REACH
Volume 5
Fall 2008
The National Research Roster for Huntington Disease Patients and Families

IMAGING IN HD

By D. Hermina Rosas, M.D., Ph.D.
Assistant Professor, Department of Neurology, Massachusetts General Hospital
Harvard Medical School
Director, Center for Neuroimaging in Aging and Neurodegenerative Diseases
Co-Director, New England HDSA Center of Excellence

New technologies that enable high-resolution analyses of MRI images of the brain are providing a window into the complex biology of Huntington's disease. These advanced methods are showing us that many regions of the brain undergo a complex degenerative process.

In particular, the cerebral cortex, which is responsible for complex thought, purposeful movement, memory function and visuospatial functions, is dramatically atrophied in HD. Importantly, different regions of the cortex appear to be affected at different times in the disease and correspond to unique symptoms. This is one possible explanation of how symptoms of HD can be so different from one person to the next.

For example, in individuals who have more prominent dystonia, stiffness and slowness of movements, the frontal cortex, which is involved in the planning and initiation of movement, is much more severely atrophied than in patients who have more prominent chorea. Early changes in the anterior cingulate, a region important in complex cognitive processes, are found as long as a decade before motor symptoms manifest. Importantly, specific patterns of cortical thinning correlate with the total functional capacity score, a measure of functional status in HD that has been used as a primary outcome measure, a way to gauge if a drug works, in clinical trials seeking to slow HD. Significant changes have also been found in the white matter, the cables that connect one brain region to another, in similar areas. Together, these findings support an important role for the cortex and its connections in the symptoms of HD. These findings also suggest that a non-invasive MRI, coupled with novel analysis tools, may provide new and more efficient ways to study the effect of drugs in clinical trials in slowing progression of the pathology of HD.

While much remains to be done, these findings are important because they broaden our focus from the basal ganglia, the area of the brain that is the most severely affected in HD and that has historically been the primary focus of research, to the many other regions of the brain.

Understanding where brain changes occur, what their relationship is to clinical symptoms, when they occur and what drives the selective vulnerability of the cortex and white matter may provide important new insights into basic mechanisms at play in HD, the why, which will hopefully provide us with information about how to make the greatest clinical impact in treating HD.

• • • If you would like to receive **HD Roster mailings** to learn about new research studies and to have the HD Roster Reach newsletter delivered directly to your mailbox, please contact us by phone at: 1-866-818-0213, or by email: sburn@iupui.edu or at our website http://hdroster.iu.edu

WHAT IS THE HD ROSTER?

The National Research Roster for Huntington Disease Patients and Families is a unique nationwide information resource dedicated to assisting scientific research on Huntington disease (HD).

The goal of the Roster is to help researchers learn more about HD. To accomplish this goal, the Roster has involved nearly 3000 families in HD research.

The Roster collects the names of families, including information about the history of HD in the family (family trees) and other related data, received from questionnaires. Information received from the questionnaires identifies HD patients and families who are interested in participating in research projects.

- The Roster is totally VOLUNTARY.
- You can withdraw from the Roster at any time.
- No information about you will be given to anyone without your WRITTEN permission.
- No one, including your own family members can find out if you are participating in the Roster without your WRITTEN permission.
- You decide if you want to participate in any available research opportunity. You do not have to participate if you are not interested.

We would like to thank the many families who have participated in the Roster. We believe the Roster is a valuable scientific resource which will assist in the discovery of a cure for HD. We would like to extend the invitation to join the Roster to you and your family.

We are always eager to accept new participants!

in the spotlight

JANE PAULSEN

Many in the HD community know Dr. Jane Paulsen as the Co Director of the HDSA Center of Excellence at the University of Iowa. But Dr. Paulsen wears many hats and has projects that influence people and policy at the local, state, national and international level.

Dr. Jane Paulsen is Professor of Psychiatry, Neurology, Psychology and Neurosciences at the University of Iowa Carver College of Medicine and has been active in HD research for over fifteen years. Within the University community, Dr. Paulsen directs the Division of Psychology in the Department of Psychiatry and provides neuropsychology training in the Department of Psychiatry. She lectures to psychiatry residents and neuroscience graduate students. She supervises psychology graduate students on thesis and dissertation projects.

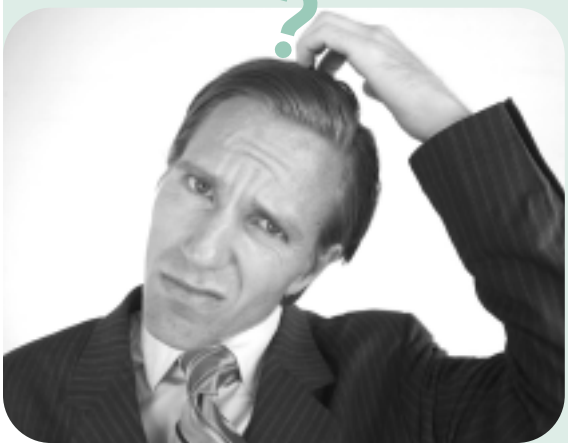
On the state level, Dr. Paulsen was recently awarded the Excellence in Medicine award from the Iowa Chapter of HDSA. She has also served as a member of the Iowa Elder Affairs committee. She routinely participates in state-led HD hoop-a-thons, holiday socials, and other HD community events.

Nationally and internationally, she is known as an engaging speaker to HD state, national and international conferences. She is the author of the book "Understanding Behavior in Huntington's disease" and strives to help HD families better appreciate the brain changes that occur in this disease and how the brain impacts behavior, emotions and activities. She is a member of several research groups and also a reviewer for many professional journals that cross disciplines from psychology to neurology to neuroscience.

She was one of the founding members of the Huntington Study Group (HSG) and served as neuropsychologist for the Venezuela Research Project from 1993 to 1998. Most recently, she has taken an active role in genetic nondiscrimination bills and policy development. She and her colleagues are currently gathering data to support better laws to protect persons with known genetic disease.

Dr. Paulsen is a long-time advocate for persons with HD and their families. Dr. Paulsen is Principal Investigator of three NIH-supported research projects. The primary research project, PREDICT-HD, is an international study to detect the earliest changes in pre-symptomatic HD. Other projects directly related to PREDICT-HD are Respond-HD and "Preclinical brain changes in HD". CHDI-supported pilot studies are currently ongoing to more rapidly establish clinical trial methodology for preclinical and very early HD. She is a co-investigator on Dr. Janet Williams' study "Family Health after Predictive Testing" and serves as a Steering Committee member of the HSG multi-site projects PHAROS (PI Ira Shoulson) and PREQUEL (PI Chris Ross). Dr. Paulsen has worked on several multi-site and Center grants through the University of California San Diego and more recently at Iowa. She has published over 120 peer reviewed manuscripts as well as two books and a video on HD.

STUDY CONFUSION.....



Roster participants have been receiving more letters than usual concerning ongoing research studies. Although the recent surge in the number of Huntington disease research studies is obviously a very good thing, it may be difficult to keep track of all of the studies and to decide which studies are most appropriate for you. It is important to remember that as a Roster contact you will usually receive an information letter about each study that has asked for our assistance in recruiting study participants. Study letters are usually sent to all Roster contacts regardless of risk status. Many Roster contacts are married into HD families and have no risk at all; however, because the letters are sent to all contacts, they go to everyone on the Roster. Additionally, many studies request that participants be "gene positive" or "diagnosed with HD". Again, the letters describing these studies are sent to all Roster contacts. The letters are not sent because of any information pertaining to an individual's HD status. In this newsletter, and in each of our upcoming newsletters we will review the studies for which the Roster is currently recruiting and also list the study criteria.

• • • If you ever have any questions about a study or study criteria please feel free to call Shelley Burnham at 1-866-818-0213.

WHAT IS IN THE PIPELINE FOR THE TREATMENT OF HUNTINGTON'S DISEASE

By Jo Anne Watton, MSW, RSW
Director of Individual and Family Services
Huntington Society of Canada

Clinical trials offer interested families a vital opportunity to contribute to the drug discovery process. One comprehensive cure involving a single compound may not emerge from the drug discovery pipeline; a combination of therapies is more likely. It is possible that a number of compounds specifically targeted to HD might go to clinical trials simultaneously in the next few years. Some foresee that certain treatments might be specifically tailored to the CAG repeat profile of the individual patient. Given the size of the HD population, and the number of compounds in the queue, the HD community will be challenged to adequately test these therapies and get them approved by regulatory bodies. Clearly, in the near future we will need all family members available to participate in a range of clinical trials.

THE PROSPECTS IN THE PIPELINE

Shown below is a list of some of the candidate technologies that show the most promise for HD drugs and may go to clinical trials in the next few years:

Antisense Oligonucleotides

When the sequence of a particular gene is known to cause a disease, it can be possible to effectively "switch off" the gene. This has been shown to effectively cure the HD mouse model from even severe disease. Antisense Oligoneucleotides are molecules that inhibit the production of the HD protein. With delivery to the brain through an implantable pump, or by a modified virus, these compounds have the potential for testing in humans relatively quickly. They can be detected comparatively easily in the brain and can be directed to specific targets. This is currently a focus of a project together with Isis Pharmaceuticals of California.

M30

This is a multifunctional neuroprotective and neurorestorative, brain permeable drug which appears to work in several different pathways that influence HD. M30 is a candidate for Parkinson disease and depression (MAO inhibitor) and is thought to remove (chelate) iron and to stimulate production of a critical factor lost in HD brains called BDNF, which can also protect neurons. It may also act as an antioxidant and help new neurons to grow.

HDAC Inibitors (histone de-acetylase)

Enzymes control the speed of chemical reactions. HDACs are a family of enzymes which help to regulate which genes are switched on and off. They offer promising protective avenues to treat HD by compensating for protein expansion. The specific

"It is possible that a number of **compounds specifically targeted to HD** might go to clinical trials simultaneously in the next few years."

HDAC inhibitors deployed for HD thus far have been inadequate and the search continues for brain permeable inhibitors with fewer side effects.

KMO Inhibitors (kynurenine 3-mono-oxygenase inhibitors)

Microglia are the brain's immune system cells, similar to white blood cells that protect the body against infections. The immune system is overactive in HD and evidence is mounting that microglia are overactive as well and may be causing damage. An enzyme found in microglia, KMO, can affect how rapidly HD progresses. Changes in quinolinic acid metabolism may be central to HD. Quinolinic acid is part of a biochemical process called the kynurenine pathway. Work in mice shows that the kynurenine pathway is activated in early-stage HD. Therefore research is underway to find drugs to switch off KMO to reduce and slow the damage done in mice and humans.

Autophagy is a new area of interest. Proteins are complex molecules that perform a wide variety of activities in cells. Autophagy is a clearance process - a way cells identify internal problems like mutant HD proteins and mark them for removal from cells. Work is continuing to find drugs like mTOR inhibitors to boost autophagy.

Coenzyme Q10

CoQ10, a compound with potential neuroprotective properties, was investigated at 600mg/day in HD patients and demonstrated a favorable, though not statistically significant trend toward slowing disease progression. New trials are expected to start shortly with higher doses of CoQ10 and new, more potent derivatives of CoQ10 that enter the brain better are being developed.

Again, this list only identifies the projects likely to come to clinical trial in the next few years. Of course many other disease processes, targets and compounds are under intensive study including Caspase-6 Inhibitors, Minocycline, Kinase Inhibitors, BDNF, mGluRs, Stem Cells, Cystamine and Cysteamine, Memantine, etc.

HD ROSTER COORDINATOR'S CORNER

23RD ANNUAL HDSA NATIONAL CONVENTION

by Shelley Burnham, Indiana University School of Medicine

On June 6-8, 2008 I traveled to Pittsburg, Pennsylvania to take part in the 23rd Annual HDSA National Convention. I was delighted at the opportunity to meet with so many researchers, volunteers, and families dedicated to the care and cure of HD.

Many convention attendees visited the Roster display to receive information on how to become a Roster contact person and to learn more. It was wonderful to meet everyone who stopped by the display.

GINA FINALLY PASSES CONGRESS

On May 21, 2008, President Bush signed into law GINA (Genetic Information Nondiscrimination Act). GINA was designed to prohibit the improper use of genetic information in health insurance and employment. It prohibits group health plans and health insurers from denying coverage to a healthy individual or charging that person higher premiums based solely on a genetic predisposition to developing a disease such as HD in the future. The legislation also bars employers from using individuals' genetic information when making hiring, firing, job placement, or promotion decisions. In April, this bill passed the Senate unanimously, and the House of Representatives by a vote of 414 to 1. This long-awaited measure, which has been debated in Congress for 13 years, will pave the way for people at risk for HD to take full advantage of the promise of personalized medicine without fear of discrimination.

HUNTINGTON SOCIETY OF CANADA

By Jo Anne Watton, MSW, RSW
Director of Individual and Family Services
Huntington Society of Canada

Over the last two years, the Huntington Society of Canada (HSC) has worked to support and complement the work being done within Canada and around the world, and to invest on behalf of Canadian donors in unique research which has the potential to generate a relatively high return.

To attract new Canadian scientists to HD research, HSC is holding competitions in partnership with the Canadian Institutes of Health Research (CIHR). The CIHR is the federal agency in charge of supporting biomedical research within Canada with tax dollars. This spring HSC will invest in doctoral candidates and post doctoral fellows through this initiative. There are six candidates in the running for these grants and their qualifications and research projects are now being assessed by CIHR.

HSC recently initiated two exciting new research projects at opposite ends of the research spectrum, which are now attracting significant attention in the worldwide scientific community. The first project is for testing experimental treatments for HD. While essential research proceeds to develop treatments to modify the underlying disease, HSC is interested in spawning therapies which offer immediate relief to families. Earlier this year clinicians in North America and Europe were invited to propose and test experimental treatments (pharmaco-therapeutic, cognitive or behavioral intervention) with this purpose. These therapies would have known safety and tolerability in humans and may already be approved for another indication or used by clinicians with little or no evidence to treat symptoms of HD. Fourteen expressions of interest have been received for the competition, which ended in April 2008.

The second new project is about fostering innovative research that will eventually lead to the next generation of targets for the treatment of HD. This is to ensure the HD community has a continuous supply of valid targets at the cutting edge of research. HSC is calling internationally for research proposals to explore the earliest mechanisms of disease, the normal functions of the huntington protein, the impact of increasing numbers of alleles or repeats and the CAG DNA expansion process. The application deadline was May 15 and the feedback from the scientific community has been very encouraging. We'll keep you posted as the process unfolds.

The goal of these international grants is to ensure that Canadians affected by HD are being kept in the discovery process without any geographic boundaries, and that the HSC is using donor funds to support research at a world-class level, both within and outside of Canada. Canadian researchers have historically been major contributors to HD research and are recognized world-wide. One of these recognitions is the hosting of the 2009 World Huntington's Congress in Vancouver.

Research Opportunities

If you are interested in any of the research studies described below, please contact the HD Roster:

- Phone: 317-274-5744
- Toll-free: 866-818-0213
- Email: sburn@iupui.edu

COHORT: Cooperative Huntington's Observational Research Trial

The COHORT study is designed to collect observational information from individuals who are affected by HD and from those who are part of an HD family, in order to learn more about HD, potential treatment and to plan future research studies of experimental drugs aimed at postponing the onset or slowing the progression of HD.

Inclusion/Exclusion Criteria

- 18 years of age and older
- Individuals who have HD or tested positive for the HD gene
- Parents, children and siblings of individuals who have HD or tested positive for the gene
- Grandparents and grandchildren of those individuals participating in COHORT who have HD or tested positive for the gene
- Spouses of those individuals participating in COHORT who have HD or tested positive for the gene
- HD family members who have tested negative for the HD gene.
- For those under 18 years of age, participation is limited to those who have been diagnosed with HD

Identification of Novel Biomarkers in HD

The Identification of Novel Biomarkers in HD study is seeking to identify potential biomarkers of early HD progression. Biomarkers are any sign or symptom of disease which can be used to measure the onset of disease even in the earliest stages. This study will test whether individuals with an expanded number of CAG repeats have progressive worsening of their saccadic eye movements, olfactory identification and neurocognitive performance as they approach clinically recognized, disease onset. The identification of such biomarkers is critical to studies of neuroprotective agents which could be used in future treatments to delay or eliminate the onset of the symptoms of HD.

Inclusion/Exclusion Criteria

- Between ages of 18 and 65
- Gene status must be known
- Have a biological parent previously diagnosed with HD
- Not be clinically diagnosable or claim to be experiencing symptoms of HD
- Not pregnant
- Not been diagnosed with a central nervous or neurological disorder
- Never had head trauma that caused the loss of consciousness and required hospitalization
- Do not have any significant abnormal eye impairments

Functional Magnetic Resonance Imaging (fMRI) in HD

Dr. Jane Paulsen's lab has contacted the Roster for help in recruiting patients for the fMRI study. The purpose of the fMRI study is to gain a better understanding of brain functioning in HD. fMRI scans will be used to identify areas of the brain that are active during certain cognitive tasks. This will provide useful data to researchers about the disease process.

Inclusion Criteria

- Between ages of 18 and 65
- Currently enrolled in Predict-HD
- Gene positive, pre-symptomatic individuals
- Gene negative individuals
- At risk for HD and tested for the HD gene

Exclusion Criteria

- Unstable medical or psychiatric illness
- Active substance abuse in the last year

Predict-HD

PREDICT-HD is an observational study; the goal of PREDICT-HD is to determine the earliest sign of active disease in persons inheriting an expanded number of CAG repeats in the HD gene. This information will allow future clinical trials of new drugs delaying the onset of HD to be administered at the earliest possible moment. This study is recruiting for gene positive/pre-symptomatic and gene negative individuals.

Inclusion Criteria

- 18 years and older
- Able to commit to a minimum of 4 yearly evaluations
- Commitment of a companion to attend visits or complete surveys via mail
- Able to undergo a MRI
- Gene negative at risk individuals
- Gene positive individuals who have not been diagnosed with symptoms of HD

Internet Information on Huntington Disease

National Research Roster for Huntington Disease Patients and Families
http://hdroster.iu.edu

Huntington Disease Society of America
www.hdsa.org

NINDS – National Institute of Neurological Disorders and Stroke
Phone: (800) 352-9424
http://www.ninds.nih.gov/health_and_medical/disorders/huntington.htm

HDF – Hereditary Disease Foundation
http://www.hdfoundation.org

WE MOVE – Worldwide Education and Awareness for Movement Disorders
Provides comprehensive educational materials for patients and health care professionals.
http://www.wemove.org

YGYH – Your Genes Your Health
Multimedia website guide for genetic disorders.
http://www.ygyh.org

Stanford HOPES – Huntington's Outreach Project for Education at Stanford University
Provides information on the scientific aspects of Huntington's disease.
http://www.stanford.edu./group/hopes

Caring for People with Huntington Disease?
Information about caring for people with HD; developed for patient's families and professionals.
www.kumc.edu/hospital/huntingtons

Huntington Disease Advocacy Center
Information, question and answers, problem-sharing, personal experiences and articles on HD.
www.hdac.org

International Huntington Association
Federation of national voluntary health agencies.
www.huntington-assoc.com

Nutrition for People affected by Huntington Disease
Nutritional information and resource links on aspects of nutritional care for people with HD.
www.lib.uchicago.edu/~rd13/hd/nutritn.html

Huntington Disease Lighthouse
Current information on treatments, drugs, support and patient resources.
http://hdlighthouse.org

Guide for Healthcare Proxies
http://www.abanet.org/aging/toolkit/tool9-lock.pdf

How to select your health care agent or proxy
http://www.abanet.org/aging/toolkit/tool1-lock.pdf

invitation

Do you have a question you would like to ask a doctor familiar with HD? Do you have a personal HD experience that you would like to share? Care givers, patients with HD, or people at risk for HD are invited to submit questions and/or share personal experiences in our "Ask the Doctor" column. If you are interested, please send your questions or story to:

The National Research Roster for Huntington Disease Patients and Families
Attention: Shelley Burnham
Department of Medical and Molecular Genetics
410 West Tenth Street • HS 4000
Indianapolis, IN 46202-3002

Or email: hdroster@iupui.edu

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

The National Research Roster for Huntington Disease Patients and Families
Department of Medical and Molecular Genetics
410 West Tenth Street, HS 4000 Indianapolis, IN 46202-3002