**PGC-1 alpha gene modifies age of onset in HD**

Researchers in Europe have identified a genetic modifier of age of onset that may point the way to a potential treatment for Huntington's Disease.

The age of onset of Huntington's Disease is highly variable, ranging from infancy to old age. The single most important influential variable is the CAG count which is negatively corrected with the age of onset. The average age of onset of a group of individuals with 40 CAG repeats is later than the average age of onset for a group of individuals 45 repeats while the average onset of a group with 45 repeats is later for those with 50 repeats, as examples.

However, if we look at individuals, we see a wide range of ages of onset for each CAG count and an individual's age of onset cannot be reliably predicted from his or her CAG count. Analysis of a large database of people with Huntington's Disease in the Lake Maracaibo area of Venezuela has lead researchers to conclude that there are both environmental and genetic modifiers of the disease but most of those factors have yet to be identified.

Dr. Patrick Weydt and colleagues have found that certain variations in the gene that codes for PGC-1 are associated with delayed onset of the disease in people with the HD gene. PGC-1 is a gene which regulates mitochondria biogenesis and metabolism. In this study, the onset of the disease was defined traditionally, as the onset of motor symptoms, and CAG counts were controlled for. The researchers found a variation which resulted in a delay of 2.8 years and another which resulted in a delay of 3.7-4.0 years.

Previous research by Dr. Weydt, Dr. Albert LaSpada, and other colleagues showed that the PGC-1 alpha gene is downregulated in the brains of Huntington's patients. They were led to look at the gene after discovering that the R6/2 HD mice have a below normal body temperature which continues to drop as the disease progresses.

*Dr. Albert LaSpada and Dr. Patrick Weydt with friend & colleague, Dr. Kurt Fischbeck, at a recent conference where the PCG-1 alpha research was presented.*

"These mice have been around for at least a decade," Dr La Spada said. "They have been the subjects of dozens, if not hundreds, of studies, but no one had checked one of their most basic vital signs. When you do, you find that the mice have a dramatic abnormality in temperature--which is normally tightly regulated."

The brains of the mice correctly perceived that the mice were cold. When that happens, the PGC-1 alpha gene should signal the mitochondria, the cell's energy factories, to generate heat rather than energy and raise body temperature. However, the mice had

lower levels of expression of that gene this process did not work properly. The researchers then confirmed lowered levels of expression of PCG-1 alpha in the brain tissue of human HD patients.

Working independently, another team of researchers from Massachusetts General and New York University Medical School found that transcription of PGC-1 is repressed by the HD protein which leads to mitochondrial dysfunction. Delivery of PGC-1 to transgenic HD mice results is neuroprotective while crossing the HD mice with PGC-1 null mice results in more severe symptoms of Huntington's.

The current study will need to be replicated and researchers will need to determine the precise mechanism by which the gene variations delay onset. However, taken together, the cumulative research suggests that the disregulation of the PGC-1 alpha gene is an important pathology in HD and a target for treatment.

Research into genetic modifiers on age of onset provides important information. Researchers have learned a lot about what goes wrong in the brain in Huntington's Disease as a result of genetically modified mouse models which recapitulate key features of human Huntington's Disease. Many insights from the HD mice have been confirmed in HD patients and knowledge about the disease process has exploded. In addition, researchers can now postpone onset and slow progression in the HD mice through drugs, supplements, and genetic approaches.

The hope is that some percentage of the successful interventions in HD mouse models will prove to be treatments for human patients. Given limited resources, the most promising preclinical interventions need to be given top priority for clinical trials. When a genetic modifier is discovered which delays onset, it identifies the function of this gene as a high priority target for drug discovery and development since in a sense this intervention is already known to be effective in people.

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- *Marsha L. Miller, Ph.D., January 16, 2009*