8-27-2013

‘Predicting’ Huntington’s disease in the heartland

Kenneth P. Serbin
University of San Diego

At Risk for Huntington's Disease

HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.

Blog Archive

- ► 2021 (12)
- ► 2020 (16)
- ► 2019 (19)
- ► 2018 (16)
- ► 2017 (14)
- ► 2016 (13)
- ► 2015 (24)
- ► 2014 (24)
- ▼ 2013 (30)
  - ► December (3)
  - ► November (3)
  - ► October (3)
  - ► September (3)
  - ▼ August (2)
    - 'Predicting' Huntington's disease in the heartland
    - A gene-positive dad's reflections on Huntington's ...
  - ► July (1)
  - ► June (1)
  - ► May (3)
  - ► April (4)
  - ► March (2)
  - ► February (3)
  - ► January (2)
- ► 2012 (26)
- ► 2011 (33)
- ► 2010 (26)
- ► 2009 (21)
- ► 2008 (7)
- ► 2007 (7)
- ► 2006 (4)
- ► 2005 (17)

About Me

GENE VERITAS

View my complete profile

HD Links

TUESDAY, AUGUST 27, 2013

'Predicting' Huntington's disease in the heartland

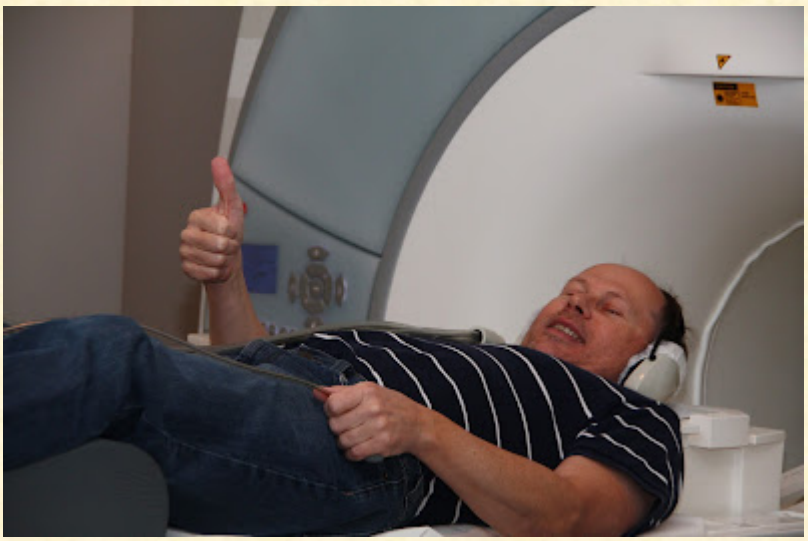
To develop treatments for a disease, researchers and physicians first need to understand how its symptoms evolve and how they affect people's lives.

In early August, I traveled to the University of Iowa in Iowa City to donate blood, urine, and saliva samples, undergo a motor coordination exam and brain MRI scan, and perform a battery of cognitive and mood tests for the long-term research study Neurobiological Predictors of Huntington's Disease, best known as PREDICT-HD, one of the largest public-private research projects in the history of the quest to defeat the disease.

My biological samples will become part of a bio-repository at the National Institute of Neurological Disorders and Stroke (NINDS), a division of the National Institutes of Health (NIH) located just outside Washington, D.C. Researchers from around the world can apply for access to these materials.

In studying gene-positive, asymptomatic people like me, the scores of researchers working at the University of Iowa, 26 other PREDICT centers in the U.S. and abroad, and many other institutions can try to analyze how the early symptoms of HD develop.

They are also seeking to identify HD "biomarkers" in the blood, cerebral spinal fluid (CSF), and brains of the study participants, who include formerly at-risk individuals who tested negative for HD. These individuals serve as a control, or comparison, group to ascertain which changes in the gene-positive people are specifically caused by HD.



Gene Veritas in preparation for PREDICT-HD MRI scan (photo by Sarah Petitt)

With biomarkers and other study data, researchers can effectively measure the effectiveness of potential treatments in upcoming clinical trials.

Huntington's Disease Society of America
International Huntington Association
Huntington's Disease Drug Works
Huntington's Disease Lighthouse
Hereditary Disease Foundation
Huntington's Disease Advocacy Center
Thomas Cellini Huntington's Foundation
HDSA Orange County (CA) Affiliate
HD Free with PGD!
Stanford HOPES
Earth Source CoQ10, Inc.

HD Blogs and Individuals

Chris Furbee: Huntingtons Dance
Angela F.: Surviving Huntington's?
Heather's Huntington's Disease Page

Patients: study us!

The lead scientist and administrator of the multi-million-dollar PREDICT study is Jane Paulsen, Ph.D., the co-director of the University of Iowa Huntington's Disease Society of America Center of Excellence and Professor of Psychiatry, Neurology, Psychology, and Neuroscience. From 1991-96, she was a postdoctoral neuropsychology fellow at the University of California, San Diego (UCSD), where she directed the HD clinical research program and came into close contact with the local HD community.

"The desire to move towards earlier detection and identification was really brought forth at UCSD from the families," Dr. Paulsen recalled in an August 6 interview. Such families, she noted, told her: "'You know, I've been dealing with this for years, and it isn't validated by the professional community. I don't have a diagnosis. A lot of people just think I'm exaggerating.'

"So just that sense of so many people who are at risk, who might be having subtle symptoms. When we would see them, we could detect maybe cognitive or certainly emotional changes that might occur. There's a lot of stages that occur before you get the motor signs and diagnosis.

"So the whole PREDICT project was sparked by families in San Diego saying, 'I've seen this forever, and we need to detect it sooner, before I lose my job or blow up at my kids or I don't take care of my home responsibilities the same or my friends don't understand me the same or my family doesn't understand me the same. If we could move it back and better understand it, then we could maintain all those additional components of my life.' So that was really the motivating factor – trying to get people to look at it this presymptomatically, before that diagnosis."

The decision to start PREDICT occurred in 1998 at an executive meeting of the physician-researcher collective known as the Huntington Study Group, of which Dr. Paulsen was a founding member. PREDICT formally began in 2001.

With its focus on the asymptomatic, PREDICT could help identify and test preventative treatments – the "holy grail" of HD research.

"Eventually, when they have a treatment, we want to intervene as soon as possible, because the sooner we intervene in the brain, the less tissue loss, the less dysfunction, the less toxicity has occurred," Dr. Paulsen explained. "Even if we slow it 15 percent, which is all that they've done in other brain diseases, since HD lasts so many years – we're thinking 40 years now – 15 percent could be many years where you could maintain a higher level of functioning."

You can watch the entire interview with Dr. Paulsen in the video below.

Fighting Huntington's Disease in the Heartland: An Interview with Dr. Jane Paulsen

from **Gene Veritas**

1:23:41

Maximizing research

PREDICT seeks to "maximize" HD research, Dr. Paulsen said. "We work with anybody who wants to work on a particular aspect of the disease."

As the PREDICT flagship, the University of Iowa has collaborated with its sister PREDICT centers and also partners and subcontractors at other academic institutions in the U.S. and abroad. The partners focus on cognitive testing, brain imaging, and motor studies. They include leading universities such as Johns Hopkins University, Brown University, and the Massachusetts Institute of Technology. On protein studies, PREDICT collaborates with Caprion, a private firm.

PREDICT had as many as 33 centers but currently has 27 active sites. Worldwide some 1,500 individuals, including 1,200 gene-positive, have participated in PREDICT. The study seeks to follow 1,000 individuals on a regular basis.

Stimulated largely by PREDICT, Iowa alone has produced a critical mass of innovative HD research in what Dr. Paulsen described as an "explosion" in knowledge about the disease over the past decade.

Among the 20-plus projects at Iowa over the past decade, Dr. Paulsen described research on clinical markers of the disease; biomarkers; proteomics (the study of HD-associated proteins); bone mass and metabolism; MRI scans; PET scans; full genome-wide scans (looking at *all* the genes in study participants); comparisons of symptoms among people with the same level of genetic mutation; the impact of discrimination and stigmatization on gene-positive people; and the possibility that HD might have vascular, immunological, or inflammatory components.

PREDICT researchers and their collaborators have published numerous scientific articles on presymptomatic HD and other aspects of the disease. These include studies seeking to refine cognitive testing; measure the relationship between estimated disease onset and the likelihood of the use of antidepressants; detect brain cell loss as an early HD imaging biomarker; and gauge the loss of perception and processing time in individuals.

Under Dr. Paulsen's leadership, Iowa has also taken a key role in the study of juvenile Huntington's disease, a form of the condition often given little attention by researchers because it accounts for just 10 percent of all HD cases.

Crunching the data

To help form research questions, search for useful biomarkers among the large amounts of data collected by PREDICT-HD, and help plan their use in clinical trials, the project enlists the skills of biostatistician Jeffrey Long, Ph.D., a professor of psychiatry.

"I mainly focus in tracking progression over time," said Dr. Long, the author of a textbook on the open-source computer program known as R, used widely by statisticians and in the PREDICT research. "We try to make use of every piece of data because we are appreciative of the time you all devoted to the study and want to make sure that we maximize the relevant information for the community."

Gene Veritas (left) interviewing Dr. Jeffrey Long (photo by Sean Thompson)

The seven-member bio-statistical team led by Dr. Long analyzes the different kinds of data collected individually and in combination. The team also helps draw comparisons between data from gene-positive and gene-negative individuals to account for factors such as cognitive loss due to natural aging.

Additionally, the scientists seek to understand the key relationship between the level of genetic mutation and the age of onset and severity of the disease. They have helped identify one key imaging biomarker: the diminishing size of the brain region known as the putamen before disease onset. They have also noted an abundance of a particular kind of protein in the bloodstream of gene-positive individuals.

A special connection

To coordinate visits by PREDICT participants and administer questionnaires and cognitive testing, the project employs several study coordinators, including research associate Stephen Cross.

"I've fallen in love with the population," said Cross. "They talk about the 'HD bug.' I've got the bug. There's something unique about this population. I think it's the family aspect of it. I would feel like I was abandoning the cause to work with another group."

With PREDICT since 2008, Cross currently has a caseload of some 80 individuals and their families.

PREDICT-HD study coordinator Stephen Cross (left) conversing with Gene Veritas (photo by Sarah Petitt)

"All of them have their lives changed by the genetic testing, regardless of the results, whether it's positive or negative," he observed.

He said that, in the case of gene-positive individuals, especially those from families who can trace the disease back a number of generations, "I think it changes their souls, when you know what's coming in the family, when it's in yourself. There's some kind of interaction in this triad of symptoms – the movement, the psychiatric and the cognitive. I think you're special because of this disease. I feel a spiritual connection with my participants."

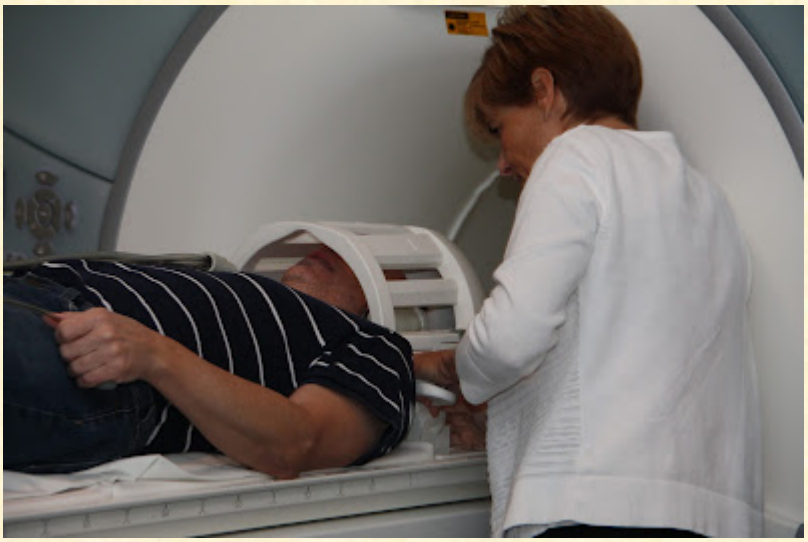
Brain and body scans

"We have many imaging studies," said Dr. Paulsen. "We're looking at the shape changes in the brain."

Imaging provides a picture of HD without the "need to poke around in the brain," Dr. Paulsen noted.

"We already have a very good imaging marker," she continued. "We can measure the volume of the part that's particularly sensitive to Huntington's disease, the striata or the basal ganglia. We can see that it changes a percentage every year of the disease. Even as far back as ten, 15 years prior to diagnosis. But we want to get are even better imaging markers, maybe ones that are earlier or maybe one that gives us a more robust signal. So that's why we have a lot of projects right now that are really trying to challenge what we can learn from brain imaging."

Gene Veritas (above) walks through a metal detector in preparation for a PREDICT-HD MRI scan performed after MRI radiology technician Marla Kleingartner (below) secures his head to prevent movement during the scan (photos by Sarah Petitt).



In addition to markers, imaging has revealed new information about the extent of the disease, Dr. Paulsen added. Scientists long thought HD affected only the basal ganglia, the area of the brain responsible for motor function.

"The imaging data that's been published over the last decade shows that it's much more widespread in the brain," she said.

With the lack so far of significant HD biomarkers in the blood and urine, PREDICT is now starting to study CSF collected from a number of its previous and current participants by way of a spinal tap.

(I could not donate CSF because a previous lower back injury made the procedure too risky for me.)

A full-body scan

As a registered nurse, Nancy Downing, Ph.D., takes a holistic approach to HD-affected individuals, always seeking to improve their quality of life.

Several years ago, an NIH seminar on genetics helped solidify Dr. Downing's interest in HD, she said. Today she seeks to integrate genetics and efforts to improve patients' quality of life. As a PREDICT researcher, she has especially focused on the effects of diet and exercise and the way in which lifestyle affects the expression of genes.

Just two months ago she helped complete a pioneering twelve-month study in which a group of PREDICT participants underwent dual x-ray absorptiometry, a scan that reveals the composition of a person's body mass (lean, fat, and bone). This same machine is used to detect osteoporosis.

Nancy Downing, Ph.D., RN, SANE-A (photo courtesy of HDSA Center of Excellence at the University of Iowa)

Dr. Downing hopes to triangulate the data from this study to help understand what HD does to areas of the body other than the brain such as muscle tissue. Evidence already suggests that gene-positive individuals have a shortage of branched-chain amino acids, necessary for muscle building and repair, she said.

Dr. Downing's work supports the growing notion that HD must be seen as a disease of the body and not just the brain.

Preparing for clinical trials

PREDICT can have an impact on clinical trials and the approach treatments might take, Dr. Paulsen said.

"It's kind of a when, where, how question," she said. "I don't think any of those questions is fully answered, so we have more work to do. But we have answers to those questions that we didn't have before.

"We didn't know that there was a when, where, how. We thought that once they get a diagnosis, we're going to try to treat them with something that

we've learned from other neurodegenerative diseases. I think in many ways Huntington's has opened up that box and made it much larger. It's a very exciting time. And I think it will continue. We're not even close to the end of the possibilities on where we intervene, (and on) the changes of Huntington's disease."

PREDICT, with its unique database of long-term data on presymptomatic individuals, could potentially furnish important data for clinical trials, she added.

"We have this entire cohort," she explained. "We know exactly how much change they have over time. If we do an intervention, we will be able to determine how much change has occurred. No other study can do that, because if you recruit someone new, you don't know that individual's trajectory. We have each individual's trajectory. We know what type of progression they have. If there was a treatment today, this is the group we should put it in, because we tell exactly what's going on with that person."

A potential key treatment

In collaboration with PREDICT and other HD projects at Iowa, the lab of Beverly Davidson, Ph.D., is engaged in research aiming for a clinical trial to test a gene-silencing drug that could at least partially halt HD at its root cause.

This approach would involve the use of RNA interference (RNAi) molecules permanently introduced into the brain via the injection of a virus by a neurosurgeon.

Similar to two separate gene-silencing clinical trials planned by Isis Pharmaceuticals, Inc., and Roche and a team involving Medtronic and the non-profit CHDI Foundation, Inc., the potential Davidson lab therapy aims to reduce the production of harmful huntingtin protein by interrupting the natural translation of the gene into protein.

In HD mouse testing, the lab has demonstrated that RNAi reduces the toxicity of the bad gene in the brain and alleviates symptoms, Dr. Davidson said.

She explained that RNAi is currently under study in a clinical trial for Leber congenital amaurosis, a retinal disorder that leads to blindness in children.

"They put this into the eyes of these children, and the children are showing remarkable, remarkable results," Dr. Davidson said.

Two of the Leber pioneers, Katherine High, M.D., and Jean Bennet,M.D., Ph.D., are "collaborating with us to develop the gene therapy vectors for Huntington's disease," Dr. Davidson noted.

Dr. Davidson said her team hopes to start a clinical trial within the next two years. "That might be aggressive, but we've been putting in a lot of effort in the background in the last year or so," she said.

To learn more about this project watch my interview with Dr. Davidson in the video below.

RNA Interference for Treating Huntington's Disease: An Interview with Dr. Beverly Davidson

from **Gene Veritas**

19:55

PREDICT's ending, gratitude to funders

Although currently operating at full steam, at least in its current form PREDICT is scheduled to end on July 1, 2014.

From 2001-2013, PREDICT received a total of $46.8 million in National Institute of Neurological Disorders and Stroke (NINDS) funding. Additional support has come from the National Human Genome Research Institute and the National Institute of Mental Health. The CHDI Foundation has also infused $15.5 million into the project and is providing further assistance.

In the last five years of the study, PREDICT received $5.6 million annually in federal funds from NINDS. The 2013-2014 fiscal year costs are being covered from funds incurred from previous years.

"I was told that NINDS won't consider any more budgets over $1 million," said Dr. Paulsen, noting the high cost of this kind of research. She said Iowa would be unable to continue the PREDICT study in its current form with so little money. Just bringing patients to Iowa is a major expense.

NINDS has experienced cuts in recent years. For fiscal year 2013, the federal government cut five percent of the NINDS budget as part of the $85 billion in overall spending cuts determined by Congress, including the sequestration provisions legislated in 2011.

In addition, CHDI is now shifting its priorities to implementing a new worldwide HD patient study and database known as Enroll-HD.

Nevertheless, Dr. Paulsen recognized the significance of NINDS funding, described by one observer as the largest HD project ever funded by the agency.

"I understand NINDS," Dr. Paulsen said. "They've been cut every year. We've been fortunate to receive funding from them for years, and CHDI has supplemented us. They had us expand and train some sites to expand. They have supplemented us when we ran into obstacles. CHDI has been very forthcoming in assisting. So they're just always there in the wings saying, 'What can we do to make this go better?' They really want to push things forward."

Assessing PREDICT's impact

Asked to reflect on the ultimate causes of PREDICT's expected termination, Dr. Paulsen stated that she's "not sure I have the right

answer. I have my opinion. There are centers that have followed research projects for decades."

The federal government has supported such ongoing centers for AIDS, Alzheimer's, Parkinson's, and alcoholism, she noted.

However, once again, HD's status as a rare disease might be leading officials to treat it as insignificant, Dr. Paulsen indicated. Others might have misunderstood PREDICT to have failed to innovate.

She rebuts those notions.

"The output of this project has been far greater than many other of the ongoing centers," she observed, adding that HD research has contributed significantly to the study of other conditions. "It's definitely been a project that has morphed and kept up and pushed the envelope. It would be nice to be funded like other centers that just are kind of automatically rolled over.

"We have to be protective of our resources, but the amount we are learning has just become exponential. It has grown so much and it isn't stopping. Most of the projects I'm talking about are brand new. They're just starting to look at CSF, at new imaging markers, at trajectories."

Despite these setbacks, Dr. Paulsen said that HD research would continue at Iowa. New grant applications are already in the works, she said.

The Iowa HDSA Center of Excellence will also continue its activities.

My future in PREDICT

In line with PREDICT's goal of tracking patients over time, the Iowa team has already notified me that I should return next year for a follow-up examination, before the July 1, 2014, end date.

Ideally, I should also make a third visit at a later date for the researchers to have sufficient data points. The uncertain budgetary situation has cast doubt on that possibility.

Regardless, I feel privileged to have contributed as an HD-positive individual to the quest for treatments, and I am thankful to the numerous researchers and support staff of PREDICT-HD and the public and for the private funding that has made this initiative possible.

(Next time: advocacy meets science and medicine in Iowa and beyond.)

Posted by Gene Veritas at 1:54 PM

Labels: asymptomatic , biomarker , CHDI , cure , diagnosis , gene-positive , HD-positive , Huntington's disease , Jane Paulsen , MRI , NINDS , pre-diagnosis , PREDICT-HD , presymptomatic , research , symptoms , treatment , University of Iowa

1 comment:

Judy Galasek said...

Hi Gene,

I've been following your blog for a while -- thanks for your words of wisdom! I just started a blog, too. It's really scary to come out of the closet. I also go to Iowa for the PREDICTHD study each year, and really appreciated your article and pictures!

4:17 PM, September 03, 2013

Post a Comment

Newer Post Home Older Post

Subscribe to: Post Comments (Atom)