

NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Huntington's Biomarker Discovery Could Set Tone for Trials

BY JEFF EVANS

FROM THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES U.S.A.

A biomarker found in the blood of patients with Huntington's disease appears to mark early stages of the disease and measure response to treatment, without confusing signs of Huntington's with those of other neurodegenerative diseases.

Yi Hu, Ph.D., of Harvard Medical School and Brigham and Women's Hospital, both in Boston, and his colleagues found the biomarker – a transcriptional modulator called H2AFY (for H2A histone family, member Y) – during a gene microarray search for messenger RNA transcripts expressed at various points in the disease process. They thought that a blood biomarker for Huntington's disease (HD) might exist, because the mutant huntingtin protein that causes the disease is expressed in nearly all tissues and “may cause detectable but clinically silent changes in gene expression and biochemistry in blood cells.”

The team found H2AFY overexpressed in the blood of HD patients relative to the controls after analyzing expression data from the genomes of 8 patients with HD and 111 control subjects, including 83 patients with other neurodegenerative diseases. The researchers found that H2AFY mRNA in blood provided high sensitivity and specificity for detecting HD in this set of patients, as well as in a second independent set (*Proc. Natl. Acad. Sci. U.S.A.* 2011;108:17141-6).

The investigators validated the association between elevated H2AFY mRNA levels and HD in two other independent, cross-sectional, case-control studies. In the first study, they compared H2AFY mRNA levels from 36 HD patients, 9 individuals with preclinical HD who carried the huntingtin gene mutation for HD, 50 healthy people, and 1 patient with spinocerebellar ataxia-1.

H2AFY mRNA levels were high only in the individuals with clinical or preclinical HD, which “is of critical importance for therapeutic biomarker discovery because patients with premanifest and early-stage HD are most likely to benefit from disease-modifying interventions,” the researchers said. The second case-control study of 25 HD patients and 21 age- and sex-matched control subjects demonstrated that the associa-

tion between high H2AFY mRNA levels and HD remained consistent over 2-3 years.

Levels of macroH2A1 – the histone protein encoded by H2AFY – in the brains of HD patients and mouse models of HD also were elevated in comparison with those in control subjects and wild-type mice, particularly in brain areas most affected by the disease.

According to Dr. Hu and his coauthors, histone deacetylase inhibitors are a leading class of potentially disease-modifying therapeutics for HD. The researchers found that they could use

macroH2A1 levels to monitor the response to treatment with the histone deacetylase inhibitor sodium phenylbutyrate (SPB) in a mouse model of HD.

To determine if a similar approach could be used with H2AFY mRNA levels in humans, the investigators analyzed frozen blood samples from HD patients participating in PHEND-HD (Safety and Tolerability Study of Phenylbutyrate in Huntington's Disease), a randomized, double-blind, phase II study. They found that longer times of patients' receiving SPB were associated with greater decreases in H2AFY mRNA levels.

Their study was funded by grants from the National Institutes of Health, the Maximilian E. & Marion O. Hoffman Foundation, the RJG Foundation, the Huntington's Disease Society of America (HDSA) Coalition for the Cure, and the New England HDSA Center for Excellence for Huntington Disease.

Two of Dr. Yu's coauthors reported serving as a consultant or scientific collaborator with companies involved in neurodegenerative disease research, as well as being coinventors listed on patent applications for diagnostics or therapeutics relating to neurodegenerative diseases. ■

One of the First to Vet Prevention Trial Designs?

ADVISER'S VIEWPOINT

HD is a heritable, neurodegenerative disorder of middle age that first effects muscle coordination and, in the advanced stages of the disease, cognitive ability. The HD causal mutation occurs in a gene called huntingtin (which encodes a protein product of the same name) and consists of an expanded trinucleotide repeat that results in the inclusion of a longer-than-normal polyglutamine tract in the mature protein. This leads to the development of multiple cellular changes that eventually lead to the death of a collection of susceptible neurons in the brain. Despite the identification of the causal genetic locus almost 2 decades ago, there is still no cure or disease-slowing treatment available to the HD patient.

The combination of HD's neurodegenerative nature, the standardized testing available for the causal mutation, and the high penetrance of the huntingtin mutation makes HD an excellent candidate for therapeutic prevention and disease-slowing trials.

Design of such clinical trials is underway as the neurodegenerative disease field explores ways to preemptively protect each disease's targeted neurons. These designs typically face complications regarding their power because of variability in disease course – and therefore therapeutic response – from individual to individual.

An ideal neurodegenerative disease prevention trial would include a well-demonstrated genetic risk factor, a

validated biomarker panel to track therapeutic progress in affected individuals, and safe therapies that target promising molecular entities.

The work by Dr. Hu and his associates may have identified a blood-based biomarker for HD that could aid in future prevention trials. In their impressive work, the researchers demonstrate that H2AFY mRNA levels are significantly elevated and associated with disease status in HD patients, that H2AFY mRNA is significantly increased in HD even before the presence of clinically recognizable symptoms, and that the macroH2A1 protein encoded by the H2AFY gene is elevated in the brains of patients and mouse models of the disease.

Perhaps most importantly, the investigators demonstrated that blood levels of H2AFY mRNA are reduced in a randomized, double-blind, phase II clinical trial of HD patients who were treated with an emerging histone deacetylase inhibitor, SPB, that was previously shown to suppress huntingtin-induced neurodegeneration in a mouse model.

The authors discuss the limitations of their work extensively with an appropriate emphasis on independent replication in a larger sample set. Assuming that the H2AFY mRNA biomarker is independently validated, HD now tentatively meets several of the above-outlined hurdles for the initiation of well-informed neurode-

generative disease-prevention trials.

Perhaps the major question left unanswered is the efficacy of available therapeutics in combating the early stages of HD. However, if the H2AFY biomarker is eventually shown to indicate the underlying pathobiology of HD, then it is very encouraging that the histone deacetylase inhibitor appeared to shift the biomarker in the direction of the placebo group.

Neurodegenerative disease-prevention trials are clearly going to test many aspects of the standard clinical trials system, including the inclination of pharmaceutical companies to explore such trial designs and the Food and Drug Administration's willingness to acknowledge the role of such trials in the vetting of novel neurodegenerative disease-treatment approaches.

The coupling of biomarker and genetic approaches with therapeutic agents administered during the disease process when they have the greatest chance to be efficacious can be nothing but motivating for the field. The new work by Dr. Hu and his colleagues could poise HD at the front of the pack for these disease-prevention trials, and should be nothing but encouraging to individuals and families at risk for the disease.

MATTHEW J. HUENTELMAN, PH.D., is head of the neurobehavioral research unit and associate professor in the neurogenomics division of the Translational Genomics Research Institute in Phoenix. He disclosed no conflict of interest.



Continued from previous page

that the UPDRS floor effect might have masked our ability to detect a difference between early and delayed start groups with this higher dose in such a mild population of patients,” he added, noting that the concept of a floor effect is “well-known” in Parkinson's disease and has been observed in previous trials where more prominent treatment effects have been observed in patients with

higher UPDRS scores at baseline.

The failure of the 2-mg dose in the ADAGIO study was “the most troubling issue” with the data and there was “no robust finding for either dose,” said Tristan Massie, Ph.D., an FDA statistician who presented the agency's statistical analysis of the data at the meeting. The absence of an effect in the 2-mg group “raised questions about the biological plausibility of the 1 mg,” he added.

The panel agreed, cited other issues

with the data, and voted unanimously that the study did not provide compelling evidence that the 1-mg, once-daily dose was effective. While they agreed that there was an unmet need for a treatment that slowed progression and that the data were promising and showed a signal for a disease-modifying effect, they said the evidence did not meet the high bar that should be set for proving such an effect, considering the enormous public health implications of a neuropro-

tection claim for a Parkinson's disease treatment.

The FDA usually follows the recommendations of its advisory panels. Panelists have been cleared of potential conflicts of interest related to the topic of the meeting. Occasionally, a panelist may be given a waiver, but not at this meeting.

In addition to Teva, the companies on Dr. Olanow's conflict of interest disclosure statement included Ceregene, Novartis, Lundbeck, and Merck Serono. ■