Pediatric Cardiac Genomics Consortium is collecting genetic information on patients. The Pediatric Heart Network is collecting clinical information. Also, surgical information is being collected in the Society for Thoracic Surgery Congenital Heart Disease database. Unfortunately, there is no current way to link the information on the same patient who may be enrolled in all three studies.

Imagine the possibilities if we could link the information. We might be able to investigate how genetic factors affect how patients do after surgery. We might be able to investigate which surgical techniques result in the best neurodevelopmental outcome. Finally, we might determine which genetic variants result in a positive or negative response to certain medications.

The GUID completely protects the patient's privacy.

To generate a GUID, four pieces of information are collected from a patient – full name, gender, date of birth, and city of birth. These identifiable pieces of information are collected at the local site, and the information stays at the local site. This information is then encrypted by computer software into special codes that cannot be traced back to the patient. These codes are then transferred to a centralized computer which further encrypts the codes into a GUID. The GUID is then transferred back to the local research site. So, **privacy is protected in two ways – the identifiable information never leaves the local site, and the GUID cannot be traced back to the patient.**

Another important feature of the GUID is that the patient or family does not need to remember it. Any time a patient enrolls into a study, he/she will provide the same four pieces of information – name, gender, date of birth, and city of birth, and the exact same GUID will be generated each time.

The GUID will be an important mechanism to advance research and accelerate the science so we can provide better care for patients with congenital heart disease.

Please call/email the study coordinator at your site to provide the information necessary to make your GUID. The contact information for your study coordinator is on the last page.

Induced Pluripotential Stem Cells

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Following the PCGC's important discovery that several genes with new mutations in individuals with congenital heart disease (CHD) altered a particular aspect of cellular function, the consortium is following with a new and exciting opportunity to study how heart defects arise. This involves a relatively new scientific technology that allows scientist to take mature cells like cells from a blood sample and revert the mature cells into an immature state called pluripotent stem cells. Pluripotent stem cells can be used to make all of the cell types in the body. Making these induced pluripotent stem cells from individuals with congenital heart disease, it is possible to induce them to become functional heart cells that actually beat in the petri dish!

The PCGC will be recruiting individuals in whom we have identified specific gene changes, taking a fresh blood sample, and making the induced pluripotent stem cells from the blood cells. Knowing the aspect of cell biology that is likely to be altered in those individuals, we will be able to study the stem cells as well as the heart cells that we will produce from the stem cells. The hope is that we will better understand what went wrong during the earliest stages of the formation of the heart. That, in turn, might help us develop new approaches to preventing congenital heart disease or limiting its impact in some children born with heart defects.

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