

NEURAL TUBE DEFECT Research

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In Memory of Marcy Carlson Speer, PhD



The lead investigator and driving force of Duke's Neural Tube Defects study, Dr. Marcy Carlson Speer, died Saturday August 4th, 2007 at age 47 in Duke Hospital following a valiant battle with breast cancer. She was born October 1, 1959, in Indianapolis, and

raised in Indiana and Illinois. Dr. Speer graduated from Indiana University and received a Master's degree in genetic counseling from Sarah Lawrence College. She obtained her Ph.D. in genetics from Duke University. A Durham, NC resident since 1985, Dr. Speer was a long-term faculty member at Duke in the Center for Human Genetics. She was named Director of the Center in 2007. Dr. Speer was an accomplished researcher with international acclaim. She published 124 papers on at least 24 different diseases and was actively working on at least 8 more manuscripts. She received 24 research grants and was an authority on the genetics of neural tube defects such as spina bifida and anencephaly.

Foremost she was a devoted mother, whose energies were always primarily directed toward her children. Marcy is survived by her husband of 24 years, Kevin P. Speer, M.D.; her daughters, Kira Carlson Speer and Casey Carlson Speer; her mother, Marsha Carlson; and brothers, Ned Carlson, of Washington, DC; and Eric and Kris Carlson of Chicago. She was predeceased by her father, Milton Carlson last year.

Though we are all grieving the loss of Dr. Speer, research at Duke will continue under the leadership of Drs. Allison Ashley-Koch and Simon Gregory.

Introduction to Drs. Allison Ashley-Koch and Simon Gregory



Allison Ashley-Koch, PhD, Associate Professor of Medicine

Dr. Ashley-Koch is a genetic epidemiologist who received a PhD in Genetics and Molecular Biology from Emory University and completed post-doctoral fellowships at the Centers for Disease Control and Prevention and the Duke Center for Human Genetics. Allison's research experience includes genetic analysis of family based data and epidemiologic analysis of population-based data. She has a particular interest in the genetic analysis of neurodevelopmental and psychiatric disorders. In addition to the NTD project, Allison is also working to identify genetic susceptibilities to AD/HD, poor birth outcomes, and genetic modifiers of sickle cell disease. Allison has had extensive experience in study design, data management and ascertainment for genetic studies, including nation-wide ascertainment, as is the case with the NTD study.

Simon G. Gregory, PhD, Assistant Professor of Medicine



Dr. Gregory obtained his undergraduate degree in his native city of Melbourne, Australia and obtained his PhD in the UK at the Sanger Institute. Simon joined the Duke Center for Human Genetics in 2003 after spending ten years at the Sanger Institute in the United Kingdom, where he directed the Institute's efforts to map and sequence human chromosome 1 for the Human Genome Project. After joining the Duke CHG Simon has been involved in understanding the genetic mechanisms associated with multiple sclerosis (where he works with Dr. Ashley-Koch), cardiovascular diseases, and has been developing novel approaches to identifying genes involved in cancer and autism. He has been instrumental in bringing high-throughput genotyping and sequencing technologies to the Duke CHG and has been pivotal to developing genome wide approaches to copy number characterization and methylation profiling.

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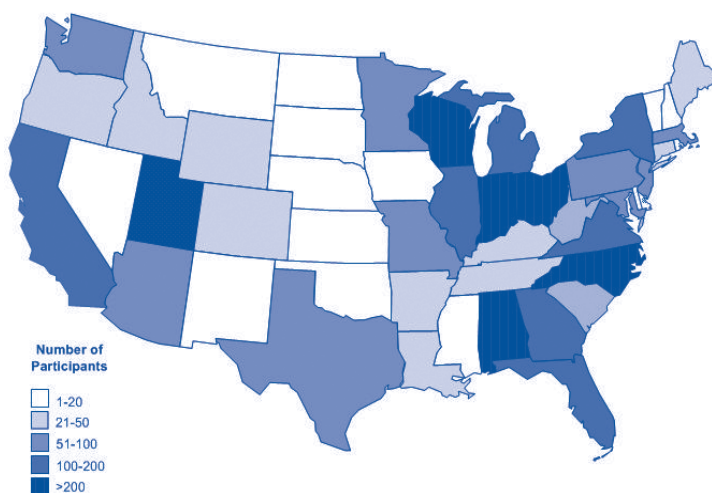
General study enrollment update

We have collected DNA samples from 4920 individuals in 1274 families. Since June 2006, we have sampled 796 individuals. Thank you to anyone who contributed a sample during the past year, or since 1993 when the study began.

We have received some inquiries as to the breakdown of families enrolled in the study. The majority (438) of our families are Caucasian families in which one family member has a lumbo-sacral myelomeningocele. The next largest group of families (352) has two or more family members diagnosed with one of the many types of NTDs. These families represent all racial and ethnic categories. For the remaining families that are Caucasian and have only one family member with an NTD, there are 56 with thoracic level myelomeningoceles, 95 with lipomyelomeningoceles, and 68 with other NTD diagnoses. We have 30 non-Caucasian families enrolled in which only one family member has an NTD. The remaining non-Caucasian families (158) have family members who have been diagnosed with anencephaly, encephalocele, craniorachischisis, Meckel-Gruber Syndrome, or other similar NTDs.

In the map below, we show the number of samples that we have collected by state as of March 1, 2008. Our goal is to collect as many samples as possible from all states. This map is not intended to represent “hot spots” of risk for NTD. It is simply demonstrating where our study has recruited heavily thus far. Additionally, this map does not include samples that have been collected at other sites by our collaborators, such as our colleagues in Guatemala.

All NTD Participants by State



Anencephaly Study Update

Families who experience an anencephaly pregnancy often ask about the other families participating in this study. The purpose of this article is to share some basic information about participating families. As of March 2008, 191 families

who experienced one or more anencephaly pregnancies have participated. Of these 191 families, 123 (64%) are singleton families, meaning there is one case of anencephaly and no other cases of neural tube defects in the family. The other 68 families (36%) are multiplex families, meaning there are two or more cases of neural tube defects in the family. These numbers do not represent the general population. Multiplex families are more likely to believe genetic factors are involved and therefore more likely to participate.

	Number of Families	Percent of Families
1 Anencephaly Pregnancy	123	64%
2 Anencephaly Pregnancies	24	13%
1 Anencephaly & 1 Spina Bifida Pregnancy	14	7%
1 Anencephaly & 1 Other NTD Pregnancy	6	3%
3 Anencephaly Pregnancies	3	2%

Twenty-five percent (25%) of families had two or more pregnancies affected with a neural tube defect. In the general population, the chance to have a second pregnancy affected with a neural tube defect (of any type, not just anencephaly) is 2-5%. In fact 30-40% of recurrences involve an NTD type that is different from the first. At last contact, 72% of families had at least one healthy child born to the same two parents. This number is likely higher as families may have had additional pregnancies since participating. If there are any updates to your family history information please call or email (1-866-385-3683 or ntd@chg.duhs.duke.edu) to update our records.

Thank you to all the families who have participated over the years. Research toward a better understanding of the causes of anencephaly is not possible without your help.

Visits from NTD Study Personnel

In many cases we are able to visit families in person to complete their enrollment in the NTD study. During visits, we answer any questions participants have about our study, draw blood samples, and complete consent forms and any other paperwork. We also briefly look at the lower back of those family members who do not have an NTD to look for signs of spina bifida occulta (such as a dimple or hairy patch over the spine). Since June 2006, NTD Staff members have visited families in over 20 states throughout the United States.

We enjoyed meeting each and every family and really appreciate your participation in the Neural Tube Defect

research study. We will continue to travel to 2-3 areas each month and can usually accommodate your scheduling needs, including evening or weekend visits. Please contact us if you would like to schedule a home visit to complete your family's enrollment in the study. We are in the process of planning trips to several areas and look forward to speaking with you!

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 more 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, mostly with lumbo/sacral myelomeningocele. At this time we are unable to report any statistically significant differences within our population compared to what would be expected, but we are continuing to pursue our investigations of this gene.

Vangl1:

Another possible gene of interest is Vangl1 (van gogh-like 1). The Vangl1 and Vangl2 (described above) genes are suspected to have similar function. In 2007 a study by another research group (Kibar et al) involved 144 participants with various forms of NTDs (primarily myelomeningocele); 137 of which were Italian. None of these mothers took folic acid prior to pregnancy. Three individuals were found with genetic changes in the Vangl1 gene. This is a small subset of the individuals involved in the study. Because of these findings in the Italian study, our group has begun testing participants involved with our study (primarily with lumbo/sacral myelomeningocele and anencephaly) in order to see if genetic changes in Vangl1 are present. We would also like to investigate possible interactions between the Vangl1 and Vangl2 genes.

Lmx1a and Lbx1:

Studies in mice have shown important roles for two genes, Lmx1 and Lbx1, in the development of the

mouse central nervous system, heart, arms and legs, and closure of the neural tube. Genetic changes in these genes could possibly lead to complex conditions like NTDs. Previously, there have been no studies of these genes in humans with NTDs. We recently screened the DNA samples of participants with NTDs for genetic changes in the human genes very similar to, Lmx1a and Lbx1. However, our results do not support either Lmx1a or Lbx1 as potential candidate genes for neural tube defects.

Tectonic:

Tectonic3 (TCTN3) on chromosome 10 is a promising NTD candidate gene in humans. The Tectonic gene in mice, which is 58% the same to TCTN3 in humans, is crucial for proper neural development. It has yet to be determined what the specific function of TCTN3 is in humans. We are in the process of investigating this gene.

MTR:

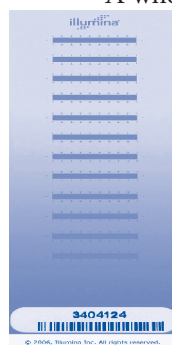
MTR on chromosome 1 is a promising candidate gene for NTD because lower levels of MTR activity can lead to higher homocysteine levels, a known risk factor for neural tube defects. MTR is part of the folate metabolic pathway, which allows the body to properly use ingested folate (folic acid). We are still working to assess if this gene is associated with NTDs.

Anencephaly whole genome association screen identified two promising candidate genes: INADL and MYT1L

Our research is based on our ability to identify changes within the DNA that may contribute to or cause certain diseases. One of these changes is known as a Single Nucleotide Polymorphism (SNP), a change in which a single letter in the DNA (DNA is made of long strings of the letters A, T, C and G) differs from the usual letter at that position. These SNPs are what make people unique and different; why some of us have brown eyes and others have blue.

A whole genome association analysis (looking at SNPs at intervals across the entire genome) was performed in 45 anencephaly families to identify genetic markers that may increase risk for anencephaly. Over 300,000 SNPs were run in these families. Analysis found 11 SNPs that may be associated with risk of developing an NTD. Some of these SNPs were located in the following genes: INADL, ACTN2, MYT1L and CHES1. We picked genes to analyze further based on our knowledge of whether these genes are turned on (active) during fetal development of the neural tube. Interestingly, INADL and MYT1L were observed to be active during neural tube closure.

INADL, which is located on chromosome 1, controls the movement of cells to their proper location in the body.



Research in mice has shown that genetic changes in genes similar to INADL in mice cause spinal neural tube defects. MYT1L, which is located on chromosome 2, controls many genes involved in the development of the nervous system. Together, these data suggest INADL and MYT1L may be important genes in neural tube defects.

We have begun more in-depth studies on these two genes in a larger set of families with cranial NTDs (anencephaly, encephalocele, etc.), and these investigations have revealed some promising results. These genes need to be studied further before any conclusions are reached. Work is currently underway to look at activity of these genes in amniocytes (fetal cells obtained from a pre-natal test called amniocentesis) from fetuses with anencephaly compared to normally developing fetuses.

Family Update

Please keep us in mind when important changes happen in your family. We like to ensure that all of 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 someone diagnosed with a new medical disorder, 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 toll-free at 866-DUKE-NTD, directly at 919-684-0767, or by sending an email to ntd@chg.duhs.duke.edu. Thanks!

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.

Recent Publications

Torres OA, Palencia E, Lopez de Pratdesaba L, Grajeda R Fuentes M, Speer MC, Merrill AH Jr, O'Donnell K, Bacon CW, Glenn AE, Riley RT. Estimated fumonisin exposure in Guatemala is in consumers of lowland maize. (2007) *Journal of Nutrition*. 137(12):2723-9.

Boyles AL, Billups AV, Deak KL, Siegel DG, Mehlretter L, Slifer SH, Bassuk AG, Kessler JA, Reed MC, Nijhout HF, George TM, Enterline DS, Gilbert JR, Speer MC. Neural tube defects and folate pathway genes: family-based association tests of gene-gene and gene-environment interactions. (2006) *Environmental Health Perspectives*. 114(10):1547-52.

Stamm DS, Rampersaud E, Slifer SH, Mehlretter L, Siegel DG, Xie J, Hu-Lince D, Graig DW, Stephan DA, George TM, Gilbert JR, Speer MC. (2006) High-density single nucleotide polymorphism screen in a large multiplex neural tube defect family refines linkage to loci at 7p21.1-pter and 2q33.1-q35. *Birth Defects Research*. 76(6):499-505.

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. Substantial funding is typically only granted to researchers with strong research plans and programs already in place. With the participation and support of the more than 1100 families already enrolled in the study, you have helped us to develop one of the strongest NTD genetic studies in the nation. 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 families that are enrolled in the study or 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. 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:

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