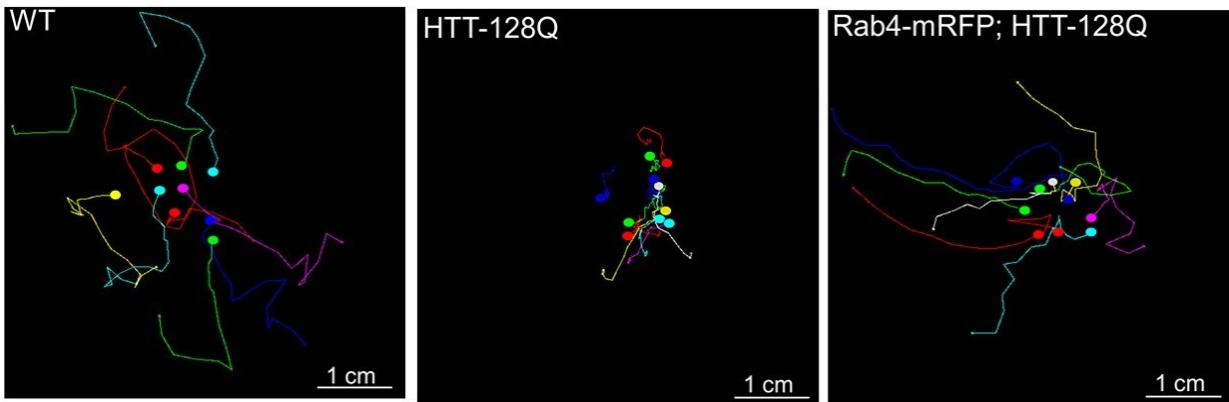


# Study reveals intricate details about Huntington's disease protein

July 17 2020, by Charlotte Hsu



Colored lines show the paths of crawling fruit fly larvae. Larvae with a mutant form of the human huntingtin protein that causes Huntington's disease crawled poorly (center) compared with normal larvae (left). But when larvae carrying the Huntington's disease protein also produced extra quantities of the Rab4 protein, crawling improved, though not completely (right). Credit: White, J.A., Krzystek, T.J., Hoffmar-Glennon, H. et al., *Acta Neuropathologica Communications*, July 2020. The image is adapted from a graphic in the journal article, which is distributed under [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/)

A new study reveals intricate details about the biology of the huntingtin protein (HTT), which is responsible for Huntington's disease.

The research focuses on [axonal transport](#)—the way in which vital materials travel along pathways called axons inside [nerve cells](#), or

neurons.

Scientists found that HTT sometimes journeys along these roadways in cellular vehicles (called vesicles) that also carry freight including a protein called Rab4. Other materials that may be present in these shipments include proteins essential to the health and function of nerve cells, scientists conclude.

The findings also point to a potential treatment avenue: In [fruit fly larvae](#), a mutated form of HTT that causes Huntington's [disease](#) disrupted the normal movement of vesicles holding HTT and Rab4. This led to problems such as defects in a part of the nerve cell called the synapse; difficulties with crawling; and decreased lifespan, the study found. But when larvae carrying the HTT mutation were engineered to also produce excess Rab4, some of these symptoms—including abnormalities in synapses, crawling and lifespan—were less pronounced.

"When it comes to finding therapies for [neurological diseases](#), a lot of the research focuses on the pathology and aggregation of proteins, but that may not be the actual cause," says Shermali Gunawardena, Ph.D., associate professor of biological sciences in the University at Buffalo College of Arts and Sciences. "We want to try to figure out what might be going on earlier. We want to come in from a different angle and say, 'OK, are huntingtin and Rab4 normally present together in healthy neurons? And then, what are they doing in the context of a disease state?'"

"This research helps shed light on the normal function of huntingtin and how it is altered in disease," says co-first author Joseph A. White II, a UB biological sciences Ph.D. graduate who is now a postdoctoral researcher at Duke University. "Based on what we're seeing, HTT seems to be important for the transport of a particular type of vesicle known as endosomes within neurons. We believe this presents a potential avenue

for therapeutics aimed at improving endosomal transport in Huntington's disease patients."

Gunawardena, the corresponding author, led the study with first authors White and Thomas J. Krzystek, a UB Ph.D. student in biological sciences.

The research, published on July 1 in *Acta Neuropathologica Communications*, builds on past work in Gunawardena's lab. Previously, her team showed that mutated HTT can also perturb the movement of some other Rab proteins. The findings suggest that potential treatments focusing on axonal pathways may also need to be multifaceted, involving a number of drugs targeting different problems, Gunawardena says.

"The idea behind our work is to tease out these details about what's going on inside neurons," she says. "It's really difficult to isolate what's going on inside the organism. But from what we have done in the lab, we can say now that huntingtin is in these different, specific kinds of cargoes. I think the bottom line is that this [protein](#) is doing a lot of different things."

"Model organisms, like the fruit fly, are excellent tools we can use to quickly investigate a variety of proteins and pathways related to human diseases," Krzystek says. "Our study highlights the advantage of using these simpler organisms to discover new information that we can then test directly in more complex systems. Through this, we learned about what huntingtin might be doing with Rab4 in healthy neurons, and how this role may become disrupted in Huntington's disease."

**More information:** Joseph A. White et al. Excess Rab4 rescues synaptic and behavioral dysfunction caused by defective HTT-Rab4 axonal transport in Huntington's disease, *Acta Neuropathologica Communications* (2020). [DOI: 10.1186/s40478-020-00964-z](https://doi.org/10.1186/s40478-020-00964-z)

Provided by University at Buffalo

Citation: Study reveals intricate details about Huntington's disease protein (2020, July 17)  
retrieved 27 April 2024 from

<https://medicalxpress.com/news/2020-07-reveals-intricate-huntington-disease-protein.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.