

# How many is too many? Exploring the toxic CAG threshold in the Huntington's disease brain

New work from researchers in London uses mice to narrow in on the number of CAG repeats needed to cause symptoms of Huntington's disease. Their work points to fewer than 185 CAGs as a threshold.

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rug hunters have been particularly interested in the repeating C-A-G letters of genetic code that lead to Huntington's disease (HD). The number of CAG repeats gets bigger in vulnerable brain cells over time and may hold the key for slowing or stopping HD. Many scientists have been asking what happens to HD symptoms if we stop this expansion. Recent work from a group in London led by Dr. Gill Bates examined exactly this, seeking to define the threshold of CAG repeats needed to cause disease. Let's discuss what her team found!

### We're all just alphabet soup

The genetic code of every living organism is made up of only 4 letters – C, A, G, and T. They're combined in different ways to make every gene in our body. That's a lot of diversity for just 4 letters!



The CAG repeat that causes HD gets bigger over time in some cells, like vulnerable brain cells. Some researchers think that if we can control the expanding CAG repeat, we may be able to stop HD.

Within the huntingtin gene that leads to HD is a stretch of repeating C-A-G letters. People 1 / 4

with HD are born with 36 or more CAG repeats in the huntingtin gene. As a person grows older, we know the number of CAG repeats can shift and wobble in some cells, getting bigger over time.

This ongoing CAG expansion is called "somatic instability". This specifically happens in brain cells damaged by HD. It's important to note that the CAG repeat size is relatively stable in blood. So a blood test showing 42 CAGs at the age of 18 will very likely still show 42 CAGs at age 50. But the brain cells of that person could have more than 100 CAG repeats, and a few may even have 200 repeats or more.

## **Expansions may be the key**

Some scientists think that preventing CAG repeats from increasing in the brain may be key to stopping HD altogether. But no one knows how many CAGs are too many in the brain, or at what age CAG increases start to happen.

Several important genetic studies in the past few years have suggested that longer CAG repeats could help explain why brain cells die in HD. For example, people who develop HD earlier or later than expected have changes in genes that impact somatic instability of the CAG repeat in huntingtin. These genes are called "modifiers" – they modify the age at which someone starts to show symptoms of HD.

"Some scientists think that preventing CAG repeats from increasing in the brain may be key to stopping HD altogether."

What's interesting is that modifier genes mostly participate in the same process in the body, called mismatch repair, which is known to affect somatic instability of the CAG repeat. Very suspicious! This suggests that somatic instability of the CAG repeat is pretty important in HD.

Since somatic instability in brain cells may contribute to how these cells die, and since mismatch repair genes impact somatic instability, HD researchers are now very interested in drugs that target mismatch repair genes. Perhaps by targeting the right mismatch repair gene, we can stop somatic instability of the CAG repeat in vulnerable brain cells. The hope is that a drug which does this could slow or stop HD.

### A numbers game

It turns out that we *can* stop somatic instability in the brain! At least we can in mice, for right now. Several pharmaceutical companies are developing HD drugs targeting mismatch repair genes and somatic instability in HD (for example, LoQus23, Rgenta, and Voyager Pharmaceuticals).

But no one really knows how long a CAG repeat must be to damage brain cells, or how early you might need to stop somatic instability in people as a treatment for HD. Recent studies in HD mice have tried to help answer these questions by looking at the impact of stopping somatic instability in HD mice with different CAG repeat lengths.



Researchers across the globe are working to halt CAG expansions. Understanding exactly when to halt and how long the CAG repeats can be before they cause disease will be critical for designing trials.

What's helpful about HD mice is that they are born with many more CAG repeats than people with HD – because HD researchers want mice to develop symptoms of HD much faster than people do. For example, a type of mouse that models HD called "Q111" has over 100 CAG repeats. Another HD mouse model called "Q175" has about 185 CAG repeats. Both the Q111 and Q175 HD mice show symptoms of HD in less than a year.

#### **Defining the threshold**

Researchers think this threshold of about 100 CAGs may be the number of repeats needed to kill brain cells in people with HD. So what happens if you stop somatic instability in these HD mice? Do the mice get better? The answer for mice born with 185 CAG repeats, surprisingly, is no. They still develop HD, even when somatic instability is halted.

In a newly published study from the lab of Dr. Gill Bates at University College London, Q175 mice having about 185 CAG repeats were altered so that they didn't have the mismatch repair gene MSH3. MSH3 is a high priority target for HD drug hunters since somatic instability stops altogether when MSH3 is gone.

As expected, somatic instability stopped almost completely in the brains of Q175 mice when MSH3 was eliminated. But these mice *still* developed features of HD, even though MSH3 was eliminated and somatic instability of the CAG repeat was halted.

What could this mean? Shouldn't stopping somatic instability prevent the mice from developing HD? Gill's group reasons that mice born with 185 CAG repeats already have too many repeats in the brain, so stopping expansions below 185 CAG will probably be necessary to treat HD in people.

"So stopping somatic instability in brain cells before they reach 100 CAG repeats may be necessary for this strategy to work in people."

This parallels the conclusions of a previous study which eliminated MSH3 in Q111 mice that have 100 CAG repeats, fewer than the 185 CAG repeats studied by Gill. In this other study, Dr. Vanessa Wheeler showed that Q111 mice without MSH3 have no somatic instability and have improved cellular markers of HD. So stopping somatic instability in brain cells before they reach 100 CAG repeats may be necessary for this strategy to work in people.

#### When should we treat HD?

This begs the question many people are asking lately: when should we treat HD? How early would a person with HD need to be treated to stop their brain cells from expanding across the threshold of 100 CAG repeats? Some brain cells appear to have 100 CAG repeats before people start to show measurable symptoms of HD. So it may be necessary to treat people even before they start to develop symptoms.

Treating people before they develop symptoms of HD poses lots of difficult questions that no one quite has the answers to yet. However, many brilliant scientists are now looking at CAG repeats directly in brains of people with HD to find answers. These insights detailing the threshold of CAG toxicity will help scientists to design better drugs and upcoming clinical trials to target somatic instability as a potential HD therapy.

Sarah is an employee of the Hereditary Disease Foundation, for which a researcher on this article sits on the Scientific Advisory Board. <u>For more information about our disclosure policy see our FAQ...</u>

#### **GLOSSARY**

**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

somatic relating to the body

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