

Regulating repetition: Gaining control of CAG repeats could slow progression of Huntington's disease

Many diseases are caused by repetitive DNA sequences. Understanding the regulation of those repetitive sequences may hold the key for unlocking therapeutics for Huntington's disease. A team from Toronto has just advanced our understanding.



By [Dr Sarah Hernandez](#)

November 30, 2023

Edited by [Dr Jeff Carroll](#)

“Somatic expansion” is a hot topic in Huntington's disease research. Somatic expansion is a process in which CAG repeats lengthen in some cells during aging. It's thought to control how early HD symptoms appear. A group of researchers from Toronto, Canada recently identified proteins that may play an important role in regulating this process. Understanding how these proteins regulate somatic expansion in Huntington's disease may hold the key for unlocking therapeutics for CAG repeat diseases.

Repetition is (the) key

Huntington's disease (HD) is referred to as a “CAG repeat expansion disease” – it's caused by an increase in the number of CAG repeats in the huntingtin gene. Everyone has the huntingtin gene – in fact, everyone even has a repetitive CAG sequence within their huntingtin gene. It's just that people who will go on to develop HD have *more* CAGs within the huntingtin gene compared to people without HD.



The CAG repeat that causes HD gets bigger in brain cells over time – something called “somatic expansion”. Understanding the protein players behind somatic expansion could

But HD isn't the only disease caused by CAG repeats. There are over 70 different diseases associated with nerve cell breakdown that are caused by repetitive DNA tracts! In a way, this is good, because we can look to the research in these other diseases and find similarities to learn more about HD.

One thing in common with many of these diseases caused by repetitive DNA tracts is something called "somatic instability", also called "somatic expansion". This is a biological phenomenon where a repetitive DNA track gets bigger in some cells as the person ages. This ongoing expansion of the disease-causing CAG tract in HD is thought to contribute to accelerated disease progression. HDBuzz recently wrote about somatic expansion, [which you can read about here](#).

For HD, somatic expansion of the CAG repeat tract in the huntingtin gene preferentially happens in brain cells. Specifically in brain cells that are vulnerable to dying as someone with HD ages. Emerging scientific research seems to suggest that if we can get a handle on the perpetual expansion of CAGs in the huntingtin gene, we may be able to keep brain cells healthy and delay when symptoms appear. In a perfect world, even pushing that into the realm of never. But to do that, we first have to understand the intricate biological details behind somatic expansion in HD.

How exactly do CAGs get added?

DNA is made up of 2 complementary strands of genetic material, creating a double helix. This may conjure up images of a gently turning, intertwined ribbon from 8th grade biology. Each strand contains letters of the genetic code – C, A, G, or T – that interlock with the genetic code on the complementary strand like Lego pieces.

“Emerging scientific research seems to suggest that if we can get a handle on the perpetual expansion of CAGs in the huntingtin gene, we may be able to keep brain cells healthy and delay when symptoms appear.”

When cells need to make a protein coded by a certain gene, the DNA strands are unwound, and the Lego pieces are unlocked. After the protein is made, the DNA strands snap back together, with complementary strands finding their original alphabetic partners.

However, when the DNA contains a repetitive sequence, like a long strand of CAGs repeated over and over, it can be difficult to discern exactly which Lego piece went where. This can cause some of the genetic code to misalign and match with the complementary strand ahead of where it should. This creates a loop-out structure – one strand is nice and straight, and the other has a looped-out piece of DNA with no mate. This is a big no-no in cell biology...

There's a reason your mind conjures the smooth-sided, intertwined ribbon when "double helix" is mentioned. DNA strands *always* bind to their complementary mate. DNA is never single stranded. When it is, proteins immediately intervene, chopping out or adding DNA to the looped-out structure that threatens the elegant, softly twisted natural form of DNA.

Often, to ensure that DNA strands once again perfectly match with their alphabetic mates, additional letters are added – like adding additional Legos to make sure each aligns with the matching pieces on the other side. This ensures that both DNA strands have matching mates on each side. For the huntingtin gene, this can mean that additional CAG repeats are added, and the CAG repeat expansion gets longer. The result is often earlier onset of HD symptoms. Understanding how the cell decides whether to chop or add DNA letters to a loop out structure could be the key to understanding somatic expansion, and to controlling it.

Cellular editing decisions defined



If every DNA building block is represented by a different color Lego, they're easy to match up if you pull the two strands apart. But when you have 35 or more of the same color in a row, you might lose track of exactly which Lego went with the other after they're separated. The same is true when DNA comes apart and reforms – repetitive DNA tracts can get misaligned.

Researchers at the Hospital for Sick Children (SickKids) in Toronto, Canada recently identified proteins that play a key role in the cellular decision process of chopping or adding DNA to loop outs. This work, spearheaded by Dr. Terence Gall-Duncan and led by Dr. Christopher Pearson, was recently published in the prestigious scientific journal *Cell*. The work from the team at SickKids adds to our understanding of somatic instability in HD while identifying proteins that could be targeted for therapeutic gain.

The team broke down the science behind a protein called RPA – replication protein A. The job of RPA in the cell is to bind to DNA when the helix is unwound and it's single stranded. There's a different version of RPA that is unique to humans and monkeys, creating an alternative version of RPA called Alt-RPA. Both versions, RPA and Alt-RPA, bind to DNA loop-outs, like the ones that are created when CAGs in the huntingtin gene can't find their mate when DNA strands are separated.

The experiments in this new paper show that when cells have more Alt-RPA, CAG expansions get bigger. But when the standard version of RPA is present, fewer CAG expansions are added. So it seems that Alt-RPA controls the cellular decision to add DNA to loop-outs while RPA decides to chop!

Something else interesting about this finding is that Alt-RPA is only found in monkeys and humans, with very strong levels found in humans – the only species to have HD. This may be a start to understanding why HD specifically and only affects humans.

The team did a large-scale interaction study to identify other proteins with which RPA and Alt-RPA were interacting. They found that Alt-RPA specifically interacted with proteins that regulate CAG repeat instability! One of the most striking proteins identified that specifically interacts with Alt-RPA was MSH3.

“They found that Alt-RPA specifically interacted with proteins that regulate CAG repeat instability!”

MSH3 is a major regulator of age of symptom onset in HD and was originally identified from samples given by thousands of HD families for a study called Gem-HD. Having lots of samples from HD families, from studies like GeM-HD and Enroll-HD, has rapidly advanced the identification genes that modify age of symptom onset, like MSH3. This new work from the group at SickKids may be the link for understanding *how* MSH3 helps to control somatic expansion in the huntingtin gene.

The team tested the effect of changing levels of RPA in mice that model a disease similar to HD – spinocerebellar ataxia (SCA1), which is also caused by a CAG repeat. When they increased levels of the standard version of RPA, the SCA1 mice's symptoms improved, including the instability of its CAG repeats.

What does this all mean for HD?

There are several companies currently working on drugs as a treatment option for HD that target MSH3 as a modifier associated with somatic instability. Voyager Therapeutics is working to develop a harmless virus that targets MSH3 that can be injected into the blood to reach the brain. LoQus23 Therapeutics is working to target MSH3 using small molecules that could be taken as a pill. Pfizer has also jumped on the MSH3 bandwagon and is testing drugs to move toward clinical trials.

These new results from the team at SickKids don't mean that we're ready to add RPA or Alt-RPA to the drug lineup just yet though. This work still needs to be tested in mice that model HD to see if changing these proteins can improve behavior and molecular effects associated with HD. However, they do get the research world closer to understanding the precise mechanism that controls somatic instability. Knowing exactly how the cell makes the decision to add or chop DNA when a loop out structure is formed opens the door for designing more drugs to test in trials, not just those that target MSH3.

Sarah is an employee of the Hereditary Disease Foundation, which has provided or is providing funding to several researchers listed on this publication. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

spinocerebellar ataxia A family of diseases which result in characteristic movement disorders. Many types of spinocerebellar ataxia are caused by the same type of mutation as HD – a CAG expansion.

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

somatic relating to the body

© HDBuzz 2011-2024. HDBuzz content is free to share, under a Creative Commons Attribution-ShareAlike 3.0 Unported License.

HDBuzz is not a source of medical advice. For more information visit hdbuzz.net

Generated on May 04, 2024 — Downloaded from <https://en.hdbuzz.net/353>