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Scientists correct Huntington's disease mutation in induced pluripotent stem cells

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Johns Hopkins researchers, working with an international consortium, say they have generated stem cells from skin cells from a person with a severe, early-onset form of Huntington's disease (HD), and turned them into neurons that degenerate just like those affected by the fatal inherited disorder.

By creating "HD in a dish," the researchers say they have taken a major step forward in efforts to better understand what disables and kills the cells in people with HD, and to test the effects of potential drug therapies on cells that are otherwise locked deep in the brain.

Although the autosomal dominant gene mutation responsible for HD was identified in 1993, there is no cure. No treatments are available even to slow its progression.

The research, published in the journal *Cell Stem Cell*, is the work of a Huntington's Disease iPSC Consortium, including scientists from the Johns Hopkins University School of Medicine in Baltimore, Cedars-Sinai Medical Center in Los Angeles and the University of California, Irvine, as well as six other groups. The consortium studied several other HD cell lines and control cell lines in order to make sure results were consistent and reproducible in different labs.

The general midlife onset and progressive brain damage of HD are especially cruel, slowly causing jerky, twitch-like movements, lack of muscle control, psychiatric disorders and dementia, and — eventually —

death. In some cases (as in the patient who donated the material for the cells made at Johns Hopkins), the disease can strike earlier, even in childhood.

"Having these cells will allow us to screen for therapeutics in a way we haven't been able to before in Huntington's disease," says Christopher A. Ross, M.D., Ph.D., a professor of psychiatry and behavioral sciences, neurology, pharmacology and neuroscience at the Johns Hopkins University School of Medicine and one of the study's lead researchers. "For the first time, we will be able to study how drugs work on human HD neurons and hopefully take those findings directly to the clinic."

Ross and his team, as well as other collaborators at Johns Hopkins and Emory University, are already testing small molecules for the ability to block HD iPSC degeneration. These small molecules have the potential to be developed into novel drugs for HD.

The ability to generate from stem cells the same neurons found in Huntington's disease may also have implications for similar research in other neurodegenerative diseases such as Alzheimer's and Parkinson's.

To conduct their experiment, Ross took a skin biopsy from a patient with very early onset HD. When seen by Ross at the HD Center at Hopkins, the patient was just seven years old. She had a very severe form of the disease, which rarely appears in childhood, and of the mutation that causes it. Using cells from a patient with a more rapidly progressing form of the disease gave Ross' team the best tools with which to replicate HD in a way that is applicable to patients with all forms of HD.

Her skin cells were grown in culture and then reprogrammed by the lab of Hongjun Song, Ph.D., a professor at Johns Hopkins' Institute for Cell Engineering, into induced pluripotent stem cells. A second cell line was

generated in an identical fashion in Dr. Ross's lab from someone without HD. Simultaneously, other HD and control iPS cell lines were generated as part of the NINDS funded HD iPS cell consortium.

Scientists at Johns Hopkins and other consortium labs converted those cells into generic neurons and then into medium spiny neurons, a process that took three months. What they found was that the medium spiny neurons deriving from HD cells behaved just as they expected medium spiny neurons from an HD patient would. They showed rapid degeneration when cultured in the lab using basic culture medium without extensive supporting nutrients. By contrast, control cell lines did not show neuronal degeneration.

"These HD cells acted just as we were hoping," says Ross, director of the Baltimore Huntington's Disease Center. "A lot of people said, 'You'll never be able to get a model in a dish of a human neurodegenerative disease like this.' Now, we have them where we can really study and manipulate them, and try to cure them of this horrible disease. The fact that we are able to do this at all still amazes us."

Specifically, the damage caused by HD is due to a mutation in the huntingtin gene (HTT), which leads to the production of an abnormal and toxic version of the huntingtin protein. Although all of the cells in a person with HD contain the mutation, HD mainly targets the medium spiny neurons in the striatum, part of the brain's basal ganglia that coordinates movement, thought and emotion. The ability to work directly with human medium spiny neurons is the best way, researchers believe, to determine why these specific cells are susceptible to cell stress and degeneration and, in turn, to help find a way to halt progression of HD.

Much HD research is conducted in mice. And while mouse models have been helpful in understanding some aspects of the disease, researchers

say nothing compares with being able to study actual human neurons affected by HD.

For years, scientists have been excited about the prospect of making breakthroughs in curing disease through the use of stem cells, which have the remarkable potential to develop into many different cell types. In the form of embryonic stem cells, they do so naturally during gestation and early life. In recent years, researchers have been able to produce induced pluripotent stem cells (iPSCs), which are adult cells (like the skin cells used in Ross's experiments) that have been genetically reprogrammed back to the most primitive state. In this state, under the right circumstances, they can then develop into most or all of the 200 cell types in the human body.

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