

Leading researchers report on the elusive search for biomarkers in Huntington's disease

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While Huntington's disease (HD) is currently incurable, the HD research community anticipates that new disease-modifying therapies in development may slow or minimize disease progression. The success of HD research depends upon the identification of reliable and sensitive biomarkers to track disease and evaluate therapies, and these biomarkers may eventually be used as outcome measures in clinical trials.

Biomarkers could be especially helpful to monitor changes during the time prior to diagnosis and appearance of overt symptomatology. Three reports in the current issue of the *Journal of Huntington's Disease* explore the potential of neuroimaging, proteomic analysis of brain tissue, and plasma inflammatory markers as biomarkers for Huntington's disease.

"Characteristics of an ideal biomarker include quantification which is reliable, reproducible across sites, minimally invasive and widely available. The biomarker should show low variability in the normal population and change linearly with [disease progression](#), ideally over short time intervals. Finally, the biomarker should respond predictably to an intervention which modifies the disease," says Elin Rees, researcher at UCL Institute of Neurology, London.

In the first report, Rees and colleagues explore the use of neuroimaging biomarkers. She says they are strong candidates as outcome measures in future clinical trials because of their clear relevance to the

[neuropathology](#) of disease and their increased precision and sensitivity compared with some standard functional measures. This review looks at results from longitudinal imaging studies, focusing on the most widely available imaging modalities: structural MRI (volumetric and diffusion), functional MRI, and PET.

"All imaging modalities are logistically complicated and expensive compared with standard clinical or cognitive end-points and their sensitivity is generally reduced in individuals with later stage HD due to movement," says Rees. "Nevertheless, imaging has several advantages including the ability to track progression in the pre-manifest stage before any detectable clinical or cognitive change."

Current evidence suggests that the best neuroimaging biomarkers are structural MRI and PET using [11C] raclopride (RACLO-PET) as the tracer, in order to assess changes in the basal ganglia, especially the caudate.

A study led by Garth J.S. Cooper, PhD, professor of Biochemistry and Clinical Biochemistry at the School of Biological Sciences and the Department of Medicine at the University of Auckland, used comparative proteome analysis to identify how protein expression might correlate with Huntington's neurodegeneration in two regions of human brain: the middle frontal gyrus (MFG) and the visual cortex (VC). The investigators studied post mortem human [brain tissue](#) from seven HD brains and eight matched controls. They found that the MFG of HD brains differentially expressed 22 proteins compared to controls, while only seven were different in the VC. Several of these proteins had not been linked to HD previous. Investigators categorized these proteins into six general functional categories: stress response, apoptosis, glycolysis, vesicular trafficking, and endocytosis. They determined that there is a common thread in the degenerative processes associated with HD, Alzheimer's disease, and diabetes.

The third report explores the possibility that inflammatory markers in plasma can be used to track HD, noting that immune changes are apparent even during the preclinical stage. "The innate immune system orchestrates an inflammatory response involving complex interactions between cytokines, chemokines and acute phase proteins and is thus a rich source of potential biomarkers," says Maria Björkqvist, PhD, head of the Brain Disease [Biomarker](#) Unit, Department of Experimental Science of Lund University, Sweden.

The authors compare plasma levels of several markers involved in inflammation and innate immunity of healthy controls and HD patients at different stages of disease. Two methods were used to analyze plasma: antibody-based technologies and multiple reaction monitoring (MRM).

None of the measures were significantly altered in both HD cohorts tested and none correlated with HD disease stage. Only one substance, C-reactive protein (CRP), was decreased in early HD – but this was found in only one of the two cohorts, so the finding may not be reliable. The investigators were unable to confirm other studies that had found HD-related changes in other [inflammatory markers](#), including components of the complement system.

Some markers correlated with clinical measures. For instance, ApoE was positively correlated with depression and irritability scores, suggesting an association between ApoE and mood changes.

Even though recent data suggest that the immune system is likely to be a modifier of HD disease, inflammatory proteins do not seem to be likely candidates to be biomarkers for HD. "Many proteomic studies designed to provide potential biomarkers of disease have generated significant findings, however, often these biomarkers fail to replicate during the validation process," says Björkqvist.

More information: "Review Article: Longitudinal Neuroimaging Biomarkers in Huntington's Disease," by Elin M. Rees, Rachael I. Scahill, and Nicola Z. Hobbs. [DOI 10.3233/JHD-120030](https://doi.org/10.3233/JHD-120030).

"Proteomic Analysis of the Human Brain in Huntington's Disease Indicates Pathogenesis by Molecular Processes Linked to Other Neurodegenerative Diseases and to Type-2 Diabetes," by Sarah J. Schönberger, Dina Jezdic, Richard L. M. Faull, and Garth J. S. Cooper. [DOI 10.3233/JHD-120044](https://doi.org/10.3233/JHD-120044).

"A Critical Evaluation of Inflammatory Markers in Huntington's Disease Plasma" by Edina Silajdžić, Melinda Rezeli, Ákos Végvári, Nayana Lahiri, Ralph Andre, Anna Magnusson-Lind, Rajasree Nambron, Eirini Kalliolia, György Marko-Varga, Thomas T Warner, Thomas Laurell, Sarah J Tabrizi, and Maria Björkqvist. [DOI 10.3233/JHD-130049](https://doi.org/10.3233/JHD-130049).

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