Promising new research on Huntington's disease zeros in on transporter protein

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New research led by a University of Ottawa Faculty of Medicine team is providing compelling insights into the mechanisms underlying the progression of Huntington's disease in an animal model. The results could lead to a greater understanding of the harrowing neurological disease in humans and help pave the way for viable drug targets and treatment approaches.

That's potentially very significant because there are presently no drugs to slow or stop the progression of the genetic brain disorder that occurs at a rate of about 1 in every 10,000 people. Huntington's disease (HD) gradually breaks down neurons in areas of the brain, progressively ravaging a patient's mind and spurring involuntary movements until sufferers are unable to walk, communicate, or even swallow. It can be passed from parent to child, typically becoming evident in middle age.

The study, published in *The Journal of Neuroscience*, focuses on a transporter protein referred to as VGLUT3. In the brain, this tiny protein packages glutamate into vesicles for release from neurons. Glutamate is an excitatory neurotransmitter that is involved in the most complex brain circuits. There needs to be a balance of glutamate for your brain to function properly; too much of it is associated with Huntington's and other neurological ailments.

Over the span of years, researchers led by Dr. Stephen Ferguson discovered that VGLUT3 plays a surprisingly vital role in modulating the development of Huntington's disease in the gold-standard mouse model. They bred so-called "knockout" mice that lack the transporter protein with mutant "huntingtin" mice so they could run comparisons to unveil animal models of the rare disease in both male and female mice.

Individuals diagnosed with Huntington's disease accumulate a specific mutated form of the "huntingtin" protein. This scaffolding protein is found in cells throughout the body, but the genetic defect that produces a mutant version appears to only impact the brain. The mutant triggers cell death.

Results showing the disease-modifying capacity of the VGLUT3 transporter protein were "quite remarkable," says Dr. Ferguson, a prominent professor at the uOttawa Faculty of Medicine's Department of Cellular and Molecular Medicine and Distinguished Research Chair in

Neurodegeneration.

"We saw a complete reversal of Huntington disease progression in mutant huntingtin mice lacking VGLUT3," he says. "From 6 to 15 months of age, the knockout mice behaviorally were indistinguishable from wild-type mice, whereas the Huntington's mice continued to be more and more impaired over time on the various motor behavior and cognitive tasks that we tested on."

The only aspect of the symptom progression that didn't show reversal in the mouse model was anxiety behavior. But this too could prove significant because the transporter protein—which has been shown to regulate conditions such as eating disorders and drug addiction—is likely also involved in anxiety and depression.

One of the paper's reviewers described the overall results as a "substantive contribution" that "should be of wide interest to researchers in HD as well as those studying the role of VGLUT3 in cognition and motor control."

The uOttawa-led study was also chosen to be highlighted in a special feature section of the *Journal of Neuroscience*.

The publication's first author is Dr. Karim Ibrahim, a member of Dr. Ferguson's lab who is a newly minted Ph.D. at uOttawa. In recent years, he methodically conducted a range of behavioral experiments to generate the study's data. This included rotarod tests—one of the classic tests of motor skills in mice—and a horizontal ladder test that clearly exposed some of the impairments in the Huntington's mouse model as the animals tried to traverse it.

Efforts to develop drug targets and treatment approaches for HD must take into consideration that the "huntingtin" protein is widely expressed

in the body.

"You don't really want to knock down the wild-type copy of the huntingtin gene if you can avoid it because the huntingtin protein is absolutely essential. You're better off finding a way of tricking the brain into using its circuitry slightly differently so that you can reestablish motor coordination," Dr. Ferguson says.

Ultimately, that's the goal for his lab and its collaborators in their Huntington's disease efforts. They are working on a toolkit for the pharmacological suppression of the VGLUT3 protein and exploring ways of potentially altering glutamate release in specific subsets of neurons.

"We've shown that if you block glutamate release through the activation of presynaptic receptors, that you can get an amelioration of Huntington's disease. So it may be that it will eventually require two or three different drugs to effectively treat the disease," he says.

More information: Karim S. Ibrahim et al, VGLUT3 deletion rescues motor deficits and neuronal loss in the zQ175 mouse model of Huntington's disease, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.0014-23.2023

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