NEIL WEBB

HUNTINGTON'S DISEASE

4 BIG QUESTIONS

Although potential treatments are now entering the pipeline, the molecular cause and progression of Huntington's disease continue to elude researchers.

BY ANNA NOWOGRODZKI

	QUESTION	WHY IT MATTERS	WHAT WE KNOW	NEXT STEPS
1	***How does the mutant protein huntingtin cause Huntington's disease?***	Huntington's disease is caused by a mutation in a single gene called huntingtin (*HTT*), which encodes the protein huntingtin. Understanding how the mutant protein causes disease could open up avenues for treating the condition and its symptoms.	Mutant huntingtin forms clumps inside the cell that seem to interfere with communication along the axons of neurons. Such aggregates can also throw a wrench into the transcription of other genes and hinder cells' waste-removal systems.	Various projects led by researchers, companies and non-profit organizations are using computational methods to better understand the shape of mutant huntingtin, how it aggregates, and how it interacts with other proteins in the cell.
2	***What is the role of normal huntingtin?***	To help develop treatments for Huntington's disease, including those that use RNA interference, antisense oligonucleotides (ASOs) or gene editing, it's important to determine whether normal huntingtin, as well as the mutant version, can be reduced or eliminated safely.	Blocking *Htt* expression in mouse embryos is lethal. In adult mice, some studies show that removing normal huntingtin has only limited effects, whereas others indicate it shortens lifespan and causes nerve and behavioural problems. The effect of reducing huntingtin in people is unknown.	Researchers are eliminating normal huntingtin in mammals with lifespans longer than those of mice to determine any long-term effects. Efforts are also underway to inactivate just the mutated copy of *HTT*, leaving the normal version intact, using the gene-editing tool CRISPR–Cas9.
3	***How can we better characterize the progression of Huntington's disease?***	To more effectively assess treatments in trials, doctors need improved ways of measuring whether they slow disease progression. The current best tool is the clinician-rated Unified Huntington's Disease Rating Scale, which is reliable but prone to the power of the placebo effect.	A 2017 study showed that changes in levels of neurofilament light polypeptide (NF-L) in blood correlate with the onset of Huntington's disease, making it a possible biomarker. Other biomarkers that correlate with the condition can be measured by functional brain imaging.	Three large long-term observational studies have been designed to assess the ability of potential biomarkers to measure disease progression. The team investigating NF-L has launched a 600-participant study, and is already monitoring NF-L levels in at least 80 people.
4	***Will ASOs be the first effective treatment for Huntington's disease?***	ASOs are the first potential treatment to have successfully lowered levels of mutant huntingtin in trials conducted in people. But it's uncertain whether these molecules can slow or halt progression of Huntington's disease.	In a phase I/IIa trial, an ASO called IONIS-HTT$_{Rx}$ reduced the levels of mutant huntingtin in participants' cerebrospinal fluid. But the trial was too short to determine the treatment's long-term effects. The drug is delivered once a month via an injection into the spine.	Further trials of IONIS-HTT$_{Rx}$ with larger numbers of participants are needed to determine whether the drug is effective at treating Huntington's disease. Researchers are also monitoring the 46 participants of the initial trial for any long-term effects.

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