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ASHG 2008: Increased Gene Expression Improves Neurologic Function in Mouse Model of Huntington's Disease

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November 16, 2008 (Philadelphia, Pennsylvania) — A study in transgenic mouse models of Huntington's disease (HD) has identified a promising approach to treating human HD patients. PGC-1alpha (PPAR gamma coactivator 1 alpha), a transcription coactivator that regulates mitochondrial function, seems to be targeted by the mutant huntingtin protein that impairs transcription. In studies of transgenic HD mice in which PGC-1alpha expression was induced to twice that of normal levels, neurologic function improved and accumulation of misfolded huntingtin protein actually decreased in brain cells.

The results were presented here at the American Society of Human Genetics 58th Annual Meeting, by lead investigator Albert R. La Spada, MD, PhD, FACMG, associate professor and director of the Center for Neurogenetics and Neurotherapeutics, and associate professor of Laboratory Medicine, Medical Genetics, Pathology, and Neurology, University of Washington, Seattle. Dr. La Spada also participated in today's press briefing.

"All the major neurodegenerative diseases are caused by misfolded proteins, or involve protein misfolding," Dr. La Spada said during the press briefing. "This occurs in Alzheimer's disease, in Parkinson's disease, in ALS, and in the prion diseases like mad cow disease. You have proteins that misfold and they form aggregates that you can see at the light microscope level."

The misfolded protein in HD, called "huntingtin," forms aggregates in neuronal nuclei and interferes with transcription, the process by which RNAs are formed on DNA templates. Patients with HD, an autosomal dominant disease, experience neural degeneration, involuntary movements, loss of cognitive function, and eventually death.

Dr. La Spada referred to the study as "serendipitous," because their investigation of PGC-1alpha began after noting that HD transgenic mice developed low body temperatures, falling below 34°C for 2 to 10 days before death. Further study determined that target genes of PGC-1alpha, which regulates mitochondrial function, have reduced expression in the brains of HD mice and humans. Significantly, mitochondria in the brains of HD mice show decreased oxygen consumption.

PGC-1alpha is a positive modulator of PPARdelta, which interacts with the huntingtin protein. Altered function of PPARdelta leads to HD degeneration, but increased levels of PGC-1alpha (noted above to improve HD functioning and decrease huntingtin aggregation) boost PPARdelta activity. Selective PPARdelta agonists are already undergoing clinical trials; in addition, PPARdelta mediates cellular responses to retinoic acid, a substance already approved for the treatment of patients with brain tumors and leukemia.

Dr. La Spada talked with *Medscape Pathology & Lab Medicine* about the clinical future of their findings. "We still are a little way off from that," he said. The results suggest potential therapies, but "we would test them in animal models for HD, mouse models, and that's something that still needs to be done.... If it's successful, one can envision going into a phase 2/3 trial, since the agents are either being used in human patients already, or are already in phase 2/3 clinical trials. That would be like a 3- to 5-year window in reality."

The comoderator of the session, Michael Lovett, PhD, professor of human genetics and joint director of the Division of Human Genetics, Washington University School of Medicine, St. Louis, Missouri, shared his impressions with *Medscape*

Pathology & Lab Medicine.

"In a model system there...what that means is that he has apparently reversed the course of the disease for Huntington's — if it translates to humans," Dr. Lovett observed. "He's also shown that the retinoic acid receptor pathway is involved, and that's probably 'drugable.' So what he showed there was that there were a couple of drugs that he could use that would influence the degree to which he could essentially rescue the mice.

"Prior to this you would think 'Huntington's is there' and maybe you could arrest its further decline," said Dr. Lovett. "But to see in those mice the destruction of the Huntington's protein, the bad one, is the most amazing thing! So I think it's highly significant. If it translates to humans, it's truly amazing."

Dr. Lovett continued, "What he did that was significant was to show that this PGC-1alpha was interacting with PPAR-delta and therefore put together that part of the puzzle. So the PGC-1alpha was a bit that he's contributed, then he finds that it hits PPAR-delta, he knows that is in the retinoic acid receptor pathway.

"So I think it's a triumph of putting disparate bits of knowledge together, in which he contributed quite significantly," Dr. Lovett concluded. "I think it's fascinating and it's highly significant and encouraging."

Dr. La Spada and Dr. Lovett have disclosed no relevant financial relationships.

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