New Insights Into Why Huntington's Disease Has Delayed Onset

A highly-anticipated scientific paper has landed! This new work challenges current theories in Huntington's disease research, uncovering how runaway CAG repeats erode cell identity in certain types of brain cells, leading to their death.

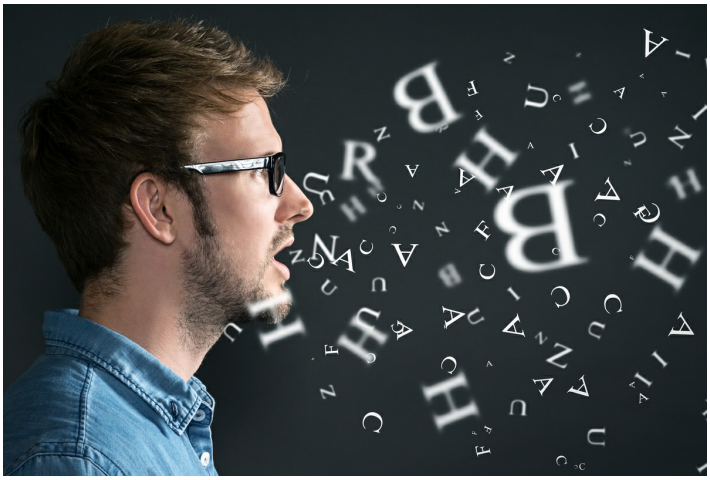
By Dr Sarah Hernandez | January 20, 2025 | Edited by Dr Rachel Harding

---

People who develop Huntington's disease (HD) are born with the genetic change that causes the disease. So why does it take decades, usually around 40 to 50 years, for the symptoms of the disease to appear? And why are certain brain cells more vulnerable to death than others? These have always been key questions in HD research. A new paper from the lab of Dr. Steven McCarroll gives us new insights into these questions, and it points a finger at the CAG repeats that are the genetic basis for HD.

Genetic stutter

At the genetic level, HD is caused by repeating C-A-G letters in the genetic code within the gene huntingtin, or HTT. However, we all have the HTT gene. In fact, we all have a stretch of CAGs that repeat within our HTT gene. It's just that people who go on to develop HD have *extra* CAGs within their HTT gene - 36 or more. You can think of it like a genetic stutter.



We all have the huntingtin gene and a repeating CAG tract within that gene. People who develop Huntington's disease have an expansion of these CAG repeats, like a genetic stutter.

In one of the biggest breakthroughs in HD research, scientists found that this genetic stutter actually gets bigger in some cells over time. This is a biological phenomenon called "somatic instability", which is also sometimes referred to as "somatic expansion". It's the perpetual expansion of the CAG repeat in some types of "somatic" cells, or cells of the body. Researchers have found that the number of CAGs balloon in some cells, at times reaching up to 1,000 repeats!

However, some cells are more vulnerable than others to these effects of HD. Even though the CAG expansion that causes HD is found in every cell type in a person's body, molecular signs of the disease are much more apparent in some types of cells compared to others.

All cells aren't equal

Brain cells are most affected by HD. However, there are lots of different types of cells in the brain, and they're not all affected in the same way. When people think of brain cells, they typically think of neurons - the tree-shaped cells responsible for directing our thoughts, feelings, and movements.

But there are other types of cells in the brain too. Glia are support cells that provide structure, nutrients, and maintain a healthy brain. Endothelial cells help form the blood-brain barrier, keeping harmful substances like viruses and some medications out of the brain. There are even different subtypes of neurons!

> **"The authors suggest that we should perhaps reframe our thinking - rather than asking why MSNs are particularly vulnerable to cell death in HD, maybe we should be asking why somatic expansion is more prevalent in certain cell types, like MSNs. "**

Medium spiny neurons, or MSNs, are a type of brain cell found in a region of the brain called the striatum that is almost exactly in the middle of our heads. MSNs help to control movement and coordination, and are particularly vulnerable to dying off as HD progresses. While we've known this for decades, no one really knew why. However, new experimental techniques, like those used by the McCarroll group, are getting us closer to the answer.

The beach vs. a sand grain

McCarroll's team used a technique called "single nucleus RNA sequencing". This let them look at the individual genetic signatures of every single cell in the brain samples they analyzed. It's incredibly impressive! New single nucleus techniques, like those used here, are advancing what researchers know about HD because it transforms how they analyze samples.

About a decade ago, if you wanted to look at molecular changes in a tissue sample, you would chop it up and analyze it. Pretty crude in hindsight. This would give you a decent idea of the levels of molecules within an entire sample, but you wouldn't be able to tell which

cells were producing what molecules. This is kind of like taking a picture of the sand on a beach. You could probably tell if it was tan, or rocky, but that's about it.

Single nuclei techniques allow researchers to zoom in and look at every single cell within a tissue sample. This would be like taking a sample of that beach and putting it under the microscope. So now instead of a uniform tan sample, you might see that some grains of sand are actually white fragments of shell, or blue pieces of sea glass; you get a much deeper understanding of the composition of that sample.

Advancements in techniques that analyze tissue allow researchers to look at single cells within a tissue sample. This is like analyzing individual grains of sand for differences, rather than looking at the entire beach.

Expansions in single cells

When the researchers used single nucleus sequencing on brains of people who had HD, they found that CAG expansions were profound in MSNs, but not in other types of brain cells, like glia or other kinds of neurons. The authors suggest that we should perhaps reframe our thinking - rather than asking why MSNs are particularly vulnerable to cell death in HD, maybe we should be asking why somatic expansion is more prevalent in certain cell types, like MSNs.

From there, they could pull out the exact number of CAG repeats within each MSN for each brain sample. They could then map that against all the other genetic changes within each cell. Hopefully you're starting to appreciate that this is **a lot** of data!

Mapping the number of CAG repeats with genetic changes, allowed them to calculate disruptions in those cells. Interestingly, they found that certain CAG repeat lengths were linked to the amount of genetic disruptions in the MSNs. So cells with CAG expansions between 36 and 150 didn't seem to show signs of genetic disturbances. But once the repeats expanded beyond 150 CAGs, the changes they measured were huge. This suggests that something is going on inside the MSNs once the CAG length reaches 150 or more to disrupt the genetic signatures of the cell. But what?

Identity eroded

> **“Notably, in MSNs with ultra-long repeats, they found that the cells appeared to be turning on genes that cause cell death, perhaps providing a clue as to why this specific cell type is so vulnerable in HD. ”**

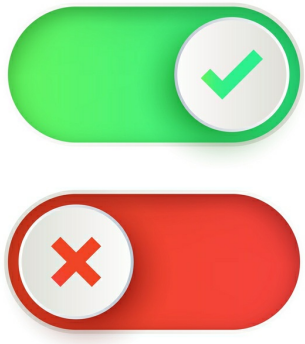
They dug deeper into the molecular changes that were happening inside the MSNs that had ultra-long CAG repeats of 150 or more. They were involved in the identity of the MSN itself - genes that make an MSN an MSN, and not another type of nerve cell.

As we covered, there are different subtypes of neurons in the brain. What gives them their unique identity is the genes and molecules that they produce. Some neurons produce molecules that inhibit the activity of other neurons, ensuring controlled and accurate movements. These are known as ‘inhibitory neurons’. Others produce molecules that accelerate and excite signaling between brain cells, which defines them as 'excitatory neurons’. These definitions help researchers to classify neurons with identities.

As the CAG repeats stretched to 150 and beyond, the researchers found that MSNs began losing the genetic signatures of their cellular identity. Genes that should be off were on, and genes that should be on were off. The features that helped define them as MSNs were being eroded. Notably, in MSNs with ultra-long repeats, they found that the cells appeared to be turning on genes that cause cell death, perhaps providing a clue as to why this specific cell type is so vulnerable in HD.

Armadillo model

To explain their hypothesis, the authors describe their data as an armadillo-shaped curve. For our non-American readers, an armadillo is a small, armored mammal with a hard shell made of bony plates, native to the southern United States and South America. (Picture for reference.) They’re low to the ground, with a curved body, and long flat tail.



When brain cells acquire too many CAGs in their huntingtin gene, genetic programing goes awry - genes that should be off are on and vice versa. It seems the cells turn on genes programming them for death.

With the armadillo body shape in mind, the CAG lengths of most MSNs seem to fall under the curved body part of the animal during the initial decades of life. Once the cells get to about 80 CAGs, the expansions begin happening more rapidly, on the order of years. These few cells with increasingly longer CAG lengths fall under the long flat tail part of the armadillo. At 150 this process speeds up even further in this model, taking only months to acquire hundreds of more CAG repeats. It's only when CAGs reach a length of 150 or more that they start to see detrimental effects on the cells.

Armadillo schmarmadillo, what about people?

To describe their model of a slow acceleration in CAG expansion, the authors detail a hypothetical situation for someone who inherited 40 CAGs. They postulate that the first phase of expansion occurs slowly in MSNs, taking about 50 years to go from 40 to 60 CAGs. The next phase occurs a bit faster, taking about 12 years to expand from 68 to 80 CAGs. From there, the cell reaches a tipping point, where expansion occurs more rapidly. In just a few years a cell could go from 80 to 150 CAGs. After that, the expansion to hundreds of CAG repeats could occur in a matter of months. During this last phase, genetic identity of the MSNs is lost, and the cell begins turning on genetic programs leading to its death.

It's critical to note that this is a**hypothetical situation**. None of the time values stated here are set in stone and are only being used to describe this model. This does not depict an exact situation of what's happening to the MSNs in the brain of someone with 40 CAG repeats.

It's also important to know that this doesn't happen inside every MSN in someone's brain all at the same time. This is an asynchronous process, meaning MSNs will acquire additional CAG repeats at different rates, producing a mosaic of CAG repeat lengths. Timing here will also be highly dependent on environmental factors, lifestyle choices, and genetic modifiers, all known to contribute to the age of symptom onset.

> **"This new paper stands firmly in the second camp - that "HD pathogenesis is a DNA process", caused by instability in the genetic code brought about because of a tipping point in the number of CAGs in the HTT gene in certain types of cells. "**

Advancing what we know

This work challenges long-standing theories of some of the ways we think about HD. When protein aggregates were first discovered in the late 1990s, most researchers thought that those sticky protein clumps were causing the signs and symptoms of HD. Over the decades,

the thought in the field has broadened, where many researchers now feel various molecular components contribute to disease, including a component that's contributed by the genetic material itself.

This new paper stands firmly in the second camp - that "HD pathogenesis is a DNA process", caused by instability in the genetic code brought about because of a tipping point in the number of CAGs in the HTT gene in certain types of cells.

This is the first paper to deeply analyze these ultra-long CAG repeat lengths. Previous work could really only sequence the CAGs out to about 150 repeats. While we've known since 2003 that these ultra-long repeats exist, we just haven't been able to read the DNA sequence. It's actually technically quite challenging to get accurate sequences of very long stretches of repeating DNA letters!

The best time to treat HD

Armadillos have a new found use in Huntington's disease research. Their body shape reflects a new model in how some brain cells acquire CAG repeat expansions - with many cells slowly acquire repeats (represented by the round body of the armadillo) that speeds up as CAGs are added with few cells having hundreds of repeats (like the long flat armadillo tail).

Image credit: Victor Miyata

There's been rigorous debate about the best time to treat HD. Of course it's always easier to preserve something rather than trying to restore it. So general consensus has become that treating HD before symptoms appear would be the best time. But does that mean treating HD after symptoms appear wouldn't have any benefit?

Encouragingly, this new work suggests that approaches targeting somatic instability may be successful even after symptom onset. That's because CAG repeat expansion happens in neurons asynchronously. So even if some MSNs have acquired so many CAGs that they're already turning on genetic programs leading to their death, other MSNs haven't. Those are the ones that could be targeted to slow or stop HD progression.

What does this mean for HTT lowering?

The first potential disease-modifying approach out of the gate was HTT lowering. Afterall, we know the genetic cause of HD is expanded HTT, so it's a very logical approach to lower expanded HTT levels for therapeutic gain.

There's also lots of hope with other approaches, including targeting somatic instability. Lots of people are focusing on this area, and we'll undoubtedly see these approaches coming to the clinic soon. **But this doesn't mean we should abandon HTT lowering approaches!**

> **"These types of findings that challenge current thinking in the field are what drive research forward and take us in new scientific directions, helping to define truth in this disease and discover new treatments. "**

HTT lowering approaches had a rocky start, but we've recently received positive updates from several clinical trials suggesting that HTT lowering as an approach may be having clinical benefit. These studies are the first evidence we've ever had that something could be working to slow clinical signs of HD. So we definitely don't want to stop now!

Zooming out for clarity

For the HD community, it's important to remember that this type of deep molecular work is looking at cellular and molecular changes in a particular cell type. While the striatum is the most affected area of the brain by HD with MSNs certainly being the most vulnerable cell type, other areas of the brain and body are also affected by HD. Since this paper specifically looked at the striatum, we don't yet know if these same types of mechanisms related to somatic instability are also at play in other areas of the brain and body.

It would be nice if science were black and white, but unfortunately it's not. Somatic instability does seem to be a key in understanding HD, but it's likely not the only driver of disease. There are likely various biological mechanisms contributing. Other work suggests that ultra-long CAG repeats aren't causing death of cells in the cortex (the wrinkly outer bit

of the brain). Since this part of the brain is also affected by HD, it suggests that somatic instability isn't the *only* thing we should focus on. So diversifying therapeutic approaches, like with HTT lowering as well as targeting somatic instability, is our best bet.

And finally, we'd be remiss if we didn't mention the people and families who made the selfless and generous decision to donate their brains to advance this research - **thank you!** These types of findings that challenge current thinking in the field are what drive research forward and take us in new scientific directions, helping to define truth in this disease and discover new treatments. That all relies on the strong partnership we have between the researchers and the HD family community.

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

GLOSSARY

blood-brain barrier A natural barrier, made from reinforcements to blood vessels, that prevents many chemicals from getting into the brain from the bloodstream

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

aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

nucleus A part of the cell containing genes (DNA)

neuron Brain cells that store and transmit information

somatic relating to the body

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
