AN OVERVIEW OF TESTING FOR HD

Dr. Marsha L. Miller, PhD Huntington Disease Lighthouse Family (www.hdlf.org)

Confirming a diagnosis

The development of the DNA test has been useful for confirming a diagnosis of Huntington disease that a physician may make based on clinical signs. The DNA testing is especially helpful for those with earlier or later than average onset as well as when someone develops HD without a family history. A Canadian study reported that a quarter of those who tested positive for the disease-causing allele were unaware of any family history of HD. The reasons for this were misdiagnoses, family secrecy, and new mutations. About ten percent of patients with HD in a given generation are estimated to have experienced an increase in CAG counts from a parent who did not have HD but had a count in the unstable range (27-35).

Predictive testing

The test is also available for those who are not experiencing symptoms but want to find out whether they have the disease-causing allele of the gene. Under these circumstances, the test is called 'predictive'.

HD families are pioneers in this form of genetic testing and there were many concerns expressed from doctors, labs, psychologists, social workers, and advocates about how this could best be done. International guidelines were established for the predictive test. They can be found at the following link, along with the reasoning behind each component: http://www.hdfoundation.org/html/testwfn.php
These guidelines reflect concerns that people who take the test be well informed about the disease and genetic testing, be emotionally prepared for the results, and have the health, life, disability, and long term care insurance plans that they want in place before testing.

Other issues relate to being aware of how the results might impact other family members. A young adult might seek testing before getting married and having children, for example. However, a positive result would also communicate that an untested, at-risk parent also had the gene, a result that the parent might be unprepared to hear.

Taking the test is always a personal decision. Friends who are unfamiliar with HD will often express surprise that the at-risk individual doesn't immediately go and get a test. This is because they haven't thought through the ramifications of learning that one will get a disease for which there is currently no treatment.

Significant others may want someone to test because of joint decisions that will be made about marriage, having children, taking financial risks, etc. Ultimately however, it is the person at risk who must make the decision that is best for him or her. Those who decide to have predictive testing are making a definitive decision. The testing process can be interrupted at any time, but you cannot "unring the bell" of a result once you have heard it. Deciding not to test is always provisional. It may help those at risk who decide not to test to realize that they are making a decision that can be revisited later. Their attitudes about predictive testing may change at a later time, they may become symptomatic and want to confirm the diagnosis, or a major treatment may become available which causes them to want to test.

Testing Results

A testing result of 40 or more CAG repeats means that the individual has tested positive for the disease-causing allele of the HD gene. A result of 36-39 repeats is less predictive. In that range, some will develop symptoms and some will not. Some researchers believe that this is indeed the disease-causing allele of the HD gene and that it would result in HD symptoms if the individual lived to an extreme old age.

A test result of 35 repeats and below means that the individual will not develop HD. However, it is possible for those with 27 through 35 repeats to pass along an expanded number of CAG repeats, which could result in an individual in a subsequent generation developing the disease.

For the most up-to-date information published about intermediate alleles, visit the following link: http://www.hdlf.org/node/824

As mentioned above, sometimes a clinical diagnosis of HD is not confirmed by a DNA test. To read about other possible diagnoses, visit the following link: http://www.hdlf.org/node/315

The Consequences of Testing

Testing positive has obvious consequences. Anger, anxiety, and depression are all normal emotions. There is likely to be a period of mourning for the more carefree future that the person hoped to have. People may try to put it out of their minds, change life plans, become involved in advocacy, do research to develop a proactive strategy of 'best bets' for healthy living, or develop some other coping strategy.

Less obvious are the consequences of testing negative. Certainly this is the preferred result, but many may feel ambivalent about 'celebrating' when other friends and family members have not been so fortunate. Sometimes survivor's guilt will cause people to do too much in the way of advocacy, fundraising, and support for others rather than keeping volunteer work in a healthy balance. And life doesn't change overnight.

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It takes a while to stop watching for symptoms and it is not uncommon for those who test negative to wonder if a mistake was made with the test.

Even deciding to test may bring about certain unanticipated consequences because another at-risk family member or friend in the support group could feel uncomfortable about their own choice not to test and become distant.

We thank the Huntington's Disease Lighthouse Family and Dr. Miller for the use of this article. More information about testing, including personal stories, can be found on the HDLF website at http://www.hdlf.org.

QUESTIONS AND ANSWERS Continued from page 4

What Treatments are there for the Disease?

There are currently no treatments which will stop or reverse the disease. It is possible to treat some of the symptoms, such as depression and involuntary movements, with various medications. Improvements in general health, such as good nutrition, will bring about improvements in the condition of the person and in their enjoyment of life. Many scientists are working on finding treatments and a cure for HD.

Where Can I Go with Questions?

We are here to help! If you have any questions about any of the issues discussed in this newsletter, please contact us toll-free at (866) 818-0213. We will be happy to provide you with more information at your request.

Internet Information on Huntington Disease

Hereditary Disease Foundation
www.hdfoundation.org

Huntington Disease Society of America
www.hdsa.org

Huntington Study Group
www.huntington-study-group.org

Help 4 HD International
Features a web-based radio program, "The HD View"
http://help4hd-international.org

NINDS - National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/health_and_medical/disorders/huntington.htm

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

YGYH - Your Genes Your Health
Multimedia website guide for genetic disorders
www.ygyh.org

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

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

Huntington Disease Advocacy Center
Information, questions and answers, and personal experiences
www.hdac.org

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

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

The Huntington's Disease Project - We Have a Face
Awareness and advocacy
www.wehaveaface.org

The National Research Roster for Huntington Disease Patients and Families • Department of Medical and Molecular Genetics
410 West 10th Street, HS 4000 Indianapolis, IN 46202

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 by connecting families interested in participating in research with researchers who are studying HD.

The Roster collects information from families, including information about the history of HD in the family, family trees, and other related data from various forms and questionnaires. This information helps to identify HD patients and families who may be interested in participating in research projects.

Scientists interested in studying HD may submit two types of requests for information contained in the Roster: anonymous information and identifiable information. Anonymous information is de-identified, meaning that all names and personal identifiers are removed and can be given to researchers without having to contact Roster families. Identifiable information includes data such as names, dates of birth, and family structure. Identifiable information can also be used to help researchers find volunteers who are willing to participate in HD research projects. In any instance where identifiable information may be given to a researcher, the Roster will contact participants to ask whether they are willing to share their identifiable information for a research project.

Participation in the Roster is totally VOLUNTARY; participants may withdraw at any time. No information about participants will be given to anyone without their WRITTEN permission. No one, including other family members, can find out if an individual is participating in the Roster without their WRITTEN permission. Each participant may decide if they wish to participate in any available research opportunity- there is no obligation to participate in any project.

We would like to thank the many families who have participated in the Roster. We believe that the Roster is a valuable scientific resource which will assist in the discovery of treatments or even a cure for HD.

We are always eager to accept new participants!
Toll-free (866) 818-0213

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The National Research Roster for Huntington Disease Patients and Families

CHANGES AT THE ROSTER

The National Research Roster for Huntington Disease Patients and Families (HD Roster) was established at Indiana University, in the Department of Medical and Molecular Genetics, in 1979. The Roster operated for 32 years under funding from the National Institutes of Health (NIH). Unfortunately, NIH funding for the Roster recently ended. However, we are excited to inform you that the Roster has secured funding from the Hereditary Disease Foundation (HDF). The Hereditary Disease Foundation is committed to promoting research projects to identify treatments and cures for Huntington disease. We are immensely grateful to the Hereditary Disease Foundation and HDF President, Dr. Nancy Wexler, for their support. For more information about the HDF, please visit: www.hdfoundation.org.

We would also like to announce that the Roster has a new Research Coordinator, Danielle Smith. Danielle has worked in our department for over six years, most recently on an Alzheimer disease research study. She will be the main point of contact for current and potential Roster participants as well as researchers who may be interested in utilizing the Roster. Overseeing the Roster are Dr. Tatiana Foroud, Chair of the department's Division of Hereditary Genomics, and Jacqueline Jackson, who has been involved with the Roster since its inception.

In addition to the other changes, we have revised and updated the Roster website (http://roster.iu.edu). We hope that the site will be a great resource for persons seeking information on HD and on the Roster itself. In an effort to streamline our costs, we are hoping to correspond with as many participants as possible by e-mail. Using e-mail for communications will allow us to reduce the use of paper and envelopes, save postage, and possibly provide a more convenient method of communication for our participants. The Roster is asking for e-mail addresses for participants who may prefer to be contacted by e-mail rather than by traditional "snail mail." We assure you that any e-mail addresses provided will not be sold or otherwise given out to third parties, but merely used for communications from the Roster, such as family history updates, study recruitment letters, and even this newsletter (Adobe PDF copy). There is no obligation for you to receive Roster correspondence via e-mail if you would still prefer to receive it through the mail. We thank you in advance for helping us to reduce costs by opting to use e-mail if at all possible. Enclosed with this newsletter, you will find a letter and corresponding reply form where you may indicate your preferred method of contact by the Roster.

We at the Roster are so grateful for the participation and interest of our Roster families and researchers and look forward to continuing to serve you!

Left to right: Jacqueline Jackson, Tatiana Foroud and Danielle Smith.

SUCCESS OF THE ROSTER

Since the establishment of the HD Roster in 1979, our primary goal has been to advance Huntington disease research by acting as the "middle man" between researchers interested in studying HD and patients and families interested in participating in research. Over the years the Roster has continued to grow and is now composed of data from over 158,000 individuals from over 2,600 families, with over 2,300 active contacts who continue to provide us with information.

The Roster is currently assisting with recruitment for six studies, and has helped to facilitate research recruitment for many, many studies over the years. Researchers who have used the Roster to recruit study participants and/or to obtain de-identified data about HD have published nearly 400 scientific publications to date!

We are currently assisting a number of researchers with their research studies. These studies are listed on page 3. If you are interested in more information or participating in these studies, please let us know. Getting more information about participating in a research study is easy-just contact the Roster!

We are available by phone, toll-free, at 866-818-0213, by e-mail at hdroster@iupui.edu, and on the web at http://hdroster.iu.edu. We are here to help!

THE COGNITIVE ASSESSMENT BATTERY (CAB) BETA STUDY - A CLOSER LOOK

The aim of the Cognitive Assessment Battery (CAB) Study is to develop a 60-minute set of cognitive tests for use in future Huntington disease clinical drug trials. To select the final list of tests, it is necessary to start with a larger set of tests requiring about 90 minutes to 2 hours per test session. This larger set of tests can then be evaluated to select the tests that best fit the needs for a clinical trial. Many of the tests included in the CAB Study are known to be sensitive in either the early stages of HD or in people with the HD gene. Other tests included have some promise but need further study. Because clinical trials repeat the same tests at several test sessions usually across weeks or months, the CAB study participants are asked to perform the tasks at three time points: the initial study visit, the following day, and six weeks after the initial visit.

The total number of people needed for the CAB Study is 50 participants in the early stages of HD, 100 participants who are not diagnosed but who have been tested as having the disease-causing allele of the HD gene, and 100 control participants who do not have the disease-causing allele of the HD gene.

CHDI is funding this study in hopes of developing an excellent cognitive battery that will be available to anyone evaluating new treatments for HD.

Using these groups of participants will allow researchers to determine if there are cognitive changes which are detectable early in the onset of HD. Data collection is currently underway at 22 English speaking sites and is planned to be finalized by mid-2012.

The CAB study is jointly conducted by the CHDI Foundation, Inc., and Dr. Julie Stout's lab at Monash University in Melbourne, Australia. CHDI is funding this study in hopes of developing an excellent cognitive battery that will be available to anyone evaluating new treatments for HD. The CHDI Foundation is a not-for-profit company whose sole aim is to find treatments for HD. For more information about the CAB Beta study, please contact the Roster directly.

DID YOU KNOW?

- There are many different types of research studies being conducted to study Huntington disease, all with different criteria. Not all studies require that participants be affected with HD. Some studies hope to recruit at-risk individuals and even those with no family history of the disease. In addition, some studies are simply observational and don't require participants to take any study medications or complete any medical testing. For more information about the requirements of studies that the Roster is assisting with, turn to page 3. If you have any questions about study criteria, feel free to contact us!

Research Opportunities

2CARE: Coenzyme Q10 (CoQ) in Huntington's Disease
The 2CARE study is a therapeutic clinical trial that examines the effects of Coenzyme Q10 (CoQ) on the progression of functional decline in HD, as well as the long-term safety and tolerability of CoQ at the study dosage. CoQ, which has been used to treat a variety of human disorders, is being studied as an investigational drug at a higher dosage than what is currently available over-the-counter.

Eligibility Criteria
- 16 years of age or older
- Early (mild or moderate) HD
- Able to walk independently
- Fully self-sufficient in activities of daily living (eating, dressing, bathing)
- Medically and psychiatrically stable (if taking psychotropic medication, must be at a stable dose)
- A study partner who will maintain control of and supervise the dosing of study medication
- No exposure to any other investigational drug within 30 days of first study visit
- Not pregnant or breast feeding
- No current or history of drug or alcohol abuse, within 1 year of first visit
- No known sensitivity or intolerability to CoQ or FD&C #5 Yellow Lake (also known as tartrazine) or any other ingredients in the study medication

CREST-E: Creatine Safety, Tolerability, and Efficacy in HD
The CREST-E study will test whether creatine can slow the progressive functional decline that occurs in adults with early HD, as well as the long-term safety, tolerability, and effectiveness of creatine at the study dosage. Creatine is being studied as an investigational drug at a higher dosage than what is currently available over-the-counter.

Eligibility Criteria
- 18 years of age or older
- Early (mild to moderate) HD
- Able to walk independently
- No requirement for skilled nursing care
- Medically and psychiatrically stable (if taking psychotropic medication, must be at a stable dose)
- Not pregnant or breast feeding
- No known sensitivity or intolerability to creatine

Genetic Testing for Huntington Disease in At Risk Adolescents and Young Adults
The Genetic Testing for HD in At Risk Adolescents and Young Adults study will explore how this at-risk population approaches the issue of genetic testing. Study interviews can be completed in person, over the phone, or via e-mail.

Eligibility Criteria
- Between the ages of 14 and 29
- At risk for HD by virtue of having an affected parent
- Able to read and speak English

iPS for HD Research: Induced Pluripotent Stem Cells for Huntington's Disease Research
The iPS for HD Research study will use blood and skin samples from HD patients and their families to make cell types that can be stored and used for research and to search for genes that affect when family members develop symptoms (age of onset), as well as which symptoms develop. The research team believes that there are genes that run in families which may influence how HD manifests (age of onset and disease symptoms). Identification of such genes could lead to new therapeutic strategies in HD.

Eligibility Criteria
- 13 years of age or older
- At least two generations in which there are HD-affected and unaffected people in each generation
- At least 1 family member who has tested positive for the disease-causing allele of the HD gene in each of the two generations
- Other eligible family members (this may include healthy spouses, children, siblings, and parents of the HD-affected individuals)

PREDICT-HD 2.0: Predictors of Huntington's Disease
PREDICT-HD is an observational study of healthy persons without any HD symptoms. This may include both individuals who have the disease-causing allele of the HD gene as well as those who do not. The goal of the study is to define the earliest biological and clinical features of HD before at-risk individuals have disease symptoms that can be diagnosed. This may make it possible to test treatments that could potentially delay or prevent the onset of HD and to design future studies of drugs that could help at-risk individuals.

Eligibility criteria
- 18 years of age or older
- Commitment to undergo an MRI evaluation as well as annual evaluation
- Support person who will accompany the research subject to all study visits
- Known HD gene status, may be either individuals who have the disease-causing allele of the HD gene or those who do not
- No current HD symptoms
- Medically and psychiatrically stable
- No current or history of drug or alcohol abuse, within one year of first visit
- Not taking anti-psychotic or phenothiazine-derivation antiemetic medications
- No history of a severe learning disability or mental retardation
- No central nervous system disease or event (i.e. seizures, head trauma)
- No pacemaker or metallic implant

QUESTIONS AND ANSWERS

What is Huntington Disease?
Huntington disease is a hereditary neurological disorder. The disease causes certain areas of the brain to atrophy (break down) faster than normal, causing gradual decline of a person's ability to walk, talk, and reason. Symptoms usually appear between the ages of 30 and 45. Although rare, symptoms of HD can appear as early as childhood as well as very late in life. The average duration of the disease is 15 to 25 years.

How Did the Disease Get Its Name?
HD is named after Dr. George Huntington, an American doctor who was the first to publish a complete description of the symptoms and course of the disease in an article written in 1872.

How Common is the Disease?
The disease was once thought to affect about one person in 20,000. However, more current information leads us to believe that the disease is more common than originally thought, possibly affecting one in 10,000.

How is HD Diagnosed?
The diagnosis of HD is made by a doctor's examination of an individual's disease symptoms. Genetic testing to determine if a person has the disease-causing allele of the HD gene can be performed before a person begins to show signs of the disease or after symptoms have appeared. Once a person has begun to show symptoms of the disease, a gene test can be used to positively confirm that the symptoms are caused by HD and not some other condition or disease, such as other movement disorders like Parkinson's disease, or schizophrenia, alcoholism, or depression. Gene testing is not to be used in place of a complete neurological exam by a doctor (usually a neurologist) familiar with the signs and symptoms of HD. It is important to understand that a gene test can only confirm if a person has the genetic defect that causes HD. It does not tell us when a person will begin to show signs of the disease and/or whether or not the problems a person is currently experiencing are in fact symptoms of HD. A complete exam by a neurologist is the only way to determine exactly when disease symptoms have begun to appear.

What is Happening to the Brain of Someone with HD?
Cells in the brain are dying and not being replaced. Over time, thousands of brain cells will be lost, and with their loss, patients experience a decline in emotional, physical and reasoning abilities. During an autopsy, the brain of a person with advanced HD weighs less than a normal brain, and there are areas of substantial cell death. Much has been learned about the structure and function of brain cells, and about the chemical substances that transfer messages throughout the brain. However, much remains to be learned and that is why support of HD research is important.

What is the Person with HD Like?
There is great variation in the clinical symptoms of HD. Every person affected with HD is different and will have different symptoms. In the early stages, perhaps even before a diagnosis is made, there can be some changes in reasoning, movement, and emotions. Often the affected person either does not notice or denies the changes. In some cases, a family member, employer, or health care professional may be the first to notice that something is different or "wrong." In the early stage, individuals can go about doing all of their usual daily tasks and are able to be active and maintain employment. Some of the most common early symptoms of HD include clumsiness, forgetfulness and depression. Of course, these are problems that anyone can experience in daily life, which makes it difficult to determine if these problems are indeed caused by the onset of HD.

As the disease progresses, individuals typically begin to have trouble accomplishing daily tasks, especially employment. They can perform most of their usual roles, just not in the way they used to. They may be depressed, somewhat easy to anger, and resentful of suggestions that they are not performing well, but they continue to be independent and active.

In the later disease stages, individuals can usually no longer manage employment or full household tasks and require assistance and supervision in handling financial affairs. Activities of daily life, such as dressing and going to the bathroom, are impaired but can be managed with minimal help.

In the advanced stages of the disease, people are typically no longer independent in function, but they are capable of being supported within the family home or by minimal care in an extended care facility. Throughout the advanced stages, symptoms typically continue to worsen until the person is no longer able to complete normal activities of daily living. Some affected persons will eventually no longer be able to function independently and may require continued professional health care for complete support with the activities of daily living. The cause of death is usually from an associated condition, such as pneumonia or choking.

Remember that this is just a general list of symptoms. Every person affected with HD is different. Some people will have involuntary movements, some will not. Some will lose the power of speech; some will be able to speak. Many symptoms depend on the individual and on the availability of help and encouragement from family, friends, and health care professionals.

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