

News About...

# Neural Tube Defects Research

Summer 2017

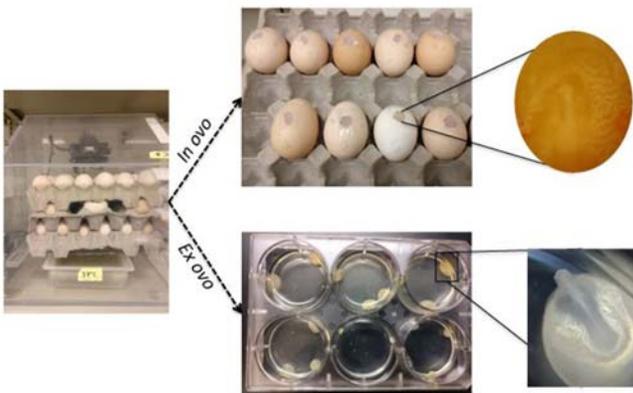
## Chick Embryos Provide Insight into the Causes of Neural Tube Defects

Studying the process of neural tube closure in humans is difficult; therefore, researchers often use animal models such as mouse, chicken, frog, fish and worms. Our group has previously worked with both mouse and zebrafish and has recently started working with chick embryos. About 60% of chicken genes have a similar gene in humans. Chick embryos are easy to access (develop in an egg vs. a uterus), making it much easier to observe neural tube closure, and are inexpensive and easy to maintain.

Our lab is using chick embryos to test candidate genes (genes thought to play a role in causing neural tube defects). The candidate genes were previously identified by whole exome sequencing (see genetics terms defined on page 5) of individuals with neural tube defects. If a candidate gene is disrupted in the developing chick and the chick develops a neural tube defect, this provides evidence that the gene is necessary for normal neural tube closure.

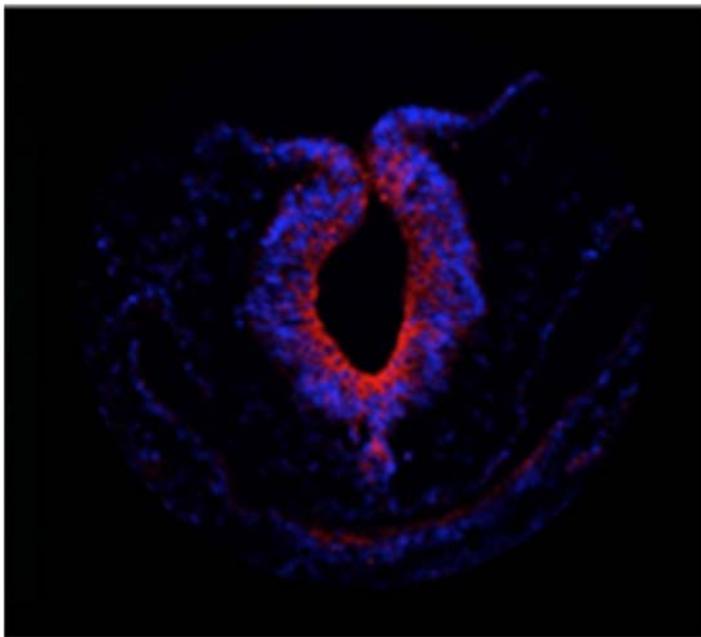
There are two ways to study chick embryos; 1) maintain the embryo inside of the eggshell and observe development through a small hole created in the eggshell (*in ovo*), or 2) remove the embryo from the eggshell and grow in culture (*ex ovo*).

First, we inject the human version of the gene along with a fluorescence protein (will glow and show where the gene is turned on) into the neural tube of the chick embryo during early development, when the neural tube is still open. The embryos grow until after neural tube closure should occur and are then stained and visualized under a microscope.



Chick embryo development using two different techniques: *in ovo*, and *ex ovo*

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Chick embryo's neural tube before complete closure

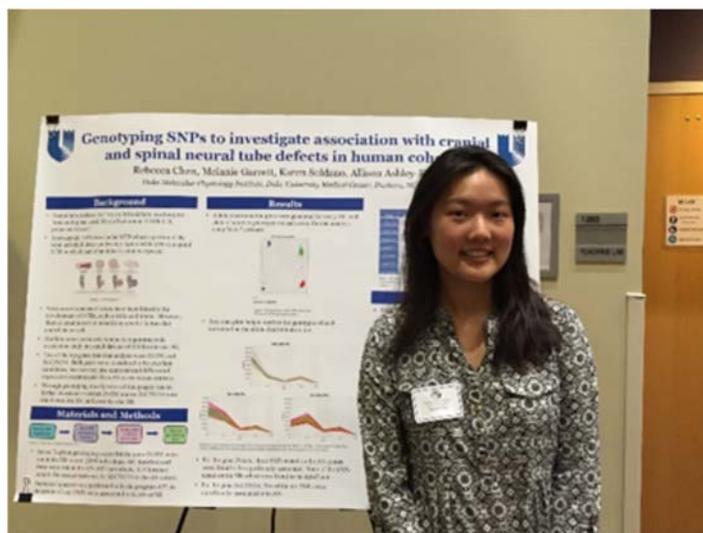
This research is being developed in collaboration with Dr. Mary Hutson's lab (Department of Pediatrics, Duke University). Dr. Hutson is an expert on using chick embryos as an animal model to study development.

### Heat Exposure and NTDs

One underexplored factor that can cause neural tube defects (NTDs) is heat exposure early in pregnancy. Heat exposure may occur due to maternal fever, hot tub or sauna use, or hot yoga participation. Maternal heat exposure may play a role in up to 20% of NTDs, and triples the risk for an NTD in the baby. However, not all pregnancies exposed to heat result in an NTD. This may be due to underlying genetic risk factors, which make some pregnancies more susceptible to the effects of heat. We are beginning to examine genetic variants in temperature sensitive genes that may predispose some pregnancies with maternal heat exposure to develop NTDs. To avoid the potential impact of heat exposure early in pregnancy, women who may become pregnant should avoid extreme heat and talk with their doctor about taking Tylenol to reduce fever.

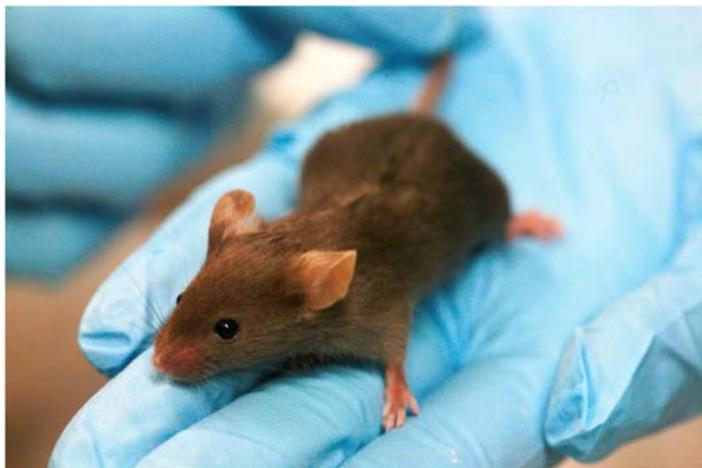
### Genes Implicated in Anencephaly but Not Spina Bifida

For the past four years, Rebecca Chen, a Duke undergraduate student, has worked with our team to investigate the genetic causes of neural tube defects. Rebecca recently presented her work genotyping the genes *INADL* and *SLC39A14* in participants with anencephaly and spina bifida. Previous research in our lab implicated both of these genes in the development of anencephaly. *INADL* is active in the human brain and is involved in regulation of tight junctions (physical connections between cells), which are important for neural tube closure. *SLC39A14* is involved in the transport of zinc, which is required by the body for growth and development. Results from Rebecca's work indicate that both genes may play a role in causing anencephaly, but there is no evidence for involvement in spina bifida. While the causes of anencephaly and spina bifida are thought to overlap, different genes may be involved in causing different types of neural tube defects. Rebecca will enter medical school at Washington University in St. Louis this fall and we wish her the best!



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## **Patj Mice Will Help Us Understand the Role of Cell Connections in NTDs**



As described above, one of the candidate genes we are investigating is *INADL*. *INADL* also goes by another name, *PATJ*. The major function of this gene is to help neighboring cells stay connected to each other, but we still do not understand how disrupting that function might lead to NTDs. Recently, we obtained two sets of mouse parents who have one copy of their *Patj* gene disrupted. We are happy to report that both sets of parents recently had litters! So far, these pups are developing normally and without any NTDs. During these pregnancies, the parents were fed a normal mouse chow. For the next pregnancy, we will feed the parents folate-deficient chow to determine if that causes NTDs like it does in humans. Stay tuned!

### **How Baby Luca Built a Foundation: The Participants' Point of View** By Rachel Gilbertsen-Hill

It was Tuesday September 2, 2014 and we had been anxiously awaiting our ultrasound scheduled for that morning. Our baby was 14 weeks and 2 days! We were certain that, if the tech would let us, we would find out if our bundle of baby was a boy or girl.

The ultrasound tech called me back. She was incredibly kind and let me look at every square inch of my baby's cute little body. As she swooped by the baby's cute little butt I saw something awesome!

"It's a boy! Isn't it?" I exclaimed.

She laughed and said "Yup! Of course you are only 14 weeks and it's too early to completely tell (I think they have to say that) but it looks like a boy to me!"

"It's my Luca!" I said with glee.

The tech left to go get the doctor and I brainstormed all the ways I could tell Jeff we were having another boy! I was so thrilled and I knew he would be too! The tech came back in, reapplied the goo, and got my sweet boy ready for his debut for the doctor. Dr. O entered and went straight to the monitor.

"Let me get a look at his face." he said. "Stop. Right there." He peered in closer. "Okay. Turn it off."

Panic flushed through my body and I knew I looked just as terrified as I felt. My heart was racing. My stomach flipped and flopped. I couldn't breathe. Tears filled my eyes. Something was wrong.



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Dr. O came over to the side of the bed. I immediately covered my face and braced myself. It is all a complete blur. In the few sentences that he spoke he explained that my baby, my Luca, had something wrong. Something about his skull. Something about his brain. Something wasn't right with him.

Our sweet boy was diagnosed with Anencephaly (later re-diagnosed with Isolated Acrania). We were heartbroken. Devastated.

That afternoon when we arrived back home we cried a million tears and started our journey of trying to fix our boy. In those first few hours we googled, searched, re-googled, re-searched what was being done to help these babies. The one constant in our search was Duke. The Duke Anencephaly Study and their amazing team were looking for the answers we longed for and we knew we had to participate.

Heidi was one of the very first phone calls we made after Luca's diagnosis and we enrolled in the study without hesitation. Throughout our journey with Luca and in the months after his birth, Heidi and her team (led by Dr. Allison Ashley-Koch) were a constant support of answering questions and helping us fully understand the full magnitude of Luca's diagnosis. With each passing month, we grew more and more fond of the research they were doing and appreciated their efforts in finding what did this to our boy. They were the only group specifically studying the causes of Anencephaly and with each passing day we realized how immensely important their work was to helping these babies and families. When we read how seriously

underfunded their research was, and how this effects the amount of work they can examine and study, we knew we had to help.

On February 11, 2015 our Luca Joseph Hill was born. After four hours of being surrounded by all who adored him, he snuggled in my arms, held his Daddy's hand, and said hello to Jesus. Before he left us we promised him that we would fix this. It was in that moment that the Luca Hill Acrania and Anencephaly Foundation (LHAAF) was formed.



LUCA HILL ACRANIA & ANENCEPHALY FOUNDATION

We have dedicated the past two years to helping families who are walking this path and hosting fundraisers to support the research being conducted at Duke. We full heartedly believe in the Duke Anencephaly Research team and stand side-by-side with them in their mission. That is why every penny of what LHAAF raises in our yearly fundraisers goes into their research and back to the courageous families fighting for their children. We believe that because of the research being conducted by the Duke team that they will one day be able to locate the genes involved in Anencephaly and that this will lead to better screening, prevention, and one day, a cure.

## Anencephaly: Insights for Health Care Providers

One hundred and sixty women and 110 of their male partners who received a prenatal diagnosis of anencephaly completed questionnaires about their pregnancy, their decisions and recommendations for health care providers. Around 44% of participants chose to end the pregnancy early and around 56% chose to carry to term. Participants reported many different factors that influenced their decision to end or continue the pregnancy. The number one reason why participants chose to end the pregnancy early was the fact that there was no chance the baby would survive. Religious views factored most into the decision to carry to term. As a group, participants who continued the pregnancy were less likely to regret pregnancy management decisions than those who terminated. Recommendations for health care providers were numerous and varied but primarily involved giving comprehensive information to allow informed decision-making and provision of support and resources. A detailed report of factors that influenced pregnancy management decisions and recommendations for health care providers will be submitted for publication soon. We wish to thank those of you who shared your experiences and thoughts with us.

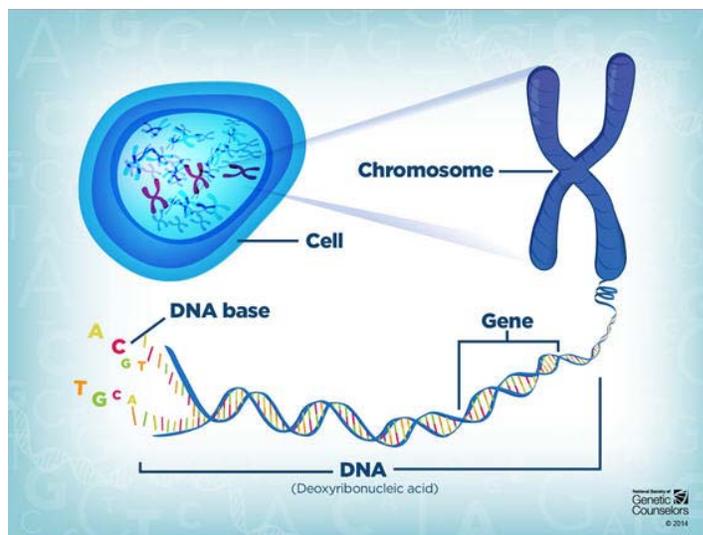
### Genetics Terms Defined

**Gene** - Genes are made up of DNA. Genes are segments of DNA that serve as the instructions for your body. A gene contains information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child. We have two copies of most of our genes, one copy inherited from each parent.

**DNA** - DNA is short for deoxyribonucleic acid. DNA is a genetic code made up of a

four-letter alphabet (each letter called a DNA base, or nucleotide) commonly denoted by the letters A, C, T, and G.

**Chromosome** - A chromosome is a tightly wound string of DNA containing hundreds to thousands of genes. Most of the cells in a human body contain 23 pairs of chromosomes (for a total of 46 chromosomes). For each pair, one chromosome comes from each parent. One pair, called the sex chromosomes, determines if we are male or female. Males have one X and one Y chromosome and females have two X chromosomes.



**Genome** - The collection of all DNA found in a human (3.2 billion letters of DNA) is called the genome.

**Exome** - Within the genome are about 30,000 genes. These genes account for only about 2% of the genome. This 2% - the collection of all genes - is called the exome.

**Exome sequencing** - The spelling out and reading of a person's DNA within the exome.

**DNA variant** - Sometimes called a mutation, a DNA variant is a change or difference in the DNA in comparison to most people.

## Enrollment Update

Due to funding limitations, study enrollment has been limited to anencephaly trios (baby with anencephaly plus both parents) for the last few years. In 2016, 28 additional trios joined the study and so far 15 trios have joined in 2017. In total, we have collected DNA samples from 5,829 individuals in 1,542 families. Participating families come from all across the United States and Canada with all types of NTDs; however the majority of participants have either spina bifida or anencephaly.

We would also like to inform you that our study is currently not accepting new families for participation. We are very grateful to the families that have participated over the years. They have provided us with a wealth of information

and samples without which we could not perform the exciting studies that we have described in this newsletter. The study and our research will indeed continue. But because funds are limited, we are shifting our focus more to the research rather than enrollment.

## In Loving Memory

We would like to express our sincere condolences to families who have lost a baby or other family member to a neural tube defect. We appreciate your sharing with us such precious information about your loved-one and the time and effort you have taken to enroll in our research study. Please know that the memory of your family member is honored by your participation and we are truly grateful.



## Follow us on Facebook

For periodic updates on anencephaly research being conducted at the Duke University Medical Center “like” us on Facebook at:  
<https://www.facebook.com/DukeAnencephaly/>

## Who Pays for Research?

Conducting genetic research studies is painstaking and expensive work that relies on funding support from both public and private sources. Over the years the Duke team has been awarded research funds or grants from March of Dimes, National Institute of Health (NIH) and from private donors whose lives have been touched by neural tube defects.

We are often asked if we can accept donations to support the NTD research, sometimes in memory of a baby or loved one who has passed away. The answer is yes, and these donations are very much appreciated!

To make a financial gift to the NTD research, you may visit the secure web site of the Office of Alumni and Development Records at [www.giftrecords.duke.edu](http://www.giftrecords.duke.edu) and click on “Make a Gift Now!” and then “Make a Credit Card Gift.” **Under “choose an area” click on “Still can’t find your designation of choice?” and type in 3912359.** Or you can mail your tax-deductible donation to :

Duke University Medical Center  
NTD Research Fund  
300 N Duke Street  
Durham, NC 27701.