

News about...

NEURAL TUBE DEFECT Research

Study Introduction Edition, Winter 2004

.....

Welcome

This newsletter is published by the Center for Human Genetics (CHG), part of the Duke University Health System, for the families who participate in our research study on the genetics of neural tube defects (NTDs). We have included background information about genetics, some general information about NTDs, an explanation of how genetic research works, and information on study participation. You may want to save this newsletter to use as a resource for future updates we will send you.

What is the study goal?

The goal of this research study is to discover the genetic and environmental factors that contribute to the cause of neural tube defects. We hope to answer some important questions about

NTDs. What causes NTDs? Can better tests be created to diagnose NTDs? Can better preventions or treatments be found? The Center for Human Genetics at Duke University Medical Center is looking for the answers. By working together, our physicians, neurosurgeons, human geneticists, and families can find the answers to these questions.

The goal of this research study is to discover the genetic and environmental factors that contribute to NTDs.

The Duke Center for Human Genetics building (below) opened in November 2002.



Thank you!

We are indebted to all the individuals and family members who have so generously agreed to participate in this ongoing genetic research study for neural tube defects. Each individual and, in turn, each family that participates, helps the pieces of this research puzzle fall into place.

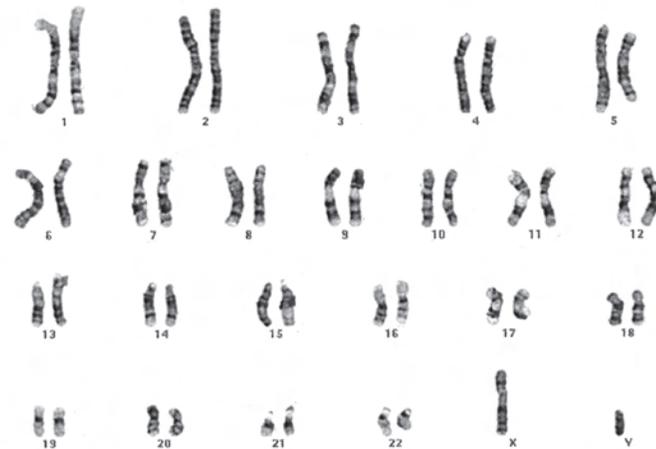
The research described in this newsletter is only possible because of the many, many individuals and family members who agree to participate. We look forward to continuing to work with all of you over the next few years. Together, we will move closer to our common goal of understanding why and how neural tube defects develop.

We also want to thank all of the families who have helped spread the word about our research. We have received many phone calls and email messages from families who learned about the study through other families already enrolled in the study. Please keep telling other families about the study, as we continue to enroll additional interested families.

An Introduction to Genetics

What is a Gene?

Genes are very small structures inside almost every cell of the body. Genes are the instructions, or blueprints, that tell our body how to grow and develop, build necessary proteins, and, thus, determine an individual's characteristics, such as eye color and blood type. It is estimated there are 30,000-40,000 genes, each of which is an instruction guiding the cells of the body to grow and survive. Genes come in pairs and are made of strands of genetic material called deoxyribonucleic acid, or DNA. Genes line up similar to beads on a string to form larger structures called chromosomes. Genetic disorders are caused by change(s) in the instruction code of a particular gene or genes, preventing the gene(s) from performing their proper function.



What is a Chromosome?

Just as genes come in pairs, chromosomes also come in pairs. Each cell in our body has 23 pairs of chromosomes (for a total of 46); one member of each pair is inherited from the mother and the other from the father. The first 22 pairs (numbered 1 through 22) are called autosomes and they determine most of our features. The last pair are the sex chromosomes and they determine if we are male or female. Females have two X chromosomes and males have one X chromosome and one Y chromosome.

The Genetics of Complex Disorders

Some disorders are determined by changes in more than one gene. These disorders, known as complex disorders, do not follow a predicted pattern of inheritance as is seen in other rarer genetic disorders caused by a change (mutation) in only one gene, such as cystic fibrosis, sickle cell anemia, or hemophilia. Sometimes changes in the genes that contribute to complex disorders must be in combination

with certain environmental factors, such as exposure to certain chemicals, medications, or maybe even diet. This type of inheritance is often referred to as multifactorial, or "complex," because many different factors, genetic and/or environmental, are involved. A person will have a complex disorder if he or she has the right combination of changed genes and environmental exposures. Sometimes the genes that contribute to complex disorders are called susceptibility genes because they make a person susceptible to developing the disorder after exposure to specific environmental factors, but they do not cause the disorder alone. The close relatives of someone with a complex disorder have a higher chance of developing the disorder than the close relatives of someone who does not have the disorder. Diabetes, heart disease, autism, Alzheimer disease, neural tube defects, Parkinson disease, and many cancer syndromes are examples of disorders that can be caused by multifactorial or complex inheritance.

How Do We Find Genes that Contribute to NTDs?

Following is a description of the two strategies we use to identify the genes that contribute to NTDs. We hope you will find this section helpful in understanding the research your participation supports.

Genome Screen and Linkage Analysis

Genome screens and linkage analysis have been very successful in discovering the genes that cause many genetic disorders. Advances in laboratory and computer technology have now made this approach possible for complex disorders like neural tube defects. The genome comprises all of a human's genetic material. A genomic screen consists of DNA laboratory studies and a statistical analysis called linkage analysis. Linkage analysis is the first step towards finding a gene.

Looking for the genes that cause a genetic disorder is similar to locating someone's house without

knowing the exact address. By narrowing down the area you are searching in (from state to city to street), eventually you can find the address of a particular person. Just as gas stations or restaurants can be used as landmarks when locating a friend's house, scientists use markers to help find a gene. The instructions encoded in genes are written in a special genetic alphabet consisting of four letters – A, T, C, and G (called nucleotide bases). These bases are the critical chemicals from which DNA is made. The sequence (order in which these letters occur) tells the body how to make certain proteins our bodies need to grow and function. Markers are the small sequences of DNA along the chromosomes that may differ slightly from individual to individual. These differences (called polymorphisms) do not usually affect a person's health, but can be easily identified and used to look for genes.

Linkage analysis is performed by

testing many different markers on all the chromosomes (our whole genome), trying to find

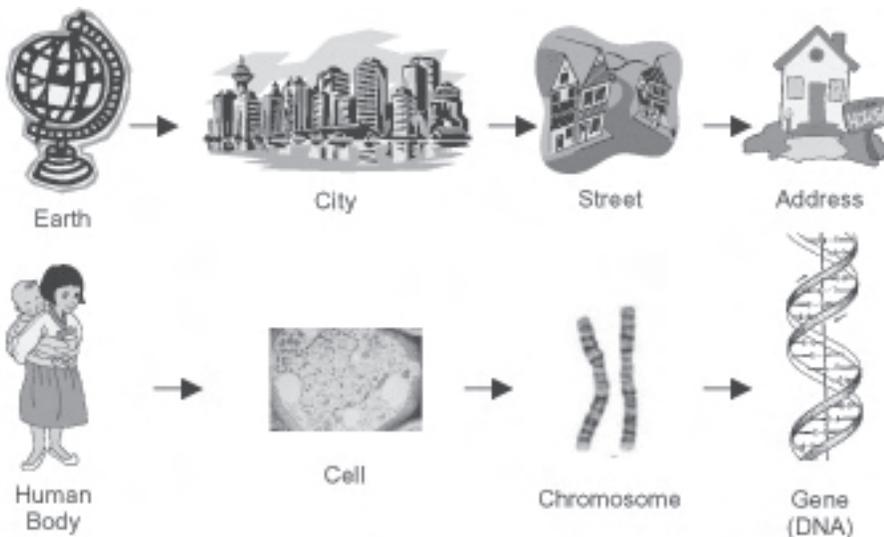


markers that are consistently found in family members who have an NTD, but are not found in family members without an NTD. These markers are used as landmarks to identify exactly which chromosome, or section of a chromosome, a gene causing a disorder is located on (like which street a house is on). Certain statistical methods can tell scientists how close these landmarks are to a gene. If a marker is believed to lie very close to a gene, then the marker is "linked" to the gene. This is why we call this DNA analysis linkage analysis. Further research must be done to determine the exact location of the gene(s) that contribute to the cause of NTDs.

Candidate Gene Analysis

Candidate genes are genes scientists know something about, such as their exact location on a particular chromosome and their function. Candidate genes for neural tube defects may be genes known to be involved in the development of the nervous system, genes involved in the metabolism (the chemical processes our bodies use to breakdown and use nutrients) of folic acid, or genes already identified that contribute to the development of NTDs in animals other than humans, such as mice or chickens. Thus, the function of candidate

continued on page 4



What Are We Looking For? Finding genes is like finding someone's house without knowing their address.

Continued from page 3

genes “make sense” to be involved in the biology of neural tube defects; these genes are good “candidates” for being related to the development of NTDs.

Candidate gene analysis for NTDs involves studying the potential candidate gene in individuals with an NTD to see if the gene has a genetic change (mutation) that is not seen in the genes of individuals who do not have an NTD. If genetic changes in candidate genes are identified, then it is possible the candidate gene contributes to the development of NTDs in humans.

So far, our laboratory has studied many different candidate genes. However, none of the genes we have studied so far seem to play a major role in the development of NTDs in humans. However, there are many, many more candidate genes we have not yet been able to investigate. We continue to systematically study different candidate genes. Just like the genomic screen and linkage analysis, it is a laborious process and often takes many months to a year to thoroughly study just one candidate gene.

A Combined Strategy is Best

Our laboratory strategy is to study candidate genes in families in which only one individual has a neural tube defect. We also plan to combine the study of candidate genes with linkage analysis using DNA samples from families with more than one individual with an NTD. Thus, once an area, such as a particular piece of one chromosome, is identified as being linked through the genomic screen, we try to study candidate

Sources of Information and Support about Neural Tube Defects

There are many organizations that provide factual information about neural tube defects for individuals and families. Here are some you may find useful:

Spina Bifida Association of America
4590 MacArthur Blvd., NW, Suite 250
Washington, DC 20007-4226
(800) 621-3141 or (202) 944-3285
Fax: (202) 944-3295
Email: sbaa@sbaa.org
<http://www.sbaa.org>

Spina Bifida and Hydrocephalus Association of Canada
#977-167 Lombard Avenue
Winnipeg, Manitoba, Canada R3B 0V3
(800) 565-9488 or (204) 925-3650
Fax: (204) 925-3654
Email: spinab@mts.net
<http://www.sbhac.ca/>

Lipomyelomeningocele Family Support Network
<http://www.lfsn.org/>

Spina Bifida Village
Spina Bifida Foundation
3720 Campus Dr., Suite 200
Newport Beach, CA 92660
(800) 891-2622 x 221 or (949) 223-8946
<http://www.spinabifida.us/>

Children with Spina Bifida
<http://www.waisman.wisc.edu/~rowley/sb-kids/index.html>

National Council on Folic Acid
<http://www.cdc.gov/ncbddd/folicacid/council.htm> or
<http://www.marchofdimess.com/pnhec/887.asp>

Moving???



If you are moving and want to continue receiving this newsletter and future updates on the study, please let us know your new address and telephone number by calling us toll-free at 866-DUKE-NTD, directly at (919) 668-0736, or by sending an email to ntd@chg.duhs.duke.edu. Thanks!

genes located in that particular area. This combined strategy helps narrow down the potential candidate genes we choose to study by allowing us to select candidate genes located in the area of interest identified by the genome screen. We use computer databases, developed in part by the Human Genome Project, to identify which genes are located on a particular piece of a chromosome. We then study these potential candidate genes to determine if they truly are related

to NTD development in humans. Therefore, the results of the genomic screen and linkage analysis give us the street on which an individual’s house is located. Candidate gene analysis is like knocking on the door of a house on that street, looking for our friend. We are confident that using this combined strategy will increase the chance we will also be successful in discovering which genes are involved in the development of NTDs.

Folic Acid: General Information and Recommendations

Folic acid is a known environmental factor for neural tube defects. Studies have shown that women who take folic acid prior to getting pregnant and through the first trimester reduce the chance of having a child with an NTD by 50-70%. Folic acid does not prevent all cases of NTDs. And, despite taking folic acid in the recommended dose during the recommended time period, it is still possible to have a child with an NTD. Unfortunately, it is not yet understood how folic acid works to decrease the chance of having a child with an NTD.

Prevention of NTDs by pre-conceptional folic acid supplementation has only been studied in women who have had a previous pregnancy or child with an NTD, spina bifida, encephalocele, or anencephaly. Therefore, there are no specific recommendations for taking high doses of folic acid for women who have an NTD themselves, for other relatives, such as sisters, aunts, or cousins of someone with an NTD, or for the female partners of men who have an NTD. In addition, there are no specific recommendations or studies to determine if folic acid reduces the change of having a child with one of the more rare neural tube defects, such as lipomyelomeningocele, lipoma, etc.

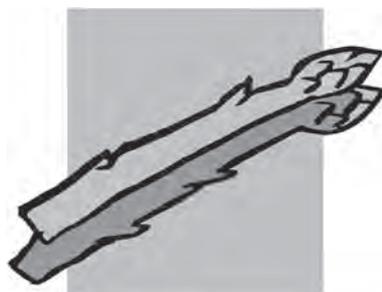


All women of childbearing age:

Should eat a diet high in folic acid or take a multivitamin with 0.4 mg (400 mcg) of folic acid each day, especially one month prior to conception and through the first three months of pregnancy. This is the recommended daily allowance (RDA).

Women who have had a previous pregnancy or child with an NTD (specifically spina bifida, encephalocele or anencephaly):

Should eat a diet high in folic acid or take a multivitamin with 0.4mg (400 mcg) of folic acid every day, as discussed above. Before planning a pregnancy, these women should increase the daily dose of folic acid from 0.4mg to 4.0mg for at least one month prior to becoming pregnant and through the first three months of pregnancy. The



4.0mg of folic acid should be obtained through a prescription and be taken under supervision of a physician. Do not obtain this higher dose by taking larger doses of multivitamins, as high doses of other vitamins can be harmful. It is important to note that most women are not able to obtain this higher dose of folic acid through diet alone.

HIPAA

You have probably received information from your doctors, dentists, pharmacies, etc. about how they maintain the confidentiality of their patients. Federal law (Health Insurance Portability and Accountability Act of 1996) dictated that health care groups had to document their procedures for confidentiality by April 2003. Duke University Medical Center has recently begun distributing the Notice of Privacy Practices (NPP) brochure to all patients and participants in research studies. The NPP brochure describes how patient medical information may be used and disclosed. The information presented in this brochure is information regarding the entire Duke Health Enterprise and is not specific to the Duke Center for Human Genetics; therefore much of this information may not be applicable to your family. As always, research conducted at the Duke Center for Human Genetics is done with a fundamental respect for research participants and their privacy. Information collected about your family as part of our research study is never released to anyone without your written consent. Specific information about how confidentiality is maintained at the Duke Center for Human Genetics is given on the consent forms.

If you have not received a copy of the NPP brochure, an electronic version is available at http://www.chg.duhs.duke.edu/patients/NPP_Brochure.pdf.



Genetic Counseling

Where should you go for more information? If you or another family member want to discuss the personal chance of having a child with an NTD, prenatal testing, genetic testing, or folic acid, then please consult a genetic counselor. Please contact us for a referral, or contact the National Society of Genetic Counselors at <http://www.nsgc.org/resourcelink.asp> or (610) 872-7608.

Please Update Us

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. Please give us your updates by calling us toll-free at 866-DUKE-NTD, directly at (919) 668-0736 or you may email us at ntd@chg.duhs.duke.edu. Thanks!

Message from a Participating Family

By Mike and Jo Scott

We are very blessed with three beautiful children who bring enormous joy into our lives. We live in sunny Southern California and enjoy a very comfortable lifestyle. If you saw us roller-blading along Huntington Beach with the kids in a stroller you wouldn't have any idea what we've been through over the last five years, or the uncertain future Thomas and Sarah face. We are a very rare family: two of our children have spina bifida.

Despite the heartache we've experienced as our precious little ones have had surgery, many tests and endless check-ups, we consider ourselves blessed that they have done so well. Thomas was born with myelomeningocele. He had the largest lesion that Mike (who did his Master's research on causes of SB) or Jo's dad (an obstetrician) had ever seen or even heard of. He had surgery on the day he was born to close the lesion. Sarah has lipomyelomeningocele and wasn't diagnosed until she was a month old; she had surgery at four months. Andrew does not have spina bifida and is a healthy little boy.

Without any more information, you might just think that we have had a very rare run of tough luck. However, our family has a history of neural tube defects that has to be more than coincidence. We have a niece and a cousin with SB, as well as two cousins who each have a child with SB. And as far as we can tell, there may be some aunts and uncles, who died shortly after birth, who also had NTDs. With this evidence, coupled with the fact that Jo took large doses of folic acid before and during both pregnancies, we are convinced that there is a significant genetic component to the cause of SB.

Following Thomas' birth we were given information from his pediatric neurosurgeon, Dr. Michael Muhonen, about the spina bifida research being done at Duke University. We got in contact with Liz Melvin, who sent us information about their neural tube defect study and the process through which we could provide blood samples for genetic testing and family history information. Liz and her colleague, Susan, came to California to collect blood samples and meet our family. We had a wonderful dinner and visit. They also traveled to Canada that summer to meet with many of our relatives and collect more samples, while enjoying homemade cooking and good conversation.

Our whole family is extremely excited to be involved in the Duke research program. Just imagine if they could determine which genes cause or increase the risk that parents will have a child with SB. For those of us who have lived through the emotional roller coaster of dealing with this birth defect, research efforts such as Duke's study are of utmost importance. We can only hope that by making a small donation of blood and time that we can one day realize our dreams: a world where spina bifida, like polio, can be eradicated.



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 <http://www.giftrecords.duke.edu/>, and click on "Make a Credit Card Gift Online," or you can send your tax-deductible donation to

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

Our Collaborators

To help us reach our goals, we continue to collaborate with other physicians and medical centers across the United States and abroad. We are also in the process of bringing new collaborators on board. At this time, the following Myelodysplasia Clinics collaborate with us on the NTD study.

- Alabama Children's Rehabilitation Services, Birmingham, AL
- Carolinas Medical Center, Charlotte, NC
- Children's Hospital of Richmond, Richmond, VA
- Children's Hospital of Wisconsin, Milwaukee, WI
- Duke University Medical Center, Durham, NC
- Indiana University, Indianapolis, IN
- Loyola University, Chicago, IL
- Medical College of Ohio/Mercy Children's Hospital, Toledo, OH
- Northwestern University/Memorial Children's Hospital, Chicago, IL
- Oregon Health and Science University, Eugene, OR
- Park Nicolette Hospital, Minneapolis, MN
- Shriners Hospital for Children, Springfield, MA
- University at Buffalo/Women and Children's Hospital of Buffalo, Buffalo, NY
- University of Alabama at Birmingham, Birmingham, AL
- University of North Carolina at Chapel Hill, Chapel Hill, NC
- University of Utah, Salt Lake City, UT
- University of Wisconsin Hospital and Clinics, Madison, WI
- Wake Forest University School of Medicine, Winston-Salem, NC
- West Virginia University, Morgantown, WV

If the Myelodysplasia Clinic where your family receives care is not currently collaborating with us, please feel free to discuss our study with your doctor. Doctors interested in collaborating with our study or referring patients to the study should contact us toll-free at 866-DUKE-NTD or via email at ntd@chg.duhs.duke.edu.



Q&A About Study Participation

Q: What is involved in study participation?

A: The first step in joining a genetic research study is to talk with one of the researchers about your family history. Most of the time, this can be done over the phone. Depending on the family history, we may request blood samples from several family members, including individuals with and without NTDs. In many cases, a brief physical examination is done on family members without an NTD who are willing to participate in the study. This physical examination looks for subtle signs of NTDs that may not have been diagnosed. We will request permission to review the medical records and X-rays of family members who have an NTD. Lastly, we collect facial photographs of individuals who have an NTD.

Q: How will you obtain a blood sample from my family?

A: In some cases, we will travel to your home or other local meeting place to obtain blood samples and complete the paperwork or examinations needed for the study. Another option is a mailer kit, which we send to you. It contains blood tubes and instructions that you can take to your local health care provider or laboratory to have blood drawn, after which the kits are sent directly to Duke University Medical Center at no charge to the family.

Q: How long will the study take?

A: Genetic research studies take many years to complete because we must gather information and blood samples on many different families, run many experiments in the laboratory, and analyze the results. Once a gene is found, it may require many more years to understand its function and/or to develop any treatment or prevention based on that understanding. Our annual newsletters will keep you updated about our progress. The more families that participate in our study, the faster we will be able to find answers. If you know other interested families with NTDs or if you have other family members who may be interested in participating, please have them contact us toll-free at 866-DUKE-NTD, directly at (919) 668-0736, or via email at ntd@chg.duhs.duke.edu.

Q: Will my family get results from the study?

A: We are not able to give families their specific research results because a specific genetic test for NTDs is not available. Developing such tests is one of the goals of the study. If a research breakthrough is made and such a test becomes available, then families who participated in the research will be given information on how to pursue such testing, if they are interested. In the meantime, our annual newsletters will provide you and your family with updates on the overall research results and research progress.

Q: Is there any cost to my family to participate in the study?

A: No, we do not charge families for participating in our study. Any expenses incurred if a participant has his or her blood drawn by a local physician and sent to our laboratory are covered by the study. In addition, we cover the costs of blood draws and physical examinations by our research staff. If a physical examination by our research staff discovers any abnormalities that require medical follow-up, these expenses would not be covered by the research project.

Q: Who may participate in the study?

A: Any person with any kind of neural tube defect and his or her family.

Q: Will my family's medical history be kept confidential?

A: All personal and family medical history shared with the research center is kept strictly confidential, even among individuals within your family. Individuals who participate in the research are assigned a unique number in order to protect their identities. Only authorized researchers directly involved in the study can access the research records and family medical histories. In addition, our research files are kept separate from the medical records at Duke University Medical Center.