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HUNTINGTON DISEASE

Cerebrospinal fluid and MRI biomarkers for prodromal HD

Two recently published studies have described new biomarkers for measuring Huntington disease (HD) activity in people who carry the pathogenetic mutation, but do not yet show symptoms. These results could improve the monitoring of patients with so-called prodromal HD, and thereby facilitate clinical trials.

The accumulation of mutant huntingtin protein is the main histopathological correlate of HD, but it has been very difficult to detect *in vivo*. "Although several assays have been developed, we have never been able to measure huntingtin protein in the CNS of living patients," explains Douglas Macdonald, who coordinated an international study on behalf of CHDI Foundation, USA.

Macdonald and colleagues used a single-molecule counting assay to test solutions of recombinant mutant and wild-type huntingtin proteins in artificial cerebrospinal fluid (CSF). The results suggested that mutant huntingtin could be selectively dectected with high sensitivity.

The investigators then recruited nine patients with prodromal, early or moderate HD, plus three healthy controls, as part of a collaboration with Edward Wild and colleagues at University College London, UK. Mutant huntingtin was detected in CSF from each patient, but not in the control samples. To confirm this finding, the investigators then teamed up with Blair Leavitt and co-workers at the University of British Columbia, Canada, to test CSF samples from a further 28 patients with prodromal or manifest HD. In 26 of these participants—but in none of 10 controls—the assay revealed the presence of mutant protein.

"What we found with the new technology is that mutant huntingtin protein is present in CSF in the femtomolar range, which is why we could never detect it before," says Macdonald.

In both the London and Vancouver cohorts, the investigators observed positive correlations between CSF levels of mutant huntingtin and disease stage,

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with higher levels seen in more-advanced patients. The levels of mutant protein in CSF also associated with patients' clinical symptoms. Patients with high levels of mutant huntingtin scored poorly on the motor component of the Unified HD Rating Scale, and were impaired on a range of cognitive tasks. Importantly, these correlations remained significant after controlling for disease burden, age and CAG-repeat length, which suggests the CSF assay can provide additional information about disease status.

Further investigations with the single-molecule counting technique might provide greater insight into the pathogenesis of HD. Macdonald and colleagues also hope the assay will be used in upcoming clinical trials.

"The next generation of potential therapies for HD aim to decrease the amount of huntingtin protein that's made in the brains of patients, and we expect that the levels in the CSF will also decrease," explains Macdonald. The new assay could therefore provide a biomarker for measuring treatment efficacy.

In a separate study, Vincent Magnotta and co-workers at the University of Iowa, USA, turned their attention to imaging biomarkers for HD. Previous work had demonstrated that HD is associated with atrophy in the striatum and other areas, and Magnotta and colleagues hypothesized that metabolic changes might preceed this structural decline.

In 50 patients with prodromal HD and 26 controls, the investigators collected multiple quantitative MRI maps, including T1ρ relaxation time, which is sensitive to proton exchange and can provide an index of metabolic activity. Magnotta and colleagues then divided the participants with prodromal HD into two groups according to their age multiplied by the number of pathogenetic CAG repeats—an estimate of the severity of prodromal HD.

Patients with high severity estimates showed significant increases in the T1ρ signal in the striatum and surrounding areas, compared with both patients with less-severe disease and controls.

"In all of the areas we saw T1ρ changes, there were no T2 changes, which suggests these were not differences in the underlying tissue *per se*, but were actually related to brain metabolism," explains Magnotta. "The question now is whether the metabolic changes are the result of disease progression, or whether they are causing disease progression."

Magnotta's team are performing experiments in mouse models to uncover what aspect of HD pathogenesis is reflected by the T1ρ signal. The investigators also plan to start longitudinal studies in patients with prodromal HD, using T1ρ relaxation times as a biomarker of disease progression and response to treatment intervention.

Both the new CSF huntingtin assay and T1ρ MRI require further validation to assess their clinical utility for patients with HD. Nevertheless, these two studies represent important advances for research into this disease.

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Original articles Wild, E. J. *et al.* Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. *J. Clin. Invest.* doi:10.1172/JCI80743 | Wassef, S. N. *et al.* T1ρ imaging in premanifest Huntington disease reveals changes associated with disease progression. *Mov. Disord.* doi: 10.1002/mds.26203