# MICA: HD-CSF: Studying cerebrospinal fluid to understand key CNS pathobiological targets in Huntington’s disease

https://neurodegenerationresearch.eu/survey/mica-hd-csf-studying-cerebrospinal-fluid-to-understand-key-cns-pathobiological-targets-in-huntingtons-disease/

**Name of Fellow**

Dr EJ Wild

**Institution**
**Funder**

MRC

**Contact information of fellow**
**Country**

United Kingdom

**Title of project/programme**

MICA: HD-CSF: Studying cerebrospinal fluid to understand key CNS pathobiological targets in Huntington's disease

**Source of funding information**

MRC

**Total sum awarded (Euro)**

€ 1,461,911

**Start date of award**

01/05/15

**Total duration of award in years**

4.0

**The project/programme is most relevant to:**

Huntington's disease

**Keywords**

biobank | biomarker | Cerebrospinal fluid | drug development | Huntingtin | Huntington's disease

| kynurenine pathway | lumbar puncture | magnetic resonance imaging | pharmacodynamic

**Research Abstract**
Huntington’s disease (HD) is a fatal, autosomal dominantly inherited neurodegenerative disease causing motor and psychiatric symptoms and dementia. No disease-slowing treatment exists. HD is caused by an expanded CAG triplet repeat in HTT, resulting in mutant huntingtin protein (mHTT). Promising therapeutic candidates nearing human trials include nucleotide-based huntingtin-lowering drugs and kynurenine mono-oxygenase inhibitors. Huntingtin has never been quantified in the living CNS, limiting our understanding of the role of wild-type and mutant HTT and their cleaved species in patients, and how these roles change over time; and preventing demonstration of target engagement by HTT-lowering drugs. We have developed a novel, ultra-sensitive immunoassay which can quantify mHTT for the first time in patient CSF, completely distinguishing controls, premanifest mutation-carriers and patients. mHTT level correlates with neurofilament light chain, indicating likely neuronal origin. Depending on the activity of KMO, the kynurenine pathway (KP) produces either neurotoxic or neuroprotective metabolites. It is deleteriously deranged in HD but has never been studied using accurate methods in patient CSF. HD-CSF is the first comprehensive longitudinal study of CSF to elucidate key CNS pathobiological targets in HD. CSF, blood and robust phenotypic data including volumetric MRI will be collected from an 80-subject cohort at two timepoints. Samples will be analysed using our novel assays to quantify mHTT and KP metabolites and examine associations with disease progression. These core findings will be enriched through the targeted study of CNS-specific proteins in CSF. Comprehensive longitudinal study of KP metabolites and huntingtin species in patient CSF, linked to robust clinical and MRI atrophy data, will enhance our understanding of HD neuropathobiology in the living patient CNS, and provide pharmacodynamic biomarkers to accelerate therapeutic development.

**Types:**
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United Kingdom

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