

News About... Chiari Type 1/Syringomyelia Research

Study Introduction Edition, Fall 2005

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Welcome



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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 Chiari Type 1 Malformation with or without Syringomyelia (CM1/S). We have included background information about genetics, some general information about CM1/S, 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.

The goal of this research study is to discover the genetic factors that contribute to the cause of Chiari Type 1 Malformation and/or Syringomyelia. We hope to answer some important questions about CM1/S.

- What causes CM1/S?
- Can better tests be created to diagnose CM1/S?
- 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.

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HIPAA Update

In the last year, 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 material 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 a copy of the Notice of Privacy Practices brochure was not attached to this newsletter, you may download an electronic version of this brochure at http://www.chg.duke.edu/diseases/pdfs/NPP_Brochure.pdf. Please share this information with everyone in your household.

An Introduction to Human 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, Chiari Type 1 Malformation and/or Syringomyelia, Parkinson disease, and many cancer syndromes are examples of disorders that can be caused by multifactorial or complex inheritance. The following is a description of the two strategies we use to identify the genes that contribute to CM1/S. 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 Chiari Type 1 Malformation and/or Syringomyelia. 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



Duke Center for Human Genetics

The 120,000 square foot Center for Human Genetics building took \$41 million and 2 years to complete. The building opened in February 2002. It provides CHG researchers with unparalleled laboratory, computing, and office facilities that make our work to identify genes involved in Chiari Type 1 Malformation and/or Syringomyelia and other disorders possible.

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 CM1/S, but are not found in family members without CM1/S. 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 CM1/S.

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 Chiari Type 1/Syringomyelia may be genes known to be involved in the development of the skull and nervous system or known to cause other conditions related to CM1/S such as Paget's disease. Thus, the function of candidate genes "make sense" to be involved in the biology of Chiari Type 1 Malformation and/or Syringomyelia; these genes are good "candidates" for being related to the development of CM1/S.

Candidate gene analysis for CM1/S involves studying the potential candidate gene in individuals with CM1/S to see if the gene has a genetic change (mutation) that is not seen in the genes of individuals who do not have CM1/S. If genetic changes in candidate genes are identified, then it is possible the candidate gene contributes to the development of CM1/S in humans.

None of the genes we have studied seem to play a major role in the development of CM1/S in humans. However, there are 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 Most Successful

Our laboratory strategy is to study candidate genes in families in which only one individual has CM1/S. We also plan to combine the study of candidate genes with linkage analysis using DNA samples from families with more than one individual with CM1/S. 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 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 CM1/S 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. Our laboratory has been successful discovering the genes that contribute to the development of other complex disorders. Therefore, we are confident using this combined strategy will increase the chance we will also be successful in discovering which genes are involved in the development of CM1/S.

Study Contact Information

Phone: toll-free (877) 385-2626

E-mail: chiari@chg.duhs.duke.edu

Web: <http://www.chg.duke.edu/diseases/chiari.html>

Who pays for the research?

Conducting the genetic research studies that create CM1/S 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 nearly 275 families already enrolled in the study, you have helped us to develop one of the strongest CM1/S genetic studies in the nation. Since genetics of Chiari Type 1 Malformation with or without Syringomyelia study began in 1994, the Duke CHG team has been awarded research funds or grants from Bobby Jones Open Fund, the National Institutes of Health HD33400, NS26630, the American Syringomyelia Alliance Project (ASAP) and from families that are enrolled in the study or whose lives have been touched by Chiari Type 1 Malformation and/or Syringomyelia.

On occasion, we are asked if we can accept donations to support the CM1/S research, sometimes in honor or memory of a loved one with CM1/S. If you or someone you know would like to make a gift, the Center for Human Genetics has created the Duke CHG Chiari Type 1/Syringomyelia Research Fund. To make a financial gift to Chiari Type 1 Malformation and/or Syringomyelia research, you may visit the secure web site of the gift records office at <http://www.giftrecords.duke.edu>, or you can send your tax-deductible donation to:

Center for Human Genetics
Chiari Type 1/Syringomyelia Research Fund
Box 3445
Duke University Medical Center
Durham, NC 27710

Additional Information

Please note that our research is concentrated on studying genetic causes of CM1/S. With research as our primary focus, we are not in a position to communicate medical advice. If you are seeking answers to clinical, surgical or symptom-related questions, or are interested in obtaining information about particular institutions or physicians, please call your physician. In addition, there are many organizations that provide factual information about Chiari Type 1 Malformation and syringomyelia for individuals and families. Here are some you may find useful:

American Syringomyelia Alliance Project

The ASAP national network, founded in 1988, offers support, networking, and information for individuals with syringomyelia.

PO Box 1586
Longview, TX 75606-1586
Phone: (903) 236-7079
toll-free (800) 272-7282
Fax: (903) 757-7456
Web: www.asap.org

Canadian Syringomyelia Network

Barbara Forrestall,
Chair and Founder
69 Penny Crescent
Markham, Ontario L3P 5X7
Phone: (905) 471-8278
Fax: (905) 882-8367
E-mail: csn@passport.ca
Web: www.csn.ca

National Institute of Neurological Disorders and Stroke

Federal Building, Room 814
7550 Wisconsin Avenue
Bethesda, MD 20892
Phone: (301) 496-5821
Fax: (301) 402-0302
Web: www.ninds.nih.gov

National Organization for Rare Disorders

PO Box 8923
New Fairfield, CT 06812-8923
Phone: (203) 746-6518
toll-free (800) 999-6673
Web: www.rarediseases.org