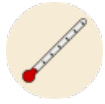


## Switching it up: variety in the HD gene affects symptom onset



Variety in the HD gene's on switch affects when symptoms arise.

By Melissa Christianson on May 29, 2015

Edited by Dr Jeff Carroll

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*Just like it is difficult to predict exactly when a storm will hit, predicting when Huntington's disease symptoms will arise for any particular person is hard to do. However, new research suggests that tiny changes in the on switch of the Huntington's gene affect symptom onset – and may provide important information in the search for Huntington's therapies.*

### Eying the Storm

Like the signs of a thunderstorm, the symptoms of Huntington's disease are unmistakable. In the place of gusting winds, pelting rain, and cracking thunder, however, Huntington's brings stereotypical movement, cognitive, and psychiatric symptoms that are remarkably consistent across the patient population. Nevertheless, just like it is difficult to predict exactly when a storm will hit, predicting exactly when Huntington's symptoms will arise for any particular person is hard to do.

We already know that the genetic mutation causing Huntington's affects the onset of symptomatic disease. This mutation centers around a set of three DNA building blocks inside the Huntington's gene that we refer to as "CAG". In Huntington's disease, these building blocks get repeated too many times and thereby lengthen the gene - and the longer the gene, the earlier (on average) symptoms arise. However, gene length doesn't tell the whole story about symptom onset: even among people whose Huntington's genes have similar lengths, the onset of symptoms can vary by as much as decades.

This variation has scientists eying the Huntington's storm in the hope of understanding, and potentially co-opting, how nature delays the onset of symptoms. These scientists think that additional genetic factors play a part in this variation – and that bits of the Huntington's gene we don't normally talk about may serve an important role.



Just like it is difficult to predict exactly when a storm will hit, predicting exactly when Huntington's symptoms will arise is hard to do.

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### Small Changes in a Big Gene

The Huntington's gene is one of the biggest genes in human DNA - it is made up of about 170,000 DNA building blocks all strung together. Even though we focus most on the extra repeats that cause the disease, these repeats make up just a tiny fraction of the whole gene. The rest of the gene is actually also full of information that could influence when symptoms arise.

One specific part of the gene, called the promoter, is particularly well positioned to affect symptom onset. A promoter is a special part of a gene devoted to turning the gene on and off. If you think of a gene like a CD sitting in a boom box, then a promoter is like the boom box's on switch: just as the on switch turns on the CD to make music, a promoter turns on a gene to make protein.

Small changes in promoters can have big effects on genes. Continuing our gene-CD analogy, imagine that we made a minor change in the on switch and moved it to the underside of the lid. By making it harder to reach the on switch, this relatively small change would make it much more difficult to play the CD. In a similar way, small changes in a gene's promoter – especially changes that make the promoter hard to reach – can make it difficult to turn on a gene.

For genetic diseases like Huntington's, such changes can have big consequences.

## Could Promoters Affect Symptom Onset?

A group of scientists based at the University of British Columbia in Vancouver wondered if variety in the Huntington's promoter could be one of the things controlling when symptoms of the disease arise.

To ask this question, they looked at a version of the Huntington's promoter occurring in a very small number of people with the disease. This rare promoter has a tiny, tiny change from normal – in it, a single one of the ~170,000 DNA building blocks in the Huntington's gene is different. However, just like in our CD analogy above, this small change makes the promoter hard to access. Consequently, Huntington's genes that use this promoter as their on switch are difficult to turn on, and they make less protein than normal.

Could this tiny change, the scientists wondered, be enough to affect the age of symptom onset in Huntington's?

## Hold On, I'm Seeing Double

However, asking this question isn't as simple as it sounds. In fact, it's *twice* as hard as you might have expected.

The reason why has to do with a central feature of human DNA. Remember that we humans get **two copies** of most genes (including the Huntington's gene) at birth – one from mom and one from dad. For individuals with Huntington's disease, every cell in the body therefore contains two copies of the Huntington's gene: a normal-length copy and an extra-long copy that causes the disease.



Either copy of the Huntington's gene - the normal-length *or* the extra-long one - can have the promoter that is linked to symptom onset.

Both copies need to have a promoter attached so that they can be turned on. However, the promoters on the two genes **do not** have to be the same. This means that either copy - the normal-length *or* the extra-long one - can have the rare promoter the scientists wanted to study.

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To ask if this promoter affects the age of symptom onset in Huntington's disease, therefore, the scientists actually had to ask **two separate questions**: does having the rare promoter attached to the extra-long Huntington's gene affect symptom onset, and does having the promoter attached to the normal-length Huntington's gene affect symptom onset?

## One Change, Two Different Consequences

So, what did the scientists find when they pulled double-duty to ask and answer these questions?

The answers to the questions may surprise you – because they were opposites!

People who had the rare promoter attached to their extra-long Huntington's gene got sick almost a decade **later** than expected, whereas people who had the rare promoter attached to the normal-length copy got sick almost four years **earlier** than expected. Thus, the rare promoter could either delay or hasten symptom onset, depending entirely on the copy of the Huntington's gene to which it was attached.

Why on earth would this be the case?

Our genes-as-CDs analogy can help us understand these surprising results. Because we all have two copies of the Huntington's gene, it is as if our cells are constantly listening to music coming from two different Huntington's CDs played simultaneously. One CD (representing the normal-length gene) plays the song cells need to hear to stay healthy, whereas the other (representing the extra-long gene) plays an altered melody that can drown out the correct song.

If we move the boom box's on switch, we make it harder to play one CD or the other. When turning on the extra-long CD is hard, cells get healthier – because they can hear the correct song much better without a competing melody. When turning on the normal-length CD hard, though, cells get sicker – because the only song left playing is the competing melody.

The real science works on exactly the same principle: making it hard to turn on the harmful, extra-long Huntington's gene delays symptom onset, whereas making it harder to turn on the good, normal-length Huntington's gene hastens symptom onset. Affecting the Huntington's gene promoter thus has the power to alter symptom onset in either direction.

## Notes of Caution

However, as with most research studies, there are a few things to consider before trying to apply these findings more broadly to patients and families.

Most importantly, the version of the Huntington's promoter the scientists studied was **quite rare**. Because only a very small portion of the Huntington's population actually has this genetic variation in their promoter, the new results may not directly apply to most of the Huntington's community.

Another thing to consider is that researchers used a strategy of looking at groups of people who had very early or very late onset of symptoms for this study. Why would they do this, rather than just looking at everyone?

Imagine you're interested in searching for genetic changes that make people really tall. Do you think you'd have better luck finding such rare changes in a random group of people, or with the Los Angeles Lakers basketball team? Probably, you're better off starting with the basketball players, who tend to be taller than normal.

That's sort of what this team of scientists did - they enriched their study population with HD patients who had very early or very late onset of symptoms. This gave them a better chance of finding rare variations that change when people get sick with HD.

However, when they looked in another group of people without ensuring a big number of people with early or late symptom onset, they didn't see the same effect.

These are early days for this research, and there's a lot more work to be done. We might need to find more common genetic variants near the HD gene, or look for interactions between more than one variation, before we can more accurately predict the age of onset of HD using genetics. However, this study is an important proof that we can find genetic changes that modify HD age of onset.

## Does This Research Help Us Find HD Therapies?

Despite these cautions, this new research is really exciting and brings several important ideas to the floor.

It emphasizes that the both normal and extra-long Huntington's genes affect symptom onset and that the balance of these two genes is important in the search for new therapies.

Additionally, this research has implications for a cool type of therapy called "gene silencing". Gene silencing is exactly what it sounds like – a way to turn off (silence) human genes. Gene silencing gets tricky in Huntington's, though, because there are two copies of the Huntington's gene (one good and one bad). The research here suggests that generically turning off both Huntington's genes might delay symptom onset, but that specifically turning off the extra-long copy could be even more effective.

Thus, this research both helps us to understand what drives the onset of Huntington's symptoms and guides the search for effective HD therapies.



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

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## **Glossary**

**gene silencing** An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

**promoter** a special part of a gene devoted to turning the gene on and off

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