When genes are unstable: targeting somatic instability in HD

CAG repeats expand in some parts of the body and brain as people with HD get older, a phenomenon known as somatic instability. Learn more about how researchers are exploring somatic instability and DNA repair to design therapies for HD.

By Dr Rachel Harding and Dr Leora Fox | **September 08, 2020**
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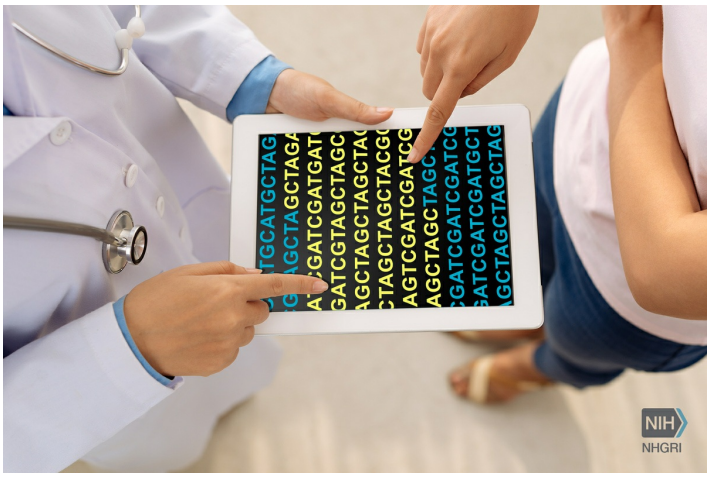
What is somatic instability?

We tend to think of DNA as a fixed blueprint, an overarching plan for the biological bricks and bridges that constitute our cells, organs, and bodies. But like any good plan, DNA is actually dynamic and adaptable. It gets frequent use as a template for creating the RNA messages that pave the way for the proteins we are made of. For this reason, DNA requires constant checking, maintenance, and repair. In fact, our cells have an entire workforce of DNA repair proteins whose main job is to ensure that our DNA is in top condition.

But sometimes the repair team makes mistakes. This is especially true when there's already a problem with the DNA – like the HD mutation, an extra-long stretch of CAG repeats in the huntingtin gene. Lengthy repeating sections of DNA can be harder to maintain. Have you ever tried to re-fold a large city map, only to end up with a bundle of paper twice as big as what you started with? When DNA repair goes awry, repeating sections of the DNA code can become unstable. In the case of Huntington's disease, this means that over a person's lifetime, the already-expanded HD gene gains even more CAGs, in certain cells of the brain and body. This phenomenon is known as somatic instability.

The more repeats in the huntingtin protein, the more likely it is to perform poorly, form toxic clumps in brain cells, and disrupt other normal functions. So the formation of longer and longer huntingtin proteins could be part of the reason that HD affects people more as they get older. In the past few years, large genetic studies have confirmed that HD symptoms may begin earlier due to somatic instability. HD scientists are now digging even deeper into the questions of when, where, and why somatic instability occurs. Armed with that knowledge, they have begun to develop the tools and drugs to combat CAG repeat expansion, and new companies have formed with the goal of testing therapies in people with HD.



By targeting DNA repair, researchers hope to stop or slow somatic instability and therefore delay symptom onset or progression.

Image credit: Darryl Leja, NHGRI

When does somatic instability occur?

Since HD has a known genetic cause (extra CAG repeats in the DNA code), adults can choose to get a blood test if they wish to confirm that their symptoms are a sign of HD, or want to learn whether they will experience symptoms later in life. This test reveals the number of repeats in the person's huntingtin gene. Since everyone inherits two copies of every gene, one from each biological parent, a person with HD will almost always have one "normal" CAG number (10-26), and one "expanded" CAG number (around 36-40 or higher). Those gene copies are found in every single cell of the body, and the expanded copy is what causes HD. If you want an in-depth refresher on the meaning of different CAG numbers, check out this previous HDBuzz article.

Because long CAG repeats can be unstable, a child who inherits an expanded copy of the HD gene from their parent doesn't necessarily inherit exactly the same number – sometimes dad has 40, and his son has 41, and his daughter has 48. CAG repeat length influences age of onset, so these closely related family members might start to experience symptoms at very different ages. Changes in CAG repeat number from generation to generation are sometimes known as "germline instability."

Somatic instability is a bit different, because it occurs during the course of an individual's lifetime, and only in certain parts of the body and brain. For example, a 25-year-old person with HD might get a blood test that shows 42 CAG repeats. If they were to repeat the test many years later, their blood would probably still show 42 CAG repeats. That's because somatic instability of CAG repeats doesn't happen frequently in blood cells. It would be too dangerous to test parts of people's brains while they are alive, but scientists can investigate somatic instability in the brain thanks to the extraordinary people who have donated their brains to HD research. Now we know that a person with HD whose blood test showed 42 repeats as a young adult, may at the time of their death thirty years later have some cells in the brain with 45, 60, 100, or even 1000 CAG repeats.

What genes influence somatic instability – and why do we care?

In the past few years, genetic studies of thousands of people with HD have clued us into several important facts about somatic instability and DNA repair. One finding is that continued expansion of CAG repeats in an individual could cause symptoms to come earlier than expected. Another important discovery is that single-letter differences in DNA repair genes can influence the age of onset of HD. One big study a few years ago showed that people with slightly different versions of a DNA repair gene called FAN1 had huge differences in when their HD symptoms began.

> **"Observational studies are essential in planning drug trials, helping researchers make informed decisions about when treatments should be given to patients and what regimens should be followed. "**

FAN1 normally contributes to DNA repair by helping to separate strands of the double helix that have gotten sticky. Without FAN1, the machinery that copies DNA seems to get stuck at CAG repeats and can accidentally add extra ones. A study published in June of 2020 dove deeper into FAN1 and its role in HD. The experiments were carried out by a consortium of HD geneticists in the US and UK, and led by Dr. Jong-Min Lee at Harvard Medical School. They found that depending on what form of the FAN1 gene a person has, there might be more or less FAN1 protein, or it might be slightly better or slightly worse at its repair job. Normally these miniscule genetic differences in FAN1 don't matter, but when a person has HD, excellence in DNA repair is critically important. People with certain forms of FAN1 had much earlier or much later onset of symptoms than would be expected.

In addition to FAN1, there are a variety of other genes found to influence the age of onset of HD, all known as "genetic modifiers". Right now, these genetic variations are NOT something that an HD specialist or genetic counselor can test for. However, the recent study suggests that screening people with HD for FAN1 and other genetic modifiers of symptom onset might be useful in the future. This personalized approach could help to better predict an individual's onset or progression, or make it possible to run smaller, faster clinical trials with a more uniform set of participants. Importantly, a better understanding of the influence of FAN1 and other DNA repair genes on HD is already leading to new therapeutic strategies to improve DNA repair and slow CAG repeat expansion. None of this is possible without the participants who donate their time, energy, and blood samples to observational studies like Enroll-HD.

Where does somatic instability happen?

Somatic instability is happening to a certain degree in every part of our body, but the levels do vary widely between different types of cells. For example, cells in our blood have low levels of instability which is why the genetic test (which uses a blood sample) may give the

same result if taken repeatedly in an HD patients lifetime, even if instability is going on elsewhere.

Recent studies have completed more extensive analysis of how much somatic instability is going on in different parts of our bodies and even breaking down the precise levels of instability in particular regions of our brains. In an international collaboration between Harvard (USA) and Bochum (Germany), Drs. Vanessa Wheeler, Ricardo Mouro Pinto, Larissa Arning and team recently showed that specific regions of the brain, called the cortex and caudate, have the highest levels of instability in the CAG repeat of the HD gene. This analysis was possible thanks to donations of HD patient brains after they had passed. Interestingly, this team also showed that other genes which have CAG repeats, like the genes associated with spinocerebellar ataxia (SCA) diseases, also have instability in the cortex and caudate.

Beyond our nervous systems, it seems that the liver and testes have the highest levels of instability. When Mouro Pinto and colleagues looked at HD patient spinal fluid samples, they could observe instability there too, although at fairly low levels. Measuring instability levels in a living patient's brain is currently impossible to do safely, so scientists are keen to find a good proxy by measuring other tissue samples. It seems that the levels of instability in the spinal fluid, although low, are a potentially good readout for overall instability levels in a patient and could be another good biomarker for healthcare practitioners to monitor disease progression.

Normally, minuscule genetic variations don't matter, but in HD, they can be critically important.

Image credit: Rachel Scopes

How can we target somatic instability to treat HD?

Scientists researching HD have known for a long time now that the levels ofsomatic instability in a patient will influence the age when disease symptoms start. The hypothesis is that increased levels of somatic instability will lead to longer CAG repeat lengths which in turn will mean that disease symptoms will start earlier. If researchers can find a way to lower the levels of instability, this may be a good strategy for making new medicines for HD.

Datasets published in the last ~5 years, which look at other genetic factors influencing HD, have shone a light on why instability might be higher in some patients than others. If patients have single letter changes in proteins like FAN1, it is thought that their levels of instability will change, and therefore the age of onset for symptoms will also change. If we can target some of these so-called modifiers of HD, we might be able to prevent expansion or even shrink the CAG repeat length.

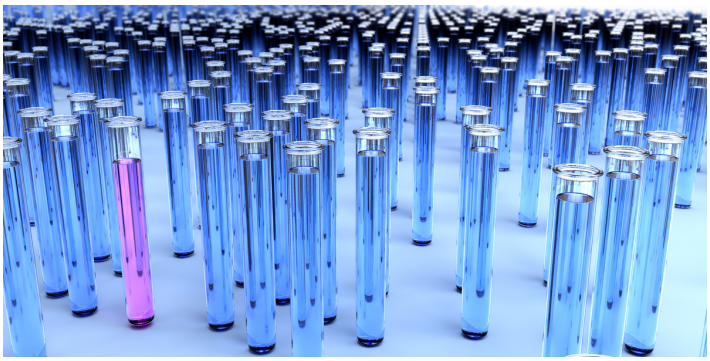
One of the most promising drug targets which has arisen from these large genetics studies is another DNA repair protein called MSH3. Single letter changes to this gene can also affect the age at which HD patients start to get symptoms. Scientists think that if they are able to make a medicine to target the MSH3 protein and stop it from working in our cells, this would reduce the levels of somatic instability which would be beneficial for patients. There are numerous teams of scientists looking into different strategies to target the MSH3 protein and some exciting unpublished discoveries were presented at the HD therapeutics meeting in Palm Springs this year.

Who is involved in making medicines to target somatic instability in HD patients?

The HD community has dozens of companies and organizations involved in discovering new therapies for patients, focused on HTT lowering as well as other strategies. One way to learn more is to check out some of the research talks presented to families at HDSA's 2020 Virtual Convention, summarized here. With many recent studies connecting somatic instability to DNA damage repair, there are now numerous companies seeing if they can make medicines to stop CAG repeats from expanding or even shrink repeats by targeting the process of somatic instability.

One company working in the DNA repair space is LoQus23 Therapeutics, a recently formed company from the folks at the Dementia Discovery Fund, a collaborative organization that invests in new medicines for neurodegenerative diseases. They are interested in targeting proteins involved in DNA damage repair, with small molecule drugs that could be taken as a tablet. During their presentation at HDSA's Virtual Convention, representatives from LoQus23 used a family of stuffed bunnies and bears to create an excellent explanation of DNA damage repair and somatic instability. Another company aiming to target somatic instability is Triplet Therapeutics, an enterprise focused on making medicines for repeat expansion diseases like HD. Similar to HTT lowering therapies, their approach uses small pieces of genetic material called antisense oligonucleotides (ASOs) and small interfering

RNAs (siRNAs) to reduce protein levels. Both companies hope that by impairing the actions or reducing levels of specific proteins involved in DNA repair, they can stop or slow somatic instability and therefore delay symptom onset or progression.



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In fact, Triplet Therapeutics has recently embarked on a study that takes a close look at HD progression, called the SHIELD-HD natural history study. It aims to observe 60 HD patients over the course of two years in order to better understand HD-related changes in somatic instability and DNA damage repair genes over time. The study will take lots of different measurements of the patients, looking at HD symptoms as well as taking samples of blood and spinal fluid for analysis. Observational studies like these are essential in planning drug trials, helping researchers make informed decisions about when treatments should be given to patients and what regimens should be followed.

Participating in the future of HD Research

Hopefully this investigative dive into the “who, what, when, where, why, and how” of somatic instability has convinced you that this growing field presents a new and exciting pathway towards novel HD therapeutics. The journey from uncovering drug targets to the beginning of an exploratory human trial like SHIELD-HD is normally far longer. One of the main reasons that HD science is moving so quickly from discovery to potential therapy is community participation in clinical trials. Data and samples collected in large observational studies are powering the analyses that will identify tomorrow’s drugs. More active participants in studies like Enroll-HD means that HD researchers in academia and industry can faster and more accurately identify the next set of targets.

In the case of somatic instability, uncovering the importance of DNA repair using thousands of donated patient samples was a game changer. Researchers were quickly able to use this information to further investigate the biology of DNA repair, decide which proteins were most important, and begin to design drugs and clinical studies. Our understanding of somatic instability in HD has continued to deepen, and the recent studies highlighted above point to the specifics of genetic modifiers and highlight shared vulnerability across different

types of brain disease. Although we have not yet reached a point where genetic testing for variations in DNA repair proteins is possible or even useful for an individual HD patient, these discoveries will no doubt drive medical innovations in the near future.

Dr. Leora Fox works for the Huntington's Disease Society of America. HDSA communicates with and has nondisclosure agreements with both Triplet Therapeutics and with LoQus23 Therapeutics, companies mentioned in this article. 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

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.

huntingtin protein The protein produced by the HD gene.

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

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

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

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.

SCA Spinocerebellar ataxia, another neurodegenerative disease caused by increased CAG size