DUKE center for HUMAN GENETICS

News About...

Neural Tube Defect Research

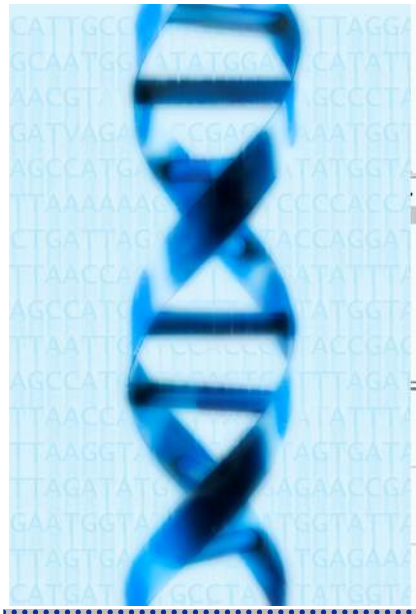
Volume 9, Summer 2012

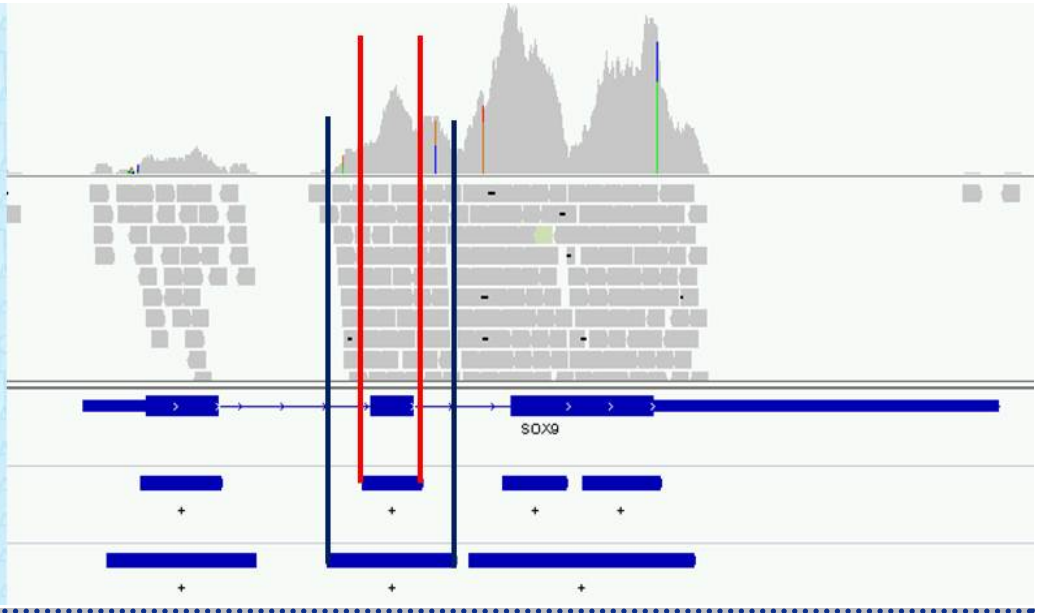
Exciting New Approaches in Genetics Research

Exome Sequencing

The human genome (all the DNA in a human) contains roughly 22,000 different genes. Genes can be thought of as instructions or recipes for how our bodies develop and function. Genetic disorders are caused by changes in a gene or genes, preventing the gene(s) from performing their proper function. Candidate genes are genes we think may be involved in causing neural tube defects which are picked based on their location in the genome or function, such as a gene that processes folic acid.

In recent years, it has become possible to read or sequence all the genes in a person (exome sequencing).





IN THIS ISSUE:

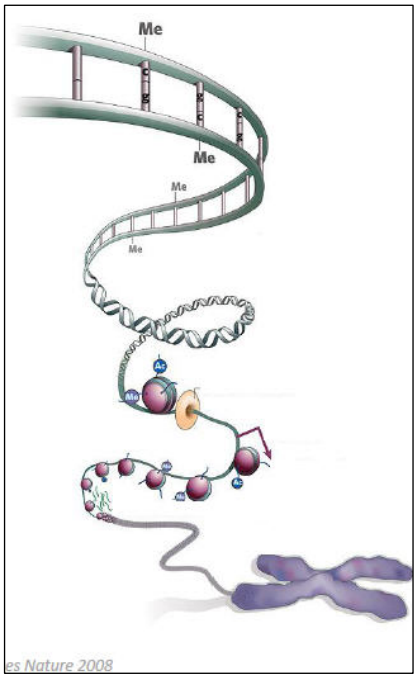
Reading all the genes allows us to find changes in genes without having to pick a candidate gene. The benefit of this type of approach is that we can look at many more genes in less time. Unfortunately, this type of testing is still fairly expensive and can only be done on a small number of samples due to funding limitations. Also, reading all the genes finds a large number of changes in each person (this is to be expected and what makes each of us unique). It can be difficult to determine which changes are normal changes and which may cause disease.

We recently applied this approach to a large family with multiple members diagnosed with spina bifida. Once all the genes were sequenced, we checked to see which gene changes were found in all the family members with spina bifida. Initial studies have been completed and several interesting gene changes are currently being followed up.

Epigenetics

Genes are made up of DNA. Chemicals or markers that sit on top of the DNA regulate gene expression (switch genes on and off). Epigenetics is the study of these chemicals or markers. Changes in these are believed to contribute to many diseases. A person's DNA remains the same throughout their life. In contrast, epigenetic markers can change throughout a person's lifetime in response to environmental factors. But like DNA, these markers can be passed to offspring.

It has recently been shown that individuals with neural tube defects (NTDs) have changes in their epigenetic markers. To confirm and further research the importance of epigenetic changes in NTDs we have begun a project looking at epigenetic markers in identical twins, one with anencephaly and one without. Identical twins have the same DNA (which we confirmed). Therefore, differences between identical twins are more likely to be caused by changes in epigenetic markers.



Collaborative Research into Fumonisin Begins

Fumonisin is a toxin produced by a mold that grows on corn in warm, relatively dry climates, including the southern United States. It has been shown to cause (NTDs) in mice, and is thought to contribute to higher numbers of babies born with NTDs in areas where corn is eaten often. We recently started work on a collaborative study with

researchers from Creighton University in Nebraska, DX Molecular in Guatemala, and the U.S. Department of Agriculture (USDA) to better understand fumonisin's impact on people exposed to it. To investigate this, our collaborators are collecting blood samples from healthy women in areas of Guatemala who either

eat a lot of corn (more than 15 tortillas) or very little corn (less than 6 tortillas) on a daily basis.

The blood samples are then sent to the USDA and our lab at Duke. Collaborators at the USDA analyze how much fumonisin is in the blood while we look for changes in gene expression (genes turned on or off). This will tell us how different people respond to fumonisin. At the same time, our collaborators at Creighton University are working with mice, one type which develops NTDs when given fumonisin, and another which does not. Our lab is sequencing or reading genes in these mice to figure out why they respond differently. We hope to identify genetic changes which determine how the body responds to fumonisin. This will provide important groundwork for investigating fumonisin as a causative factor for NTDs.

7th International Conference on NTDs

In November 2011, 130 scientists and clinicians from the US, Europe, Central America and Australia descended on Austin, Texas for the biannual International Conference on NTDs. The scientists at the meeting had backgrounds in epidemiology, biology, embryology, genetics, neurosurgery and pediatrics. Information on NTD research, prevention and treatment was presented. The Duke NTD research team, represented by Dr. Simon Gregory, Dr. Allison Ashley-Koch and graduate trainee Deidre Krupp, presented much of the findings discussed in this newsletter. In the field of genetics and genomics the Duke team showed our continued leadership and we, like other scientists at the meeting, maintain a passion to identify the causes and cures of NTDs.

Enrollment Update

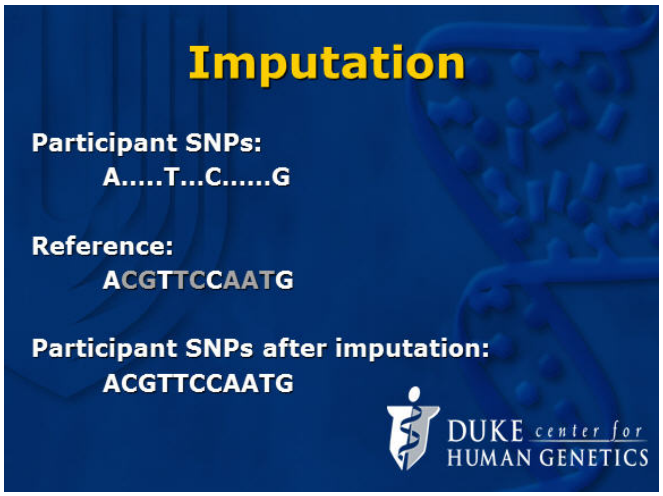
We have collected DNA samples from 5,438 individuals in 1,423 families. Participating families come from all across the United States and Canada with all types of NTDs; however the majority of participants have either

spina bifida or anencephaly.

Thank you to all the families who have participated over the years. Research toward a better understanding of the causes of neural tube defects would not be possible without your help. We continue to enroll additional participants experiencing anencephaly pregnancies.

Anencephaly GWAS Gets a Fresh Look

DNA is written in a special genetic alphabet consisting of four letters – A, T, C, and G (called nucleotide bases). The human genome (all the DNA in a human) consists of 3 billion letters. Single nucleotide polymorphisms (SNPs, pronounced "snips") are one letter



markers throughout the genome that may differ from person to person. These differences do not usually affect a person's health, but can be easily identified and used to look for genes. A genome-wide association study (GWAS) is performed in an effort to locate specific regions of the genome that may contain genes that cause or contribute to disease. SNPs are read at regular intervals throughout the genome trying to find letters that are consistently found in participants with the condition but are not found, or not found as often, in family members without the condition.

In 2007, we completed a GWAS that read 317,000 SNPs in 51 families that had experienced an anencephaly pregnancy. We recently utilized a new statistical method called imputation to learn even more information from this data. Imputation allows you to guess letters you didn't read by comparing the letters you did read to a reference sequence (see image). Using this technique, we were able to infer letters for 2 million SNPs and were therefore able to get a much better look at genetic variation across the genome. Because the genetic coverage is much more complete in this re-analysis, we have identified several new regions of interest and promising candidate genes (genes we think may be involved in causing anencephay). Follow-up of these regions is ongoing.

Gene Updates

MYT1L and INADL

Our original analysis of the anencephaly GWAS data (see above) suggested that two genes were very good candidate genes for involvement in anencephaly. The first gene, myelin transcription factor 1 like (MYT1L), is a

gene that helps turn other genes off and on and is believed to be involved in the development of neurons (brain cells). The second gene, InaD like (INADL), is active in the human brain and is involved in regulation of tight junctions, which are important for neural tube closure. When we looked at these two genes in additional anencephaly participants, the statistical evidence for these genes continued to be strong. Thus, we remain interested in the role that these two genes may play in the occurrence of anencephaly.

Nitroic Oxide (NO) Genes

The nitric oxide (NO) genes may play a role in the closure of the neural tube. Our team took a closer look at the possible role that three nitric oxide synthase genes (NOS1, NOS2 and NOS3) may play in neural tube defects. The NOS3 gene in particular was previously associated with increased homocysteine levels, particularly among smokers. Homocysteine is part of the folate pathway which has been implicated in neural tube defects. We examined all three genes across all types of neural tube defects and found evidence that these genes may indeed be linked to the occurrence of neural tube defects.

Life Experiences of Adults with Myelomeningocele

We recently collected information from 90 adults over the age of 25 with myelomeningocele (MCC) in an effort to learn more about their life experiences; particularly education, employment, relationships, reproduction and life satisfaction. A summary of the findings are below.

Education

The majority of adults with MCC obtained at least a GED or high school diploma (94%) with 33% completing college and 4% obtaining an advanced degree. Individuals in a typical classroom setting in high school were more likely to obtain education beyond high school.

Employment

Eighty four percent of adults with MMC were currently employed or held a job in the past. The majority of individuals earned a salary of less than $25,000 per year. Individuals without hydrocephalus were more likely to be employed.

Relationships

Over half of adults with MMC (52%) never had a serious partner while 28% were married either presently or in the past. Individuals who could walk

without assistance were more likely to be in a relationship while participants with hydrocephalus were more likely to have never been in a relationship. Of those individuals with a partner or spouse, 16% had a partner or spouse with a disability which included spina bifida, cerebral palsy and blindness.

Reproduction

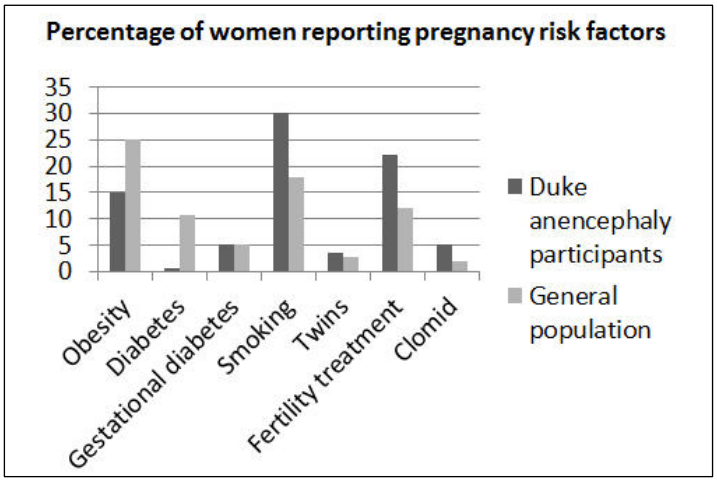
Eighteen percent of adults with MMC had biologic children. Individuals who could walk without assistance and did not have hydrocephalus were more likely to have biologic children. Three individuals had a child with a neural tube defect.

Life Satisfaction

Overall, adults with MMC reported the highest satisfaction with self-care and family life, while money, employment and partner relationships were rated the lowest. Individuals who did not live alone and could walk without assistance reported the highest life satisfaction.

Anencephaly Risk Factors

We recently examined rates of obesity, diabetes, gestational diabetes, smoking, twins and fertility treatments in 205 women who had experienced anencephaly pregnancies and compared these rates to women in the general population. Rates of obesity, diabetes and gestational diabetes were equal to or less than rates in the general population. Obesity and diabetes are known to increase the risk for anencephaly, therefore women with these risk factors may be less likely to participate in research aimed at learning about other causes of anencephaly.



While most studies have not shown smoking to increase the risk for anencephaly, we found a much higher rate of smoking in participants with anencephaly pregnancies than the general population. There have been some reports of increased risk of anencephaly in twin pregnancies or women who used fertility treatments or clomid to become pregnant. The percentage of twins, fertility treatments and clomid use in participants with anencephaly pregnancies exceeded the national rates.

Keep Us Updated

Please keep us in mind when important changes happen in your family. 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 you have had any additional pregnancies. 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!

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.

Follow us on Facebook

For periodic updates on anencephaly research being conducted at the Duke Center for Human Genetics "like" us on Facebook at:
http://www.facebook.com/pages/Anencephaly-Study-at-Duke-University-Medical-Center/256402881048244

Who Pays for Research?

Conducting genetic research studies 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.

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! 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 Gift Now!" and then "Make a Credit Card Gift." Under Additional/Other Designations make sure to type in Center for Human Genetics NTD Fund. Or you can send your tax-deductible donation to the address below:

Duke Center for Human Genetics
NTD Research Fund
Box 3445
Durham, NC 27710