Lighting the way: A new biomarker for Huntington's disease

A new biomarker reveals brain changes in early Huntington's disease.

By Melissa Christianson **April 20, 2015** **Edited by Dr Jeff Carroll**

In Huntington's disease, brain cells begin dying long before disease symptoms arise. Unfortunately, good tools for monitoring early brain changes – and testing whether new therapies slow or stop them – have not previously been available. However, a newly developed tool aiming to overcome this problem may mean big changes for the way we track Huntington's disease.

Symptoms in Huntington's disease are caused by the death of brain cells in specific parts of the brain. However, one of the curious features of the disease is that outward symptoms don't typically appear until a good many brain cells have already died. Thus, there is a big disconnect between the timing of the brain changes and the outward symptoms of Huntington's.

This disconnect makes early, proactive treatment of Huntington's disease really important. To understand why, imagine Huntington's as a fire burning inside a building. If no one calls the fire department until half the building is charred, so much of the building will be lost by the time the fire brigade arrives that no amount of effort will save it. In much the same way, waiting to treat Huntington's disease until outward symptoms appear means allowing important brain cells to die – and once these cells die, they can't be replaced.

Trying to treat Huntington's disease while blind to early brain changes is like trying to fight a fire with your eyes closed.

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Therefore, effectively treating Huntington's disease will almost certainly require intervening *before* brain cell loss causes outward symptoms. Unfortunately, good tools for tracking brain changes early in Huntington's don't yet exist. This lack of tools is a problem, because it means that doctors and scientists are essentially blind to what's going on in the brain early on in the disease.

Returning to our fire analogy, trying to treat Huntington's disease while blind to early brain changes is like trying to fight a fire with your eyes closed. If you can't see the fire, you don't know if you are containing it – or if instead you have your water hose pointed in the wrong direction entirely. Similarly, if doctors are blind to early brain changes in Huntington's disease, they can't accurately tell if new therapies prevent or slow down these changes. This means that they must spend valuable time – time that individuals with the disease don't have – waiting for outward symptoms to develop before determining if a treatment has any hope of working.

To avoid this waiting game, we are in urgent need of tools for tracking early brain changes in Huntington's disease. Just like tools for monitoring the temperature of a fire provide important information about the status of the fire, tools for monitoring early brain changes in Huntington's provide important information about the status of the disease.

Sign, Sign, Everywhere a Sign

In the clinic, such tracking tools are known as "biomarkers". Biomarkers give **signs or signals** of what's going on in diseases like Huntington's. They can be any kind of test - running the gamut from from blood tests to thinking tests to brain scans and everything in between - but they all have one thing in common: they measure something concrete about the disease. A good biomarker lets us monitor the status of the disease, which is important for predicting progression or telling if a treatment is working.

In a practical sense, therefore, biomarkers are really important for the Huntington's community because they can make clinical trials of new drugs quicker and more reliable. Having good biomarkers would be a powerful weapon in the fight against Huntington's disease.

A Biomarker for PDE10

Fortunately, a good biomarker of early brain changes in Huntington's disease may be just over the horizon.

The new biomarker is focused on PDE10 – a brain protein that has already made a splash in the Huntington's research community. Scientists think that PDE10 helps brain cells communicate with one another and that it might be a good drug target for the disease. In animals, PDE10-targeting drugs improve brain cell survival and delay the onset of Huntington's-like symptoms. In the clinic, an ongoing trial currently recruiting subjects is now testing whether PDE10-targeting drugs improve symptoms in humans with HD.

> **"The PDE10 biomarker could be really important for the Huntington's community, because it offers an easy, accurate way to monitor brain changes early in the disease. "**

Two features make PDE10 particularly well suited as a biomarker for Huntington's disease. First, it is found almost exclusively in parts of the brain where brain cells die in Huntington's disease. As a biomarker, therefore, it would give information specifically about problem areas in the disease. Second, although these brain cells normally make a lot of PDE10, they start making less and less long before they die in Huntington's. Thus, a PDE10 biomarker would provide information on brain cells that are sick but not yet dead.

Together, these two pieces of information would give PDE10 the potential to be a really powerful biomarker – one that would allow doctors to specifically monitor the health of at-risk brain cells in Huntington's disease *before* outward symptoms develop.

Glow, Little Biomarker, Glow

With this idea in mind, scientists at Pfizer created a PDE10 biomarker for tracking early brain changes in Huntington's disease.

In essence, the new biomarker is a picky, sticky substance that attaches tightly PDE10 but not other proteins in the body. Importantly, this picky, sticky substance has tiny glowing bits attached to it. Though tiny, these glowing bits are a big addition: they let scientists using a special camera track the substance wherever it goes. The substance itself is safe, so scientists can administer it to individuals with Huntington's disease – and then watch where it travels inside the human body.

Most of the new biomarker ends up stuck to PDE10 in brain cells, which means that it accumulates in exactly the brain areas that we want to watch in Huntington's disease. In these areas, healthy cells (with lots of PDE10) glow brighter than sick cells (with only a little PDE10) in danger of dying. By measuring the brightness of the glowing biomarker with a special camera, therefore, scientists can monitor the health of these at-risk brain cells over time.

Putting It to the Test

Pfizer scientists put this new tool to a practical test in a study published in the Journal of the American Medical Association.

In their study, the scientists took pictures of Huntington's-vulnerable brain regions lit up by their new glowing biomarker, and then they looked closely at the pictures to see if the regions looked different in individuals with and without early Huntington's disease. Importantly, the Huntington's individuals in this study had **very early disease**: they either only mild symptoms or no symptoms at all.

The new PDE10 biomarker may directly improve and speed up the search for Huntington's therapies.

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When the scientists analyzed the pictures, they found that the brain regions from the different groups of subjects in fact looked very different – even though there were not obvious differences in outward symptoms between subjects with and without Huntington's disease. Specifically, for important brain regions, the glow coming from the PDE10 biomarker was brighter in healthy volunteers than individuals with Huntington's disease. Further, even among Huntington's individuals, the glow in those with no outward symptoms was brighter than that in those with mildly symptomatic disease.

Thus, there was a strong relationship between the brightness of the new PDE10 biomarker and the extent of Huntington's disease. This relationship was much stronger than what scientists could detect using existing tools.

Based on these results, the scientists believe that their new biomarker is sensitive to early brain changes in Huntington's disease.

How Does This Help Us?

The PDE10 biomarker could be a really powerful tool for the Huntington's community, because it offers an easy, accurate way to monitor brain changes early in the disease. Better disease monitoring makes assessing if a potential treatment is working both easier and more accurate, which speeds up clinical trials. Thus, even though the biomarker itself is not a treatment, it may directly improve and accelerate the search for new Huntington's therapies.

Further, this biomarker could allow doctors to predict when an individual with pre-symptomatic Huntington's will begin to experience symptomatic disease. This prediction would be invaluable both for clinical studies (where it is important to test therapies in patients whose exact disease status is known) and for individuals living in the shadow of looming symptomatic disease.

The Bottom Line

It is encouraging to see a large, well-resourced pharmaceutical company invested in running efficient, effective clinical trials for Huntington's disease. Although the Pfizer scientists must do more work to verify their new biomarker's sensitivity, the potential benefits of this new tool in the search for Huntington's therapies are clear. Across the board, the development and validation of good biomarkers will speed the search for effective treatment.

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

GLOSSARY

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.

PDE10 a brain protein that may be a good drug target and biomarker in Huntington's disease. PDE10 is found almost exclusively in parts of the brain where brain cells die in HD.
