Navigating the Genetic River: How Tiny Variants Could Shift the Course of Huntington's Disease

Hidden twists in the Huntington's disease gene could shift symptoms by over a decade! Scientists have uncovered rare "genetic dams" that shape when HD begins - sometimes dramatically

By Dr Sarah Hernandez | **May 11, 2025** | **Edited by Dr Rachel Harding**

Imagine the gene that causes Huntington's disease (HD) as a vast river. At its source is the CAG repeat - a genetic letter code that dictates how the river will flow. As the river moves downstream, it transitions into the letter code CCG, forming a continuous current. But what if, hidden beneath the surface, tiny genetic changes interrupt these codes to act like dams or rapids, altering the speed and course of the river? These rare changes can impact when and how HD symptoms appear, sometimes with the potential to shift the disease timeline by over a decade.

CAGs and the Flow of Proteins

To understand the role of these genetic interruptions, we need to take a step back and look at what genetic sequences actually do. Our DNA is like a set of instructions, written in a four-letter code (A, T, C, and G). Specific sequences of these letters form codons - three-letter words that tell the cell which amino acids to use when building proteins. Amino acids are the building blocks of life, like stones forming a riverbed, shaping the flow of biological functions.

Our genetic code is made up of the letters A, T, C, and G, strung together in various

combinations. Small changes in this code make each of us unique, but other changes can lead to diseases, like Huntington's.

Image credit: MIKI Yoshihito

The huntingtin (HTT) gene, which carries the instructions for HTT protein, contains a repeating sequence of CAGs. We all have this repetitive CAG stretch within our HTT gene. Each CAG tells the cell to add an amino acid called glutamine. In people with HD, the CAG stretch is too long. This creates an excess of glutamines that change the HTT protein's behavior.

Most of the time, a genetic test provides a definitive answer - if someone has 35 or fewer CAG repeats in their HTT gene, they won't go on to develop HD. If someone has over 40 CAG repeats in their HTT gene, they should go on to develop HD if they live long enough, and they have a 50% chance of passing the gene on to their children. But there's actually a bit more nuance to the genetics:

- **27-39 CAGs:** The "gray zone". With CAG lengths in this range, there's an increased risk that future generations could develop HD, and some people themselves may develop symptoms, while others won't.
- **27-35 CAGs:** People in this range likely won't go on to develop HD, but they have an increased risk of their children developing HD.
- **36-39 CAGs:** Some people in this range will develop symptoms of HD, while others won't. So far, the research suggests this could be controlled by things like lifestyle factors, genetic modifiers, or other variables we haven't yet figured out.

CCG and Proline: Rocks in the River

We talk a lot about the CAG repeat in HD research, since this is the genetic change that leads to the disease. But there's actually a second set of repeating letters within the HTT gene. Right after the CAG repeat stretch, there's a repetitive sequence of CCG letters, which code for the protein building block proline.

Proline often acts like a bend or kink in the protein's structure, similar to how submerged rocks can disrupt the smooth flow of water. Some studies suggest that having more CCG repeats near the CAG stretch may slightly alter how the huntingtin protein folds or interacts with other molecules in the cell. However, the exact function is not fully understood.

> **"For most people from HD families, this granular level of genetic detail isn't necessary - standard genetic testing, which measures the CAG repeat length, provides enough information to predict risk. "**

Until now, the CCG proline stretch likely wasn't on the radar of HD families. Researchers have long known it was there, but its potential role in influencing disease onset or progression wasn't clear. Only recently have scientists begun to recognize that this genetic feature might subtly shape the course of HD, much like an unseen current beneath the

surface of a river.

When the Dam Breaks - LOI Variants

In most people, as the genetic river flows, the CAG region usually includes a small change - CAA. CAA is a synonymous switch to CAG, meaning it also codes for glutamine. Though CAA and CAG both lead to the same amino acid, CAA acts like a natural dam, stabilizing the sequence and keeping the river's flow more stable.

But in *rare* cases, these interruptions are lost - this is what scientists call Loss of Interruption (LOI) variants. For example, without the CAA interruption, the uninterrupted CAG section is longer, making the river flow more forcefully.

In new work from the lab of Dr. Michael Hayden at the University of British Columbia, researchers suggest that this could be leading to earlier onset of HD symptoms.This work has identified four types of LOI variants:

- **CAG-CCG LOI:** This accounts for a longer, uninterrupted stretch of both glutamines (CAG) and prolines (CCG). Losing interrupters in both the CAG and CCG repeat sequences seems to be the most impactful, potentially shifting symptom onset an average of 12.5 years earlier.
- **CCG LOI:** Some people only lose an interruption in their proline-encoding CCG repeat sequence, while maintaining a CAG glutamine interruption. Surprisingly, this also potentially altered onset by about 12.5 years.
- **CAG-LOI:** Conversely, some people maintain their proline-encoding CCG repeat interruption, but lose the glutamine-encoding CAG repeat interruption. This was a potential early-onset factor, with an estimated 6.9-year shift. However, the researchers couldn't say for sure that this genetic variant was the factor that impacted age of onset. The authors suggest the issue in pinpointing how this LOI impacts symptom onset is probably due to the limited number of people they found with this change.
- **CAG interruption duplication:** A completely different genetic change they found was a duplicated interruption. So instead of having one CAA interrupt the glutamine-encoding CAG repeats, there were at least 2. Their findings here were particularly surprising. Contrary to what would be expected based on the loss of interruption data, they found that this duplicated interruption *also* accelerated disease onset, potentially by about 3.8 years. While this doesn't seem to match with interruptions delaying onset, it does suggest we don't fully understand exactly how these particular changes in the genetic code of the HTT gene contribute to HD.

Within the gene that causes Huntington's disease, some genetic letters act like a dam, helping to regulate and control the genetic message. New research suggests that in rare cases when these genetic dams are lost, onset and progression of the disease may accelerate, like a river undammed.

Image credit: ciboulette

A Rare but Important Discovery

It's important to remember that the variants with the largest impacts examined in this study are exceedingly rare. For example, **the CAG-CCG LOI is found in only 0.04% of people with HD**. So the change in symptom onset being measured in this study was found in only a small subset of people with HD - primarily in those whose CAG repeat number placed them in the gray zone. The vast majority of individuals with HD have a typical pattern of interruptions, meaning their diagnosis and prognosis wouldn't change even if they were tested for LOI variants.

However, for those on the edge of the diagnostic spectrum, these variants could provide new insight into why some people with a borderline CAG length develop symptoms while others don't. This discovery also highlights the complexity of HD genetics - showing that even small changes in the genetic river's flow could have significant effects downstream.

Why Does This Matter?

For most people from HD families, this granular level of genetic detail isn't necessary - standard genetic testing, which measures the CAG repeat length, provides enough information to predict risk. Right now, for the vast majority of HD families, knowing about interruptions in the CAG (glutamine) or CCG (proline) repeats can't offer any additional medical or social support.

However, for those with an intermediate number of CAG repeats, between 36 and 39 CAG repeats, the presence of an LOI variant could be the difference between developing HD or not. These individuals are in the "gray zone", where some will develop symptoms, and some

won't. The authors of this new work suggest that understanding whether individuals in the gray zone have an LOI variant could provide a clearer picture of their risk of developing HD.

> **"For now, the key takeaway is that these variants are scientifically fascinating and could offer insight into the underlying mechanisms of HD. However, for the majority of people with HD, they remain a niche concern. The fundamental driver of HD is still the length of the CAG repeat. "**

For example, someone with 37 repeats who also carries an LOI variant may be more likely to develop HD than previously thought. Conversely, someone with the same CAG length but no LOI variant may have a lower risk than the raw number suggests. However, it's important to note that standard genetic tests for HD only measure CAG repeat length, but don't typically detect these LOI variants. So this isn't data that's readily accessible to most people.

The Future of Precision Genetics in HD Research

As research progresses, scientists are working toward more personalized approaches to HD diagnosis and treatment. Understanding LOI variants may help refine risk predictions, offering clearer answers to individuals in the gray zone with 36 to 39 CAG repeats. In the future, it's possible to imagine that treatments could even be tailored based on these genetic details, much like adjusting a dam to regulate water flow.

For now, the key takeaway is that these variants are scientifically fascinating and could offer insight into the underlying mechanisms of HD. However, for the majority of people with HD, they remain a niche concern. The fundamental driver of HD is still the length of the CAG repeat. But by exploring these rare variants, researchers are learning more about what makes HD flow. Just as rivers carve landscapes over time, genetics shape the course of HD in ways both predictable and surprising. Understanding these hidden currents can help us navigate toward better diagnostics, treatments, and ultimately, a cure.

If you have questions about your own or your family's genetic test results, we recommend speaking with a genetic counselor or healthcare provider.

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

GLOSSARY

huntingtin protein The protein produced by the HD gene.

amino acid the building blocks that proteins are made from

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

glutamine the amino acid building block that is repeated too many times at the beginning of the mutant huntingtin protein

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