

New study reveals a potential HD biomarker

A potential HD biomarker has been uncovered in a recent clinical study



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What if a blood test could provide information about the status and course of HD? This is the premise of seeking HD biomarkers; they may someday help guide treatment decisions and predict how symptoms will change. A team of researchers spanning multiple countries recently analyzed blood, brain images, and clinical exams from the TRACK-HD study. They found that blood levels of a protein called neurofilament light chain corresponded with the severity of HD, making it a potential biomarker.

The search for HD biomarkers

With enduring community support of cutting-edge science, there is great potential for the development of novel therapies to treat Huntington's disease. Alongside basic and clinical studies to identify the source of symptoms and investigate new drugs, it's important to seek out accurate and efficient ways to track the progression of HD. As more resources become available for treating and managing HD symptoms, it would be helpful for doctors and patients to have a sense of whether a person's symptoms are expected to worsen slowly or quickly. We also need accurate ways to determine whether an experimental drug has improved brain health.



Unlike previous biomarkers for HD, this new finding can be done using a simple blood sample.

There are established ways to address these questions: we can assess unusual movements, analyze changes in mood and thinking, and take images of the brain areas involved in HD. But these methods can be time-consuming and draining for patients and doctors, and might be uninformative for a person at risk who has not yet experienced symptoms. For these reasons, the HD community is in search of good biomarkers, tests that can be easily measured to predict disease development and response to treatment. Today, we're excited to report that researchers in the UK have identified a substance in the blood that shows promise as a biomarker for HD.

What is a biomarker, exactly?

We usually define a biomarker as a test that can predict disease onset, progression, or success of treatment. What does this actually mean? Well, with an excellent biomarker, a simple test in a routine medical check-up can generate enough information to guide decisions about current and future care. This has not yet been possible with Huntington's disease, nor with most neurological disorders. The brain is a complex organ, and treatments are limited compared to cancer, for example, or heart disease.

In fact, let's take the example of heart disease to illustrate more clearly the concept of a biomarker. In the case of heart health, a simple and universal example of a biomarker is blood pressure. Measuring blood pressure is easy, non-invasive, and inexpensive. More importantly, a century of research has determined definitively that blood pressure is a very good indication of risk for heart disease. Increasing blood pressure readings over time might warrant a change in diet or prescription of a medication, to decrease the danger of future heart problems. If the interventions cause blood pressure to decrease, the doctor and patient can be reasonably sure that the risk of heart disease is now lower. These decisions and conclusions can be made without ever directly testing the heart, and while the patient is still physically feeling fine.

The ideal biomarker for HD would serve a similar function. Although a genetic test can determine whether a person has the HD mutation, it cannot predict the short-term risk of developing symptoms, or determine the likely amount of present damage to the brain. We also lack any basic chemical tests to understand whether a new treatment is delaying symptoms or slowing damage; instead patients must undergo frequent and lengthy testing. A person at risk of developing HD may experience no symptoms for many years, but imagine if a simple yearly test could give an indication of brain health, the way blood pressure does for the heart. These are the goals of seeking HD biomarkers.

Identifying potential biomarkers for HD

One way to search for HD biomarkers in humans is to measure levels of many substances in the blood, then compare these levels with the severity of symptoms or images of damage to the brain. Combining this data from a large group of people can determine which substances should be interpreted as a sign of health or damage. When something in the

blood increases (or decreases) steadily as neurological damage and symptoms worsen, researchers start to pay attention - it could be a potential biomarker. For brain disorders, the search has been elusive. This is because it's rare for the contents of brain cells to end up in the bloodstream, and because there's huge variation in levels of blood substances among individuals.

Nevertheless, a recent study, headed by Dr. Edward Wild at University College London, has identified a protein in the blood that appears to have this property: it increases in proportion to other signs of HD. To identify this protein, the team analyzed data collected as part of TRACK-HD, a three-year study of HD mutation carriers and their unaffected partners or siblings. The clinicians were not testing a drug, but making careful observations of participants over time to understand more about the way HD develops. The 298 people who completed the trial had repeated brain imaging, clinical exams to measure movement and thinking, and gave blood samples. Their participation has fueled several years of research, including this most recent biomarkers study.

Neurofilament light chain

The protein at the center of this story is called neurofilament light chain, or NfL. It's an important structural component of nerve cells, supporting their shape, like the ribs of an umbrella. Previous research in HD and other neurological disorders has shown that when a brain cell dies, the umbrella collapses, releasing NfL protein that can end up in the blood stream. This led Wild and his team to hypothesize that increasing damage to the brain areas affected by HD would cause higher levels of NfL to accumulate in the blood. The researchers decided to investigate NfL more closely, using the blood samples, images, and exam results from TRACK-HD participants.

“Imagine if a simple test could give as good an indication of HD brain health as blood pressure does for the heart ”

The participants were divided into groups based on the status of their HD, determined by exams at the beginning of the study. There was a “control” group made up of siblings or partners who did not have the mutation. Then there were four groups of gene carriers: (1) those predicted to develop HD symptoms in a decade or more, (2) those predicted to develop symptoms in a few years, (3) those with early symptoms, and (4) those with more advanced symptoms.

The more “advanced” disease group a person was in, the higher their NfL levels, and NfL increased over time in people with the HD gene. Importantly, the highest levels of NfL corresponded with more damage to the brain and poorer scores on movement and reasoning tests. This means that NfL levels were a good indicator of brain health and HD progression. If a person had a high level of NfL at the beginning of the study but no symptoms, they often began to develop symptoms during the study. So not only were NfL levels associated with severity, they could predict whether a person might become ill soon.

What's more, the level of NfL in the blood reflected the amount found in the CSF, the fluid bathing the brain. This suggests that a blood test might be able to provide consistent information about the brain, in place of an invasive spinal tap.

NfL: potential future as a biomarker

For all of these reasons, the authors propose that NfL could be used as a blood biomarker that reflects current health of the brain in HD. This is a well-designed experiment with robust data, making for exciting news. But as with all studies, it's important to discuss the limitations of this work.

First and foremost, analyzing data from a big group of participants is an excellent way to find general trends, but the interpretation won't extend to every individual. Just as high blood pressure indicates risk of heart disease rather than setting the date of a heart attack, a person's NfL level cannot make an exact prediction about HD symptoms or brain health. The levels are simply too variable between individuals, and there's not enough data yet to apply these findings to any routine practice, such as a simple test in a doctor's office.

However, measuring NfL levels could be an added way to assess disease progression in HD clinical studies. It will be particularly interesting to see whether current or future treatments can lower levels of NfL, mirroring improvements in symptoms. One intriguing idea is that scientists could revisit samples from past clinical trials to build a larger picture of the relationship between NfL and HD progression, and to determine whether experimental treatments lowered NfL, even if they failed to improve symptoms.

Furthermore, before we can use blood NfL (or any other blood biomarker) as a proxy for damage to neurons in HD, we have to be more certain that blood levels correspond with levels in the brain. To address this issue, the team heading the recent study has also launched a global initiative called HDClarity to ensure that samples of CSF (obtained via a spinal tap) are collected and processed consistently in clinics all over the world.

If the observations about blood/CSF NfL levels and HD hold up under further scrutiny, we may have a useful biomarker on our hands. Notably, NfL is not specific for HD and has also been proposed as a marker to track the progression of other neurodegenerative diseases, including Alzheimer's and ALS. We hope it will be added to the arsenal of resources that are helping us to monitor HD and to develop new therapies. At the same time, researchers will continue to seek out biomarkers that can help guide patients and families' decisions as treatments become available.

Dr Wild is co-editor-in-chief for HDBuzz. He was not involved in the decision to write this story, nor its drafting or editing. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

neuron Brain cells that store and transmit information

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

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