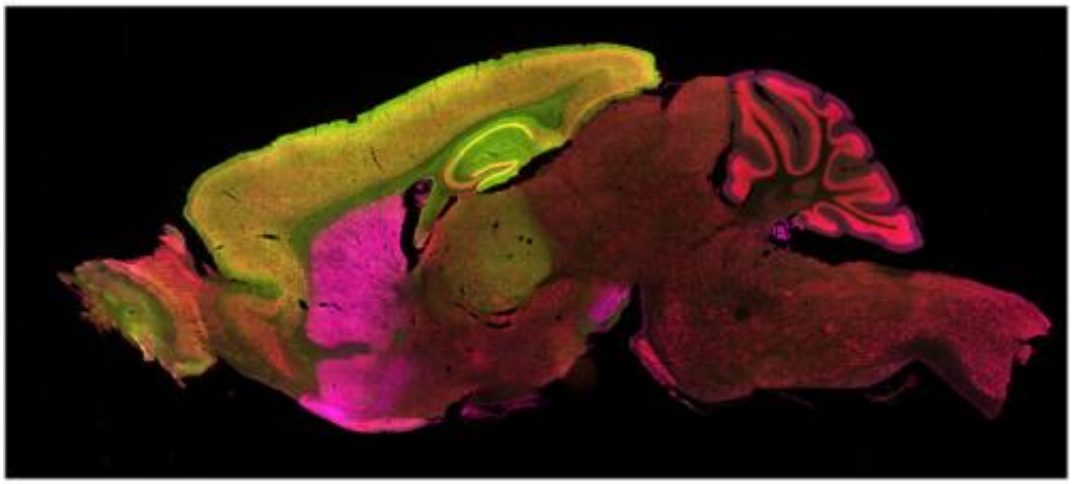
Scientists hunt down origin of Huntington's disease in the brain

April 28 2014



A color image of a mouse brain vividly shows the cortex (yellow) and striatum (pink). Huntington's disease shrinks the brain by killing cells in these two regions. Credit: UCLA

The gene mutation that causes Huntington's disease appears in every cell in the body, yet kills only two types of brain cells. Why? UCLA

scientists used a unique approach to switch the gene off in individual brain regions and zero in on those that play a role in causing the disease in mice.

Published in the April 28 online edition of *Nature Medicine*, the research sheds light on where Huntington's starts in the brain. It also suggests new targets and routes for therapeutic drugs to slow the devastating disease, which strikes an estimated 35,000 Americans.

"From day one of conception, the mutant gene that causes Huntington's appears everywhere in the body, including every cell in the brain," explained X. William Yang, professor of psychiatry and biobehavioral sciences at the Semel Institute for Neuroscience and Human Behavior at UCLA. "Before we can develop effective strategies to treat the disorder, we need to first identify where it starts and how it ravages the brain."

Huntington's disease is passed from parent to child through a mutation in a gene called huntingtin. Scientists blame a genetic "stutter"—a repetitive stretch of DNA at one end of the altered gene—for the cell death and brain atrophy that progressively deprives patients of their ability to move, speak, eat and think clearly. No cure exists, and people with aggressive cases may die in as little as 10 years.

Huntington's disease targets cells in two brain regions for destruction: the cortex and the striatum. Far more neurons die in the striatum—a cerebral region named after its striped layers of gray and white matter. But it's unclear whether cortical neurons play a role in the disease, including striatal neurons' malfunction and death.

Yang's team used a unique approach to uncover where the mutant gene wreaks the most damage in the brain.

In 2008, Yang collaborated with co-first author Michelle Gray, a former

UCLA postdoctoral researcher now at the University of Alabama, to engineer a mouse model for Huntington's disease. The scientists inserted the entire human huntintin gene, including the stutter, into the mouse genome. As the animals' brains atrophied, the mice developed motor and psychiatric-like problems similar to the human patients.

In the current study, Yang and Nan Wang, co-first author and UCLA postdoctoral researcher, took the model one step further. They integrated a "genetic scissors" that snipped off the stutter and shut down the defective gene—first in the cortical neurons, then the striatal neurons and finally in both sets of cells. In each case, they measured how the mutant gene influenced disease development in the cells and affected the animals' brain atrophy, motor and psychiatric-like symptoms.

"The genetic scissors gave us the power to study the role of any cell type in Huntington's," said Wang. "We were surprised to learn that cortical neurons play a key role in initiating aspects of the disease in the brain."

The UCLA team discovered that reducing huntingtin in the cortex partially improved the animals' symptoms. More importantly, shutting down mutant huntingtin in both the cortical and striatal neurons—while leaving it untouched in the rest of the brain— corrected every symptom they measured in the mice, including motor and psychiatric-like behavioral impairment and brain atrophy.

"We have evidence that the gene mutation highjacks communication between the cortical and striatal neurons," explained Yang. "Reducing the defective gene in the cortex normalized this communication and helped lessen the disease's impact on the striatum."

"Our research helps to shed lights on an age-old question in the field," he added. "Where does Huntington's disease start? Equally important, our findings provide crucial insights on where to target therapies to reduce

mutant gene levels in the brain—we should target both cortical and striatal neurons."

Some of the current experimental therapies can be delivered only to limited brain areas, because their properties do not allow them to broadly spread in the brain.

The UCLA team's next step will be to study how mutant huntingtin affects cortical and striatal neurons' function and communication, and to identify therapeutic targets that may normalize cellular miscommunication to help slow progression of the disease.

More information: Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington's disease, DOI: 10.1038/nm.3514

Provided by University of California, Los Angeles