



News from the Hereditary Disease Foundation

High Impact Research

February 29 is Rare Disease Day, a day set aside to raise public awareness of devastating rare diseases that collectively affect millions of people around the world. Huntington's disease is considered a rare disease, but HD research has a far-reaching and powerful impact, helping to unlock the secrets of other neurological diseases such as Alzheimer's, Parkinson's and ALS.

Two recent papers published by HDF-funded scientists in the prestigious journal *Neuron* highlight the impact and the promise of HD research.

Support for HDF-funded research goes a long way!

New Genetic Screening Technique Offers New Drug Targets for Huntington's Disease

Among some of the latest high impact research that has significant implications for HD and possibly for other diseases is a study by our Scientific Advisory Board member Myriam Heiman and Mary Wertz, who was an HDF-funded post-doctoral fellow for two years. Their work identified genes that modulate the toxic effects of the abnormal huntingtin protein.



Myriam Heiman and Mary Wertz at our 2018 Gala

Using a novel type of genetic screen of mouse models that had previously been impossible in the mammalian brain, Myriam and Mary and their colleagues at MIT have identified hundreds of genes that are necessary for neuron survival. They used the same approach to identify genes that protect against the toxic effects of the abnormal protein that causes Huntington's disease. Their efforts have yielded at least one promising drug target for HD: a family of genes that may normally help cells to break down the abnormal huntingtin protein before it can aggregate and form clumps seen in the brains of Huntington's patients. Their work was published in the January 30, 2020 issue of *Neuron*.

The new screening technique allowed the researchers to assess all of the roughly 22,000 genes found in the mouse brain. The technique could also be applied to other neurological diseases, including Alzheimer's and Parkinson's, Myriam says.

Next steps will include conducting more focused analyses of each gene to determine how they might be effectively targeted as a treatment for HD.

Myriam, who is an associate professor of neuroscience in the Department of Brain and Cognitive Sciences at MIT, a member of MIT's Picower Institute for Learning and Memory and the Broad Institute of MIT and Harvard and the study's senior author, says, "This research complements human genetic studies that are being conducted by other HDF-funded scientists. It is exciting because it points to new potential approaches for treating or modifying the progression of HD."

Changing the Track of HD: New Insights on Cleaning Up Trash in the Brain

With the help of several HDF grants, Ai Yamamoto, Leora Fox, Andrew Yoo and colleagues pointed to the role that a protein known as Alfyl plays in the process of cleaning up the abnormal huntingtin protein in the brain. Their research was published in the December 30, 2019 issue of *Neuron*.



HDF President Nancy Wexler (center) with Ai and her lab team (Left to right) Joanna Dragich, Young Joo Yang, Wendy Fong, Kiki Kim, Nancy Wexler, Leora Fox, Ai Yamamoto and Etan Aber

Ai Yamamoto is an associate professor of neurology and associate professor of pathology and cell biology at Columbia University, and a member of our Scientific Advisory Board. Leora Fox was a graduate student in Ai's lab at the time this research was conducted and is currently working at the Huntington's Disease Society of America (HDSA). Andrew Yoo is an associate professor of developmental biology at Washington University School of Medicine in St. Louis.

"Brain cells are actually pretty good at removing harmful debris, and from previous work we had suspected that the protein Alfy plays a key role in this process," says Leora. "Our recently published study shows that Alfy is important for cleaning up abnormal huntingtin in the adult mouse brain, and in human cells. When there's less Alfy, huntingtin piles up and HD-like 'symptoms' in mice begin sooner. The next step is to ask whether adding more Alfy could speed up the clean-up and delay the onset of symptoms."

The findings indicate that Alfy is responsible for eliminating the aggregates that are associated with HD in the adult brains of mice and show that it can confer disease resistance of the HD-like symptoms. The researchers found that if they decreased the levels of Alfy in the brain by half, this accelerated not only the appearance of these aggregates, but also accelerated the onset of motoric symptoms. Importantly, although symptoms manifested sooner, there did not appear to be a more rapid decline or increased cell loss, suggesting that aggregation might modulate symptoms, rather than cause them.

In addition to this work, they also used a novel model, originated by the laboratory of Andrew Yoo, that allows them to study the aggregation of the abnormal huntingtin protein in patient material. In this model, neuron-like cells are created from fibroblasts taken from patients. These neuron-like cells can potentially better capture the aggregation phenomenon in patients. The depletion of Alfy in this model also accelerated aggregation, strongly suggesting that Alfy may work similarly in patients.

In the Pipeline...

In the coming months, we will bring you news about other important studies by HDF-funded researchers, as well as updates on clinical trials happening now.

Brilliant researchers, committed corporations, and dedicated supporters - together we are making a difference for the HD community!

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