NEURODEGENERATIVE DISEASE

Tau is linked to cognitive decline in Huntington disease

Over the past year, evidence has emerged that tau pathology is a prominent feature in the brains of patients with Huntington disease (HD). A new study published in *Brain* confirms these findings and, in addition, shows that the haplotype of *MAPT*, the tau-encoding gene, is related to clinical features of the disease—in particular, cognitive decline.

“We had previously shown that in Parkinson disease (PD), the tau haplotype influences not only the risk of getting PD but also the dementia associated with this condition,” explains Roger Barker, who led the study. “We thought, therefore, that something similar may be true in HD, and might explain why some patients develop an early dementia.”

First, the researchers searched for tau pathology in postmortem cortical and striatal tissue samples from 16 patients with HD. Brain tissue sections were immunostained with the AT8 antibody, which detects abnormally phosphorylated tau, and the T22 antibody, which is specific for oligomeric tau—a tau species that is thought to be especially neurotoxic.

Aggregates of abnormally phosphorylated tau protein, sometimes colocalized with mutant huntingtin, were found in both the cortex and striatum. In addition, inclusions consisting of oligomeric tau were detected in the striatum (but not in the cortex). These findings were common to individuals with young-onset HD and older patients, indicating that the tau pathology was related to disease progression rather than simply reflecting advanced age.

Barker’s team went on to investigate a possible association between tau and cognitive decline in patients with HD. The *MAPT* gene has two haplotypes, H1 and H2, and the H1 haplotype has

Abnormally phosphorylated tau aggregates (left) and oligomeric tau inclusions (right, arrows) in the brains of patients with Huntington disease. Scale bars 50 μm. Image courtesy of R. Vuono.

been linked to early development of dementia in patients with PD.

In the new study, patients with HD were genotyped and divided into two groups—H1 homozygotes and H2 carriers (H1/H2 or H2/H2). 473 patients (283 H1 homozygotes and 190 H2 carriers) underwent a minimum of two cognitive assessments, at least 1 year apart.

The H2 carriers showed a significantly faster rate of cognitive decline than did the H1 homozygotes. By contrast, the *MAPT* haplotype seemed to have no bearing on the rate of deterioration of motor function.

“We confirmed that tau pathology really does occur in the human brain, and that it has a distinctive pattern,” concludes Barker. “Furthermore, we showed that this pathology may contribute to some of the features of the disease, including the extent of cognitive deficits that patients exhibit.”

The researchers now plan to extend their investigations to other regions of the brain, including the use of new PET ligands to examine patterns of tau pathology in living patients. They also intend to further explore the relevance of colocalization of tau with mutant huntingtin in the brains of patients with HD.

Heather Wood

Original article Vuono, R. et al. The role of tau in the pathological process and clinical expression of Huntington’s disease. *Brain* doi:10.1093/brain/aww107