023 QUANTIFYING MUTANT HUNTINGTIN IN HUNTINGTON'S DISEASE CSF

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Huntington's disease (HD) is a fatal, autosomal dominant neurodegenerative disease. No disease-modifying treatments exist, but oligonucleotide-based 'gene silencing' approaches that aim to reduce expression of the causative mutant huntingtin (mHTT) protein are in advanced development.

Low-abundance mHTT has never been quantified in the patient CNS, limiting our understanding of its role in the neuropathobiology of HD in vivo, and precluding the demonstration of target engagement by HTT-lowering drugs.

We developed a novel ultra-sensitive mHTT immunoassay using single-molecule counting technology. Using cerebrospinal fluid (CSF) collected from 9 HD mutation carriers and 3 controls, under strictly standardised conditions, mHTT was successfully quantified and its levels completely distinguished controls, premanifest mutation carriers and manifest HD patients.

mHTT level was significantly associated with disease burden score, a measure of lifetime exposure to mHTT, suggesting that soluble mHTT species increase in concentration with disease progression. An independent association with CSF neurofilament light chain level suggests the mHTT detected is neuronal in origin.

Quantifying mHTT in CSF may provide a means of monitoring disease progression in HD. Our novel assay will be refined using larger CSF collections, and used to better understand the neuropathobiology of HD and to support clinical trials of disease-modifying HD therapeutics.