Steadying genetic stumble could help slow Huntington's disease

Using CRISPR technology, scientists uncovered genes that control C-A-G genetic stumbles in Huntington's disease

By Dr Nicholas Caron | February 11, 2025 | Edited by Dr Rachel Harding

---

A new paper led by researchers at the Massachusetts General Hospital and Harvard Medical School used CRISPR to work out which genes can influence how the genetic C-A-G repeat that causes Huntington's disease (HD) can change over time. This exciting study helps us to better understand how HD works and uncovers some potential targets for therapies that could slow or halt the disease.

Genetic Stumbles Can Increase C-A-G Repeats

HD is a genetic brain disorder and everyone who has HD has an expansion of the C-A-G DNA letters in their HD gene, also called huntingtin or HTT. Over time, these C-A-G repeats can become even longer in some types of brain cells. This process is called somatic instability or more specifically somatic expansion. But somatic expansion doesn't occur in all cells. This phenomenon appears to occur more so in medium spiny neurons, the type of cells that are most affected in HD.

CRISPR is a powerful tool that acts like a tiny molecular Swiss army knife in the cell to cut and edit DNA

The topic of somatic instability has been trending in the HD field, as it is suggested to be a key driver of disease that may accelerate the age at which symptoms first appear. This is supported by large genetic studies in people with HD, which suggest that genes responsible for proofreading the genetic code can affect somatic instability.

Billions of DNA Pieces: The Puzzle of Life

Every cell in the body carries a complete set of DNA instructions, which act like a blueprint for making everything the body needs to grow, function, and stay alive. You can think of DNA like a twisted ladder, and its two strands are the sides of the ladder. The rungs of the ladder are made up of building blocks, known as A (adenine), T (thymine), C (cytosine), and G (guanine). These act like puzzle pieces that pair up in a very specific way: A always pairs with T, and C always pairs with G.

The DNA in each of our cells contains billions of these letters, so as you can imagine, sometimes there are mistakes or mismatches in the DNA puzzle leading to two pieces being paired up that don't fit together properly. Luckily our cells have repair systems that work like mini-puzzle masters, scanning for these mistakes, removing the wrong piece, and replacing it with the right one so the puzzle or DNA fits together perfectly again.

When it comes to long C-A-G repeats in the huntingtin gene, sometimes, the two DNA strands can shift or "slip". DNA slips in C-A-G repeat regions are like buttoning your shirt but skipping a button—causing a bulge that disrupts the whole pattern. This happens because the C-A-G sections of DNA are like identical puzzle pieces that can stick together in the wrong way.

> **"DNA slips are like buttoning your shirt but skipping a button, causing a bulge that disrupts the whole pattern. "**

If this happens, a loop of extra CAGs can form in one strand DNA. Since the DNA repair systems are always checking for mistakes, when they notice the loop of extra CAGs, they try fix it. But instead of removing the extra CAGs, it sometimes "corrects" the strand by adding more repeats to make everything match. This leads to expansions of the CAG repeat in huntingtin.

Measure Twice, Cut Once: Using CRISPR To Uncover Genes Behind Genetic Stumbles

In this paper, the researchers used CRISPR to turn-off specific genes in a mouse model of HD. CRISPR is a powerful tool that acts like a tiny molecular Swiss Army knife in the cell to cut or edit any DNA as long as there is a "homing" signal (or PAM site) nearby. Luckily these

homing signals are found nearly everywhere in the genome, so researchers are finding cool ways to use CRISPR to edit literally any gene in the cell!

This tool is being used to correct typos in genes, including the huntingtin gene in HD. It can also be used to turn-off certain genes, which reduces the amount of protein they make.

The researchers focused on genes involved in cell's DNA repair systems, since prior studies have suggested that some of these genes play an important role in controlling the stability of C-A-G repeats, either by making them longer or shorter.

They used CRISPR to turn-off more than 50 of these genes in HD mice and then measured the effect on C-A-G repeat changes in the striatum, the part of the brain most affected in HD, as well as in the liver.

When certain genes were turned off by CRISPR, the expansion of the Huntington's disease C-A-G repeat slowed

Expanding and Contracting: How DNA Repair Genes Play CAG Repeats Like an Accordion

The study confirmed that several genes in the DNA mismatch repair pathway, such as MSH2, MSH3, and MLH3, make proteins that can enhance expansion of the C-A-G repeat. When these genes were turned off, less of these proteins were made and the expansion slowed significantly. This emphasizes the potential of targeting these proteins as drug targets for HD.

On the other hand, switching off certain genes, like FAN1 and PMS2, made C-A-G repeats expand faster. This suggests that boosting the production of these proteins could help slow down C-A-G expansion.

Interestingly, turning off DNA repair genes had different effects depending on the tissue. For example, some genes caused more C-A-G repeat expansion in the liver than in the striatum. This shows why it's important to study these changes in the tissues most affected by the disease.

This study shows how powerful CRISPR can be for testing genes that affect C-A-G repeat instability directly in living animals. It allows scientists to study dozens of genes at once, something that wasn't possible before.

> **"The findings of this study help us better understand what drives HD and point to new potential drug targets that could slow C-A-G expansion and delay symptoms. "**

'Harness'-ing C-A-G Expansions

The findings help us better understand what drives HD and point to new potential drug targets that could slow C-A-G expansion and delay symptoms. In fact, there are lots of folks doing exactly that right now!

Rgenta Therapeutics and LoQus23 Therapeutics are two companies developing pills that aim to turn off production of proteins that make the C-A-G repeat longer, which could help slow down somatic expansion in the brain.

Another company, Latus Bio, is planning to use harmless viruses to deliver DNA-like molecules, known as microRNA, that can lower levels of a protein that can increase somatic expansion.

Harness Therapeutics is working on developing specialized DNA molecules, known as antisense oligonucleotides or ASOs, that are designed to boost production of FAN1, a protein that can actually make the C-A-G repeat shorter.

These treatment approaches are still in the research stages so be sure to check HDBuzz for updates as these programs move along.

Nicholas Caron is a paid employee of the University of British Columbia and Incisive Genetics, Inc. Rachel Harding has no conflicts to declare. For more information about our disclosure policy see our FAQ...

GLOSSARY

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

therapeutics treatments

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

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

CRISPR A system for editing DNA in precise ways

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