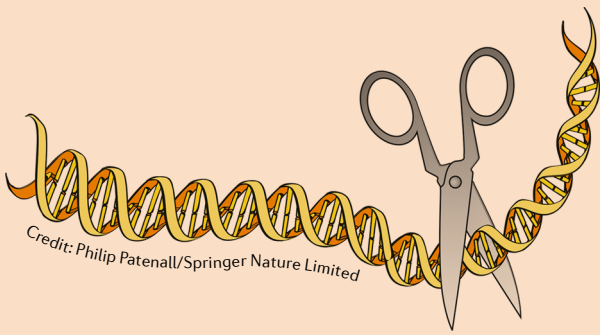
> HD has a neurodevelopmental component that provides a novel therapeutic window

The researchers found that all aspects of this phenotype could be ameliorated by treatment with the HDACi LBH589. Taken together, the findings of the study suggest that the prodromal phase of HD has a neurodevelopmental component that provides a novel therapeutic window.

"This is the first comprehensive description of a very early behavioural phenotype in models of HD, and also of a successful 'early phenotype-delaying' intervention," concludes von Hörsten. "The first 21 postnatal days in rodents largely correspond to the third trimester of human gestation, so one might argue that the present findings and approach could be translated into intrauterine development in humans."

Heather Wood

ORIGINAL ARTICLE Siebzehnrübl, F. A. et al. Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1807962115 (2018)
FURTHER READING von Hörsten, S. et al. Transgenic rat model of Huntington's disease. *Hum. Mol. Genet.* **12**, 617–624 (2003)



> Levels of dystrophin were substantially increased across a range of muscles in the dogs

These results are promising, but the investigators caution that further studies in larger numbers of animals and over longer time periods are now required. Importantly, the effects of the treatment on behaviour, function and survival in this model remain to be examined. Future research should also assess whether the therapy has any off-target mutagenic effects or causes immunogenic adverse events before clinical trials can begin.

Charlotte Ridler

ORIGINAL ARTICLE Amoasii, L. et al. Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. *Science* https://doi.org/10.1126/science.aau1549 (2018)

NEURODEGENERATIVE DISEASE

Tau folds differently between diseases

The existence of distinct tau filament folds in different human tauopathies has been established in a new study published in *Nature*. Visualization and atomic modelling of tau filaments in Pick disease revealed a distinct protein structure from that observed in Alzheimer disease (AD).

Tau filaments are hallmarks of AD and Pick disease, but they are made up of different tau isoforms in the two diseases. Filaments in Pick disease contain only tau isoforms with three microtubule-binding repeats (3R tau), whereas filaments in AD also contain tau with four repeats (4R tau). However, the structural reasons for these differences have been unclear.

Now, Michel Goedert, Sjors Scheres and colleagues at the Medical Research Council Laboratory of Molecular Biology, UK, together with collaborators at the Indiana University School of Medicine, USA, have used cryo-electron microscopy (cryo-EM) to provide new insight. "Last year, we reported the high-resolution structures of tau filaments from the AD brain," explains Goedert. "We now report the high-resolution structures of tau filaments from the Pick disease brain."

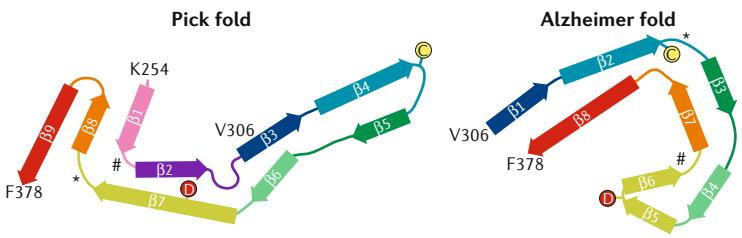
The researchers isolated tau filaments from the frontotemporal cortex of a person who had Pick disease and visualized these filaments with cryo-EM to determine the structures of their ordered cores. "Cryo-EM is the only available technique to solve structures of ex vivo amyloid filaments, which are not likely to crystallize and cannot be labelled with isotopes for nuclear magnetic resonance," says Scheres.

The cryo-EM structures showed that tau protein folds differently between Pick disease and AD. Furthermore, an atomic model of the Pick tau filament fold revealed that the tau structure adopted in Pick disease causes physical constraints that exclude the second microtubule-binding repeat that is present in 4R tau. This observation explains why Pick disease-associated filaments only contain 3R tau.

"Different molecular conformers of aggregated tau distinguish Pick disease from AD, and may explain why they are distinct clinical and neuropathological diseases," says Goedert.

The researchers say that we now need to know the atomic structures of tau filaments in other tauopathies, including those that involve only 4R tau. "Ultimately, this work may tell us something about how soluble tau protein assembles into a variety of different filament structures," says Goedert. "This may well have therapeutic consequences."

Ian Fyfe



Credit: Models of the tau folds in Pick disease and Alzheimer disease. Adapted from Falcon, B. et al. *Nature* https://doi.org/10.1038/s41586-018-0454-y (2018), Springer Nature Limited.

ORIGINAL ARTICLE Falcon, B. et al. Structures of filaments from Pick's disease reveal a novel tau protein fold. *Nature* https://doi.org/10.1038/s41586-018-0454-y (2018)
FURTHER READING Polanco, J. C. et al. Amyloid-β and tau complexity — towards improved biomarkers and targeted therapies. *Nat. Rev. Neurol.* **14**, 22–39 (2017)