

News About...

NEURAL TUBE DEFECT Research

Volume 8, Summer 2010

General Study Enrollment Update

We have collected DNA samples from 5,290 individuals in 1,374 families. Participating families include family members from all across the United States with all types of NTDs; however the majority of participants have either spina bifida or anencephaly. Thank you to anyone who participated during the past year, or since 1993 when the study first began.

Anencephaly Enrollment Update

We have enrolled 282 families who experienced one or more anencephaly pregnancies. Of these 282 families, 170 (60%)

are singleton families, meaning there is one case of anencephaly and no other cases of neural tube defects in the family. The other 112 families (40%) are multiplex families, meaning there are two or more cases of neural tube defects in the family. However, these numbers do not represent the general population. Multiplex families are more likely to believe genetic factors are involved, and therefore are more likely to participate in this study.

We would like to thank all the families who have participated over the years. Research toward a better understanding of the causes of anencephaly would not be possible without you. We continue to enroll additional participants experiencing anencephaly pregnancies.



IN THIS ISSUE....

General Study Enrollment Update.....	1	NTD Recurrence Risks.....	3
Anencephaly Study Update.....	1	Anencephaly and Gender.....	3
Gene Updates.....	2	In Loving Memory.....	4
Expression Analysis.....	2	Keep Us Updated.....	4
Copy Number Variants.....	3	Who Pays for the Research?.....	4

Gene Updates

The human genome (all the DNA in a human) contains roughly 30,000 different genes. Genes can be thought of as instructions or recipes for how our bodies develop and function. Candidate genes (genes we think may be involved in neural tube defects) are picked based on their location in the genome or function, such as a gene that metabolizes folic acid. Below are research updates for several candidate genes we have looked at recently.

Vangl2:

In mice, there is an interesting gene called Lp that has been shown to cause craniorachischisis, one of the most severe neural tube defects, when genetic changes are present in the gene. There is a gene very much like Lp in humans called Vangl2 (van gogh-like 2). We performed an initial screen of this gene in study participants with lumbo/sacral myelomeningocele (spina bifida) and did not find any evidence of Vangl2 playing a role. However, a different research study reported changes in the Vangl2 gene in individuals with cranial NTDs. We are now in the process of screening this gene in our anencephaly participants to see if we can confirm this finding.

Nitric Oxide (NO) genes:

The nitric oxide (NO) genes may play a role in the closure of the neural tube. A previous study found that the NOS3 gene may contribute to causing spina bifida. We performed a screen of three nitric oxide genes (NOS1, NOS2A and NOS3) in participating families with cranial NTDs. We did not observe any evidence for involvement of the NOS3 or NOS1 genes. The best evidence for involvement was observed for the NOS2A gene. We are currently testing these genes in families with other types of NTDs,

including spina bifida, to see whether specific NO genes contribute to specific types of NTDs.

PAX3:

Changes in the PAX3 genes have been previously described in individuals with neural tube defects and deafness. We looked at the PAX3 gene in 12 families in which the family member with the neural tube defect was also deaf. No changes in the PAX3 gene were found.

Expression Analysis

Genes can be thought of as instructions or recipes for how our bodies develop and function. Certain genes are turned on/off at different times of fetal development. We collected amniocytes (fetal cells obtained from a test performed during pregnancy called amniocentesis) from both anencephaly pregnancies and normally developing pregnancies. We then tested these samples to see if the gene expression (genes turned on/off) were different for pregnancies with anencephaly in comparison to normal pregnancies. The majority of the genes which showed differences between the two groups of pregnancies were turned on less in anencephaly pregnancies as compared to normally developing pregnancies. We are encouraged by our findings, as the genes which were under expressed in anencephaly pregnancies play important roles in fetal development and could logically contribute to the development of anencephaly. As we continue to analyze our data, we hope to uncover new candidate genes for future study.



Copy Number Variants

Our research is based on our ability to identify differences within the DNA that may contribute to or cause neural tube defects. One of these differences is known as Copy Number Variants. In theory, we should all have two copies of the human genome (all the DNA in a human). One copy we inherited from our mother and one copy from our father. However, researchers have found segments of DNA within the genome that are present in less or more than two copies. These regions are known as Copy Number Variants (CNVs). Everyone has CNVs, some of which are normal and some of which cause disease.

We recently looked for CNVs in families with anencephaly. The most interesting findings were CNVs in three genes known to be expressed in the fetal brain and may play a role in the developing neural tube. We also found a CNV on chromosome 14 in a significant number of participants with anencephaly. This CNV was not found in the parents so is a new genetic change in these pregnancies. Our research into CNVs continues.

NTD Recurrence Risks

We are often asked by participants, after having one child or pregnancy with a neural tube defect (NTD), what is the chance of having a second pregnancy with a NTD. The chance of having a second pregnancy with a NTD is called a recurrence risk. Previous studies report that between 2-5% of couples go on to have a second pregnancy with a NTD. We analyzed family trees from 1066 participating families and determined in these families, the chance to have a second pregnancy with a NTD was 6%. We also looked at the risks for half siblings. Half siblings



though the mother had a 2% chance of having a NTD and half siblings through the father had a 1% chance of having a NTD. The risk of having a second pregnancy with a NTD can be lowered by taking 4 milligrams of folic acid for three months prior to getting pregnant and during the first trimester of pregnancy. The entire article can be found in Birth Defects Research (Part A) 82:662-669 (2008).

Anencephaly and Gender

It has long been recognized that more females than males have anencephaly. Previous studies report that for every 1 male with anencephaly, there are approximately 2 females. Due to this female majority, it has been theorized that genetic and environmental factors that cause anencephaly may have more impact on a developing fetus if the fetus is female.

Family trees from anencephaly singleton (1 anencephaly pregnancy, no family history of NTDs) and multiplex (1 anencephaly pregnancy plus 1 or more additional NTDs) families were analyzed. The gender of the baby with anencephaly and the gender of healthy siblings were recorded.

Overall, we found 1.6 females for every 1 male with anencephaly (62% female). Males with anencephaly were found more often in singleton

families. In multiplex families, we found almost 2 females for every 1 male. Healthy siblings in singleton families were equally likely to be female or male. Interestingly, healthy siblings in multiplex families were twice as likely to be female.

There is an excess of females, both with anencephaly and healthy siblings, in multiplex families. Genetic factors influenced by gender may play a larger role in multiplex families.

In Loving Memory

We would like to express our sincere condolences to families who have lost a pregnancy or other family member to a neural tube defect. We realize that this process is an extremely difficult one for your family. 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.

Keep Us Updated

Please keep us in mind when important changes happen in your family. We like to ensure that all our family trees and mailing lists are accurate. We would like to know if there are any major changes in the health status of family members, such as if another family member is diagnosed with a neural tube defect or if there are new members of your family. Also, if you should move, please give us your updated contact information. You may give us your updates by calling us at 919-684-0655 or by sending an email to ntd@chg.duhs.duke.edu. Thank you!



Who Pays for the Research?

Conducting the genetic research studies that create neural tube defect breakthroughs is painstaking and expensive work that relies on funding support from both public and private sources. Since 1993, when the Hereditary Basis of Neural Tube Defects study began, the Duke CHG team has been awarded research funds or grants from March of Dimes, National Institute of Child Health and Human Development (NIH), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Environmental Health Sciences, and from private donors whose lives have been touched by neural tube defects.

On occasion, we are 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. If you or someone you know would like to make a gift, the Center for Human Genetics has created the Duke CHG Neural Tube Defect Research Fund. To make a financial gift to neural tube defect research, you may visit the secure web site of the gift records office at www.giftrecords.duke.edu and click on "Make a Credit Card Gift Online," or you can send your tax-deductible donation to the address below:

Duke Center for Human Genetics
Neural Tube Defect Research Fund
Box 3445
Durham, NC 27710