Two birds, one stone: HTT-lowering drugs also target CAG expansions

In a surprising twist, oral HTT-lowering drugs also slow somatic expansion in the HTT gene. A new study that used cells in a dish for this fortuitous discovery identified the gene PMS1 as a key player in the slowing of CAG expansions.

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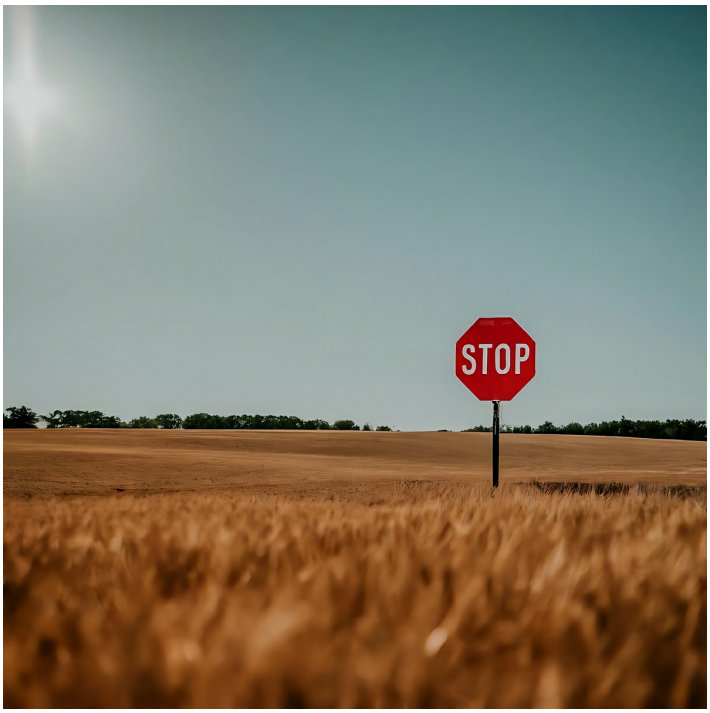
Huntingtin (HTT)-lowering and somatic expansion have been two of the hottest topics in Huntington's disease (HD) research in the past decade. Recent work from a team at Massachusetts General Hospital detailed a serendipitous overlap between the two – certain HTT-lowering drugs can also help regulate the ongoing CAG repeat expansion. Seemingly, this could allow researchers to kill two birds with one stone using a single drug. But there's more to this story.

CAG expansion causes toxicity

The CAG repeat within the HTT gene is the nefarious player leading to HD. This repeat can expand in some cells over time, which is the biological phenomenon known as somatic expansion. We've talked a lot about somatic expansion lately, which you can read more about in this recent article.



Splice modulators, like branaplam and risdiplam, work to lower protein levels by adding a

stop sign in the middle of a genetic message. The cell recognizes that the stop sign is out of place, that the message doesn't make sense, and doesn't bother turning the message into protein.

A current hypothesis for how the CAG expansion that causes HD makes people sick is a 2-step process. In this model, first, the inherited CAG length slowly expands in some cells over time. Second, once the CAG length reaches a threshold, toxicity in the cell is triggered, leading to death. This process doesn't appear to occur in all cells, which is why some scientists think that only some cells, like brain cells, get sick and die in HD.

Targeting modifiers to control toxicity

In 2015, a large study was published by the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium, a collective of scientists who pooled their ideas and resources to try and figure out why folks with the same CAG number might get symptoms of disease earlier or later in life. This study looked at the entire genetic makeup of over 4,000 people with HD. This study identified genes that can influence when symptoms of HD might begin. They dubbed the genes that alter age of onset "modifiers", since they modify when someone will show signs of disease.

Lots of the modifier genes have links to how DNA is repaired and seem to influence expansion of the CAG repeat in the HD gene. A key idea that arose from the GeM-HD team and subsequent studies is that people who have changes in these modifiers that scientists predict will slow somatic expansion, seem to get HD later.

Some researchers think if we can control modifiers so thatsomatic expansion is slowed, we could prevent the second step in the process of HD – toxicity and cell death. For this reason, a lot of scientists have been studying modifier genes that control somatic expansion. One such group is led by Jim Gusella, who was one of the key people on the 2015 GeM-HD paper.

A recently published study, driven by Zach McLean from Jim's group details something quite curious. They noticed that drugs that can lower the levels of HTT also have off-target effects on modifiers that control somatic instability.

HTT-lowering drugs

> **"It turns out that branaplam and risdiplam both lower HTT *and* can also slow the rate of CAG expansion. "**

The HTT-lowering drugs tested in this current study are branaplam and risdiplam. These drugs are small molecules that can be taken orally. Both are a type of drug called splice modulators – they work by introducing a stop sign in the middle of theHTT message. The cell reads this stop sign, sees that it's out of place and doesn't make sense, and doesn't bother turning the message into protein.

Your eyes may have widened when you saw the name branaplam. This is the same drug that was tested in the failed Phase 2 VIBRANT-HD trial by Novartis. We previously wrote about the halting of this trial for safety reasons.

Risdiplam is an agency-approved medication used for the treatment of spinal muscular atrophy (SMA). For that disease, it works by increasing the amounts of a protein that people with SMA are missing. Risdiplam, sold as Evrysdi, was approved by the FDA in August of 2020 and the European Medicines Agency (EMA) in March of 2021. Risdiplam has been approved for SMA in over 80 countries.

Interestingly, risdiplam also lowers HTT. That means that people have safely been taking a HTT-lowering drug for several years. However, those people don't have HD, which could make a difference.

Ability to target doesn't equal specificity

One thing to note about some oral splice modulators that lowerHTT is that they're not specific. They're not designed to only and specifically target HTT. They work by including bits of message, like stop signs, for many different genes. These off-target effects have caused scientists to suspect that they could have unintended consequences.

To better understand these unintended consequences, the team added branaplam and risdiplam to cells in a dish. What they found was quite serendipitous! It turns out that branaplam and risdiplam both lower HTT *and* can also slow the rate of CAG expansion. This is because these drugs also target a gene called PMS1. PMS1 just so happens to be one of those modifiers that was identified in the GeM-HD study. It's thought that the less PMS1 people have, the later they start to show symptoms of HD.

Even though HTT-lowering splice modulators work on the same premise, they're not all identical. Small differences in their makeup change how they work. So knowing one won't work for HD doesn't provide clues about others. While similar, they're all different.

In cells in a dish, branaplam and risdiplam seem to slowHTT somatic expansion by including a premature stop sign in the PMS1 message. Because of this, the cell lowers the amounts of PMS1 in the same way that it lowers HTT. With less PMS1, there is less CAG expansion in HTT. Quite fortuitous!

Not all HTT-targeting splice modulators will

work the same

The team behind this study note that there are differences between branaplam and risdiplam. While branaplam targets HTT more than PMS1, risdiplam does the opposite; risdiplam targets PMS1 more than HTT. Additionally, branaplam's effects on somatic expansion seem to only occur through PMS1, but risdiplam has effects on expansion outside of PMS1.

So while both drugs target HTT and PMS1, they each have unique effects. This means they could also be targeting other genes differently. Adding to this complexity, these drugs work by recognizing spelling in the genetic code. Since we all have little changes in our genetic spelling that make us unique, they may work differently in different people. This study highlights the caution that needs to be taken because of this.

Another similar drug that wasn't tested in this study is PTC-518. This drug works in a very similar way and is currently being tested in a Phase 2 trial by PTC Therapeutics. We can't infer anything about PTC-518 from this new work because it wasn't included in the current study. So we don't know exactly how similar or different it is from branaplam or risdiplam.

Is PMS1 the new target to beat?

This new study bolsters PMS1 as a potential target to go after to treat HD to reducesomatic expansion. However researchers need to be cautious when targeting genes that control somatic expansion. These genes also regulate how our DNA is repaired, which is critical for maintaining integrity of our genetic sequence and preventing cancer.

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Researchers also have to first work out how much to lower PMS1, or other genes that control somatic expansion. They need to find the sweet spot for lowering them enough to slow somatic expansion and provide therapeutic benefit. This study only assessed PMS1 in cells in a dish. This would have to move to mouse models next.

Does this mean a resurgence for branaplam?

You may be wondering if this new data means branaplam is coming back to clinical trials for HD. The short answer – no. While there are no immediate plans to test branaplam in the clinic for HD, other splice modulators *are* moving forward. We can still learn quite a bit about HTT lowering splice modulators that are moving forward by studying branaplam in the lab.

By studying branaplam and other drugs with similar mechanisms of action, we can get a better idea of how they're similar and how they're different. Knowing this, and studying which ones work better, can help identify other drugs with more specific effects on targets

of choice. It can also help us understand how we can reduce unwanted side-effects.

So while this study identified a positive side-effect of aHTT-lowering splice modulator, that doesn't mean it's coming back to the clinic. However, knowing that HTT-lowering drugs can also target somatic expansion could inform ongoing and future trials using this class of drugs, perhaps leading to the development of drugs that target two birds with one stone.

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

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

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