> Neurogranin levels … accurately identified patients with CJD and distinguished them from patients with AD

"In CJD, CSF neurogranin positively correlated with tau and 14-3-3, two well-established CSF CJD biomarkers used in clinical settings as surrogate markers of neuroaxonal damage," says Llorens. "Importantly, neurogranin was a good prognostic marker of survival time in CJD."

Further analysis of patients with CJD showed that CSF neurogranin levels differed according to variations in codon 129 of *PRNP*, the gene that encodes prion protein. "We plan to evaluate the prognostic ability of CSF neurogranin in a large cohort of CJD cases with a known *PRNP* codon polymorphism," says Llorens. "In combination with other CSF CJD biomarkers such as total tau, this should allow us to predict with high accuracy the survival time among the spectrum of CJD pathogenesis on the basis of pre-mortem biochemical and genetic features."

Ian Fyfe

ORIGINAL ARTICLE Blennow, K. et al. CSF neurogranin as a neuronal damage marker in CJD: a comparative study with AD. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2018-320155 (2019)

> Detailed analysis … revealed downregulation of genes that are required for synaptic signalling and brain development

alterations in our ASD samples," points out Kriegstein. Only 10% of the genes that were dysregulated in ASD emerged from the analysis of patients with epilepsy, suggesting that most of the ASD-related DEGs were more relevant to autism than to seizure activity.

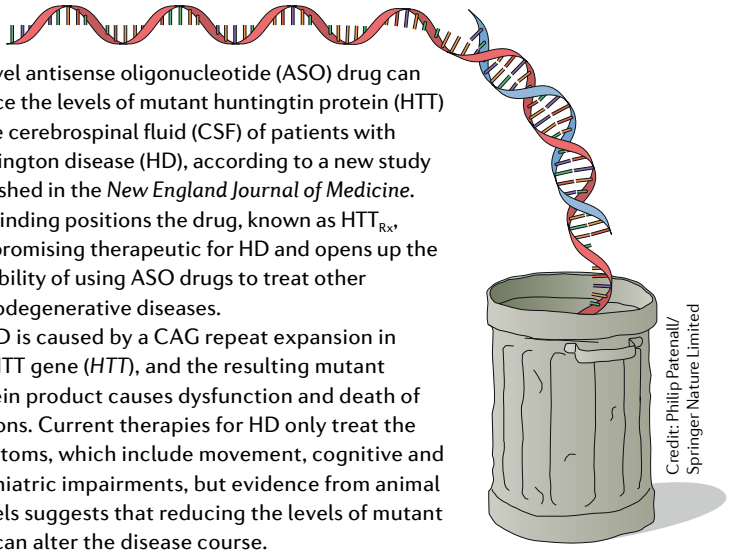
"Even though our study was based on patients who had unidentified and most probably diverse genetic causes of their autism, we nonetheless found that the resulting dysfunction converged on the same cellular processes," concludes Kriegstein. "This finding offers hope that in the future, therapies can be developed that can work broadly for many patients across the autism spectrum, even though they have different underlying gene defects."

Heather Wood

ORIGINAL ARTICLE Velmeshev, D. et al. Single-cell genomics identifies cell type-specific molecular changes in autism. *Science* **364**, 685–689 (2019)
FURTHER READING Jeste, S. S. & Geschwind, D. H. et al. Disentangling the heterogeneity of autism spectrum disorder through genetic findings. *Nat. Rev. Neurol.* **10**, 74–81 (2014)

HUNTINGTON DISEASE

Antisense oligonucleotide reduces mutant protein in patients with HD



Credit: Philip Patenall/ Springer Nature Limited

A novel antisense oligonucleotide (ASO) drug can reduce the levels of mutant huntingtin protein (HTT) in the cerebrospinal fluid (CSF) of patients with Huntington disease (HD), according to a new study published in the *New England Journal of Medicine*. This finding positions the drug, known as HTT_{Rx}, as a promising therapeutic for HD and opens up the possibility of using ASO drugs to treat other neurodegenerative diseases.

HD is caused by a CAG repeat expansion in the HTT gene (*HTT*), and the resulting mutant protein product causes dysfunction and death of neurons. Current therapies for HD only treat the symptoms, which include movement, cognitive and psychiatric impairments, but evidence from animal models suggests that reducing the levels of mutant HTT can alter the disease course.

HTT_{Rx} is a synthetic oligomer that binds to *HTT* mRNA and causes it to be degraded, thereby inhibiting translation of the HTT protein. Previous studies in animal models showed that HTT_{Rx} could lower HTT protein levels and improve disease-associated phenotypes, but the new study was the first time the drug had been given to humans.

The study, led by Sarah Tabrizi, included 46 patients with HD who were treated with placebo or one of five doses of HTT_{Rx}, in an ascending-dose design. Patients received four bolus intrathecal injections at 4-week intervals and were monitored for four further months. "This duration was expected to be sufficient to evaluate safety and tolerability of the ASO, which was the primary objective of the study," explains Tabrizi. In addition, the study team took CSF samples from patients before each administration of drug or placebo, and at either 28 or 56 days after receiving the last dose. These samples enabled the team to characterize the pharmacokinetics of HTT_{Rx} and to explore the effects of treatment on levels of mutant HTT.

HTT_{Rx} administration induced a dose-dependent reduction in the concentration of mutant HTT in CSF at the 28-day post-treatment time point. With the highest two doses, levels were reduced by 40–60% from baseline measurements. However, the team did not observe a difference in functional, cognitive, psychiatric or neurological measures in patients treated with HTT_{Rx} compared with those who received placebo.

"Now that we can significantly reduce mutant HTT in the CNS, the next step is to demonstrate that doing so provides meaningful benefit to patients," explains Tabrizi. "For this, we need larger, longer clinical trials." These further trials are already underway, and Tabrizi points out that the results of this initial study also have broader implications.

"This study is the first to demonstrate antisense-mediated protein suppression in patients with a neurodegenerative disease," she says. "These data suggest that antisense technology has the potential to provide disease-modifying benefits in other neurodegenerative diseases associated with aberrant production of proteins, including amyotrophic lateral sclerosis and Alzheimer disease."

Sarah Lemprière

ORIGINAL ARTICLE Tabrizi, S. J. et al. Targeting huntingtin expression in patients with Huntington's disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1900907 (2019)