Spotting HD Early: The Clues Hidden in Young Brains

Researchers have detected early changes in brain scans and biomarkers in young people with the Huntington's disease gene, 20 years before symptoms are predicted to appear. These findings could help develop medicines to treat HD earlier in life.

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A new study led by researchers from University College London has helped uncover some of the earliest changes that happen in people with the gene for Huntington's disease (HD), long before obvious symptoms begin. Very slight changes in brain scans and different metrics could be measured in young people with the HD gene who showed no changes in their thinking, behaviour, or movement. Measuring these very early changes paves the way for the HD community to begin thinking about testing medicines earlier in HD. Let's get into it.

Finding out where it all begins

HD is a 'CAG repeat expansion disease'. Everyone has a repetitive sequence of C-A-G DNA letters in their Huntingtin gene, but people who go on to develop HD have over 35 C-A-G repeats. The more C-A-Gs someone has in their Huntingtin gene, the earlier they are likely to experience symptoms.

The Huntington's Disease Young Adult Study (HD-YAS) studies people with the HD gene expansion to try and pinpoint some of the earliest changes that happen in disease.

HD is traditionally viewed as a disease which doesn't impact folks with the HD gene expansion until they are in middle age. And it is certainly true that for the majority of people, they may not experience any obvious symptoms until well into adulthood.

However, folks have the genetic change which causes HD from birth, so scientists have long suspected that changes could be happening much earlier in the course of someone's life if they have the HD gene expansion. We are also learning from recent clinical trial updates that some therapies might work better if we give them to people earlier, before their symptoms progress too far.

Seeing changes before they happen

But how would we know if drugs are working in young people with HD? If there aren't obvious symptoms yet, then how would we know if we are slowing or halting the disease?

To try and solve these problems, many scientists have been working to study HD in people *before* they get symptoms. The idea is that if we can identify something that we can measure in younger folks with the HD gene expansion to predict their progression of the disease, then we might be able to show whether medicines are slowing or halting how HD is progressing by looking at that measure.

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These measures are called "biomarkers" - biological metrics that we can track to see how HD is progressing in a person. The scientists in this study set out to try and pinpoint early changes in young people with the HD gene expansion in an effort to identify biomarkers for future drug trials.

HD community members made this study happen

Research like this can't happen without the selfless volunteers who sign up for these studies, to whom we are all extremely grateful. Over 150 people participated in this study in total, roughly half of whom are people with the HD gene expansion, and the rest are people of similar ages without the HD gene expansion. These folks are part of the HD Young Adult Study (HD-YAS).

All of the people in the study with the HD gene expansion were categorised according to the HD Integrated staging system, or HD-ISS.. This staging system provides clear milestones for someone's journey with HD. Stage 0 means that the HD gene is present, but there are no other changes. Stage 1 means that early changes in brain scans start to be observed. Stage 2 is when noticeable changes to movement and thinking also start to occur. Stage 3 is all of the above and when someone starts to have difficulty with daily tasks in their life.

When this study began, 81% of HD gene expansion carriers were at Stage 0, 17% were at Stage 1, and 2% were at Stage 2. So while they all had the HD gene expansion, most did not have noticeable signs or symptoms of HD. On average, these participants are about 20 years out from developing the movement symptoms associated with HD. This study took place over a very long timeframe of 4.5 years, during which about 20% of people with the HD gene expansion moved from Stage 0 to Stage 1, meaning that changes in brain scans could start to be measured.

Study participants were examined using many, many tests including brain imaging, blood collection, spinal fluid collection, assessment of cognition (planning, attention, memory), and psychiatric assessment (depression, anxiety, behaviour).

From head to toe: comprehensive assessment of participants over 4.5 years

Participants in this study were assessed and tested in all sorts of different ways so that scientists could understand which factors might be changing over the course of the 4.5 years study, before the usual signs and symptoms of HD are obvious.

Clinical measures

The study included a large number of tests to look at thinking skills such as memory, attention span, and processing speed. They also assessed symptoms of mental health such as depression, anxiety, and sleep behaviours.

Over these 4.5 years, the researchers saw no significant differences to how thinking skills or mental health changed over the timeframe of the study between people with the HD gene expansion and people without. This tallies with previous studies from the HD-YAS group, where no differences were seen between young folks with the HD gene expansion and people of the same age without the HD gene when they looked at cognitive and psychiatric symptoms.

MRI brain scans

The research team also collected very detailed brain scans of folks in the study to see how different regions of the brain might be changing in size over time. They did this because some inner parts of the brain (called the striatum) get much smaller in HD and this is an early marker of HD in HD-ISS Stage 1. Shrinking of the striatum is thought to cause many of the symptoms of HD as disease progresses.

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In people with the HD gene expansion but no symptoms, the researchers were able to measure decreases in the size of the striatum even though these individuals are two decades from when we would expect them to be diagnosed in the clinic and had no overt symptoms of disease. Some other measurements of brain volume were also more changed in people with the HD gene expansion.

When they broke down the data for people with the HD gene expansion into their respective stages, they could see a difference how quickly the striatum shrank between Stages 0 and 1, with a faster loss of brain cells in this region for people in the more progressed Stage 1. This finding aligns with our understanding that brain cells are lost at a faster rate as HD progresses.

NfL

NfL, or neurofilament light, is a biomarker that HDBuzz readers have heard a lot about recently, as it is commonly reported in HD clinical trial updates. NfL is seen as a biomarker of brain health, with increased levels generally indicating poorer brain health.

The researchers found that NfL levels in spinal fluid were shown to be much higher in people with the HD gene expansion than those without, and levels increased more rapidly for the HD gene group. Further, NfL levels also tracked with CAG number and age, with older folks with larger CAG numbers having the greatest changes to their NfL levels. Together, this further cements spinal fluid NfL as a very sensitive biomarker of HD progression, even at these very early stages of disease.

PENK

Proenkephalin, or PENK, is another marker which has been shown to track with the health of a type of brain cell called medium spiny neurons, the cells most impacted by HD. PENK differs from NfL as it *decreases* as this type of cell gets sick.

In people with HD gene expansions, the CAG number will increase slowly over time in some cells of the body, a process known as somatic instability or somatic expansion.

The researchers saw more rapid decreases in PENK in people with the HD gene expansion compared to people without the HD gene. Again, this was tied to CAG number and age, with older folks with longer CAGs having more drastic changes to their PENK levels.

Somatic expansion in blood

Somatic expansion is the phenomena by which the CAG number will increase in some cell types in the body over time. This idea is getting a lot of attention in HD research and you will have probably noticed that we are writing about it a lot as more and more studies are published.

Things really took off when genome-wide association studies pointed to somatic expansion as a potentially important factor for when symptoms of HD might begin. These studies look for genetic letter changes in our DNA code that are associated with earlier or later onset of symptoms than is predicted based on the CAG number alone. It turns out that many of these genetic letter changes are in genes which are involved in somatic expansion.

In this present study, the team looked at how much the CAG repeat number changed in cells from blood samples of participants. More expansions were found in blood cells of people with the HD gene expansion, with higher rates of expansion in folks with higher CAG numbers. The changes that are being measured here are **tiny** and it is rather incredible that the researchers can track this expansion from blood samples, where we know expansions are not very common, even in people with symptoms of HD.

Hearing these new results that detail the CAG repeat size increasing in blood samples may have you wondering if *your* CAG repeat number will get bigger over your life and if you should get re-tested for HD. In short, your repeat is very unlikely to change and you don't need to get re-tested. The changes being detected in this study are super small - a win for sensitive experiments and a weight off your shoulders.

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> **carrying the HD genetic expansion.” ”**

Other biomarkers

The researchers also looked at a host of other markers, completing an extremely thorough assessment of anything which might change more in people with the HD gene expansion compared to controls. This included the huntingtin protein itself which was barely detectable in most folks at this early stage, as well as markers of inflammation. Both huntingtin and these other markers of inflammation were no different to people without the HD gene expansion at similar ages.

How did these measures track with disease progression?

After making all of these measurements, the team next checked how they might track with disease, using the brain scan data as the mile markers for disease progression. Remember that shrinking of the striatum in brain scans is part of what defines Stage 1.

The researchers found that NfL and PENK levels at the beginning of the study could be used to predict how quickly cells are lost in the brain, even in people who are many years from experiencing symptoms. This is pretty amazing, given that these younger folks with the HD gene expansion had no detectable changes at all in cognition, memory, or their mood. The rate of somatic expansion in blood and how this changed over time also showed promise for predicting changes to brain structure and levels of NfL and PENK biomarkers.

This is the first time in humans that scientists have been able to link somatic expansion measured in blood with early brain changes, occurring approximately 20 years before movement symptoms begin. Scientists are very excited by this finding as it suggests that somatic expansion could be a key driver of brain cell loss in HD.

The Huntington’s Disease Integrated Staging System (HD-ISS) defines clear mile markers in the progression of HD.

Why does this matter?

There are a ton of HD researchers at universities and in biotechnology and pharmaceutical companies who are working to develop treatments to try to slow down, halt, or even reverse somatic expansion. Many scientists were already convinced that this was a pretty good idea based on the genome wide association study data showing that instability might be associated with how early or late someone might experience HD symptoms. This study advances the field because we now have a sensitive biomarker in measuring blood CAG levels that can be used to detect changes before symptoms appear. This opens the door for clinical trials to begin in pre-symptomatic people living with the HD gene expansion.

Professor Sarah Tabrizi, who led this study, said: “Our study underpins the importance of somatic expansion driving the earliest neuropathological changes of the disease in living humans carrying the HD genetic expansion. I want to thank the participants in our young adult study as their dedication and commitment over the last 5 years mean we are truly nearing prevention clinical trials in Huntington’s disease.”

We would like to join Sarah and her team by thanking everyone who participated in this study. This research would not have been possible without you. The HDBuzz team is excited to see where this research points to next and looks forward to reporting on that soon.

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

GLOSSARY

NfL biomarker of brain health

huntingtin protein The protein produced by the HD gene.

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

inflammation Activation of the immune system, thought to be involved in the HD disease process

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

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

somatic relating to the body

genome the name given to all the genes that contain the complete instructions for

making a person or other organism

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals