Longitudinal evaluation of mutant huntingtin and neurofilament light as biomarkers for Huntington’s disease: the HD-CSF study

HSG 2019: Navigating HD

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Huntingtin tracks with progression and is the disease agent

Neurofilament tracks with progression and reflects neuronal damage

What do they each tell us?

What are their longitudinal dynamics?
HD-CSF

Studying cerebrospinal fluid to understand key CNS pathobiological targets in Huntington's disease

• 80 participants:
  • 20 control
  • 20 preHD
  • 40 early HD > mod HD

• 24-month Follow-up
  • Repeat of all assessments

(UHDRS clinical + cog assessments)

Sampling

Screening

Enroll-HD

standardised protocol

Optional repeat sampling

-30 0 +28 +56

(optional)
NfL has stronger associations with clinical scores

mHTT does not associate with cross-sectional brain volumes

All three biomarkers are highly stable over 6 weeks

Low sample sizes needed for biomarker lowering as trial endpoints

Among earliest detectable changes in HD
24-MONTH FOLLOW UP
Raw analyte longitudinal dynamics

- CSF mHTT
- CSF NfL
- Plasma NfL

Comparison of analyte levels across different age groups and disease stages.

Legend:
- Healthy Controls
- PreHD
- Manifest HD
Mixed effects modelling of analyte dynamics in gene carriers vs controls

- **CSF mHTT**
  - Graph showing analyte dynamics with age for different groups.

- **CSF NfL**
  - Graph showing analyte dynamics with age for different groups.

- **Plasma NfL**
  - Graph showing analyte dynamics with age for different groups.

Legend:
- Healthy Controls
- PreHD
- Manifest HD
mHTT and NfL trajectories with age by CAG

CSF mHTT

CSF NfL

Plasma NfL

Age (years)

LoQ

LoD

Age (years)

Age (years)
Motor, cognitive, and functional declines contribute to a single progressive factor in early HD

ABSTRACT

Objective: To identify an improved measure of clinical progression in early Huntington's Disease (HD) using data from prospective observational cohort studies and placebo group dominated double-blind clinical trials.
Association with overall clinical progression as measured by $\Delta cUHDRS$

Rate of change in analyte predicting clinical change

Baseline analyte predicting clinical change
Faster progressors have higher analyte values at baseline

Higher baseline analyte is faster progressors

Non-progressors < 1.2 ΔcUHDRS  
Progressors ≥ 1.2 decrease in cUHDRS
Baseline analyte values have stronger associations with subsequent disease worsening than rate of change.

Annualised change in clinical measures:

ΔcUHDRS
ΔTFC
ΔTMS
ΔSDMT
ΔSWR
ΔSCN
ΔVerb_Flu
ΔWhole brain
ΔWhite matter
ΔGrey matter
ΔCaudate

Δ = annualised rate of change
Could we use biofluid biomarkers to design more efficient trials?
NFL and mHTT have great potential as biomarkers for HD

Longitudinal dynamics of NfL and mHTT are distinct from controls and are CAG dependent

Baseline CSF mHTT is not associated with brain volume cross-sectionally but does predict subsequent atrophy and progression

A single measurement at baseline has more predictive value than rates of change

However, longitudinal changes are seen and have their own importance

Our data will enable modelling of biomarker changes to design longitudinal clinical trials
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Today's huntingtons disease
#HDResearchHero donating CSF is a bit of a celeb en.wikipedia.org/wiki/Charles_S…

An Irish donor of Rost fluid at @UCLHD for #HuntingtonsDisease

didn't feel a thing thanks you Dr Philpe

Post LP cuddles for an amazing couple! #HD-CSF #HDResearchHeroes @mattwardfromage @wildcatward @DrEdWild
Figure S4. (A) NFL and (B) ventricular boundary shift interval (mean ± SD) over time by dose group. Arrowheads indicate dosing days.

By the start of the extension study (7 to 27 months after the final doses were administered in this trial), the concentrations of neurofilament light protein in the CSF had generally returned to pretrial concentrations.
Further exploration of 9-month OLE data shows sustained lowering of mHTT and transient changes in NfL

CSF mHTT lowering occurs from first follow-up measurement and is persistent. CSF NfL increases at ~Month 5 then decreases while on continued treatment.

Data points represent mean values and error bars represent standard deviations. CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light chain; OLE, open-label extension; Q4W, once every month; Q8W, every 2 months.
1. We don’t know why NfL goes up

2. It goes down in both cohorts in the presence of continued HTT lowering

3. The temptation is to infer neuronal damage

4. That may be the case but other explanations are possible