Working as a team: Changes in brain development mean some brain regions may be slacking off

Scientists use human fetal tissue to look at HD brain development. But what do developmental changes mean when symptoms don't occur until decades after birth?

By Dr Sarah Hernandez | **August 17, 2020** | **Edited by Dr Jeff Carroll**

The effect of the HD genetic expansion on brain development has been a hot topic in HD research. A team of researchers led by Dr. Sandrine Humbert at the Grenoble Institut Neurosciences, examined human fetal tissue to show that the mutant HD gene causes very early changes in the patterns of early brain development. But what type of influence do these changes in development actually have? People born with the mutant HD gene obviously survive and thrive for many years, and even decades before symptoms in the brain develop. So while these findings don't suggest that developmental changes cause immediate effects, they do justify careful interpretation.

A little of this, a little of that

Before we start – a quick Bio 101 refresher might be helpful to clear up some jargon we commonly use. We talk about Huntington's disease, but use the word huntingtin a lot. HD refers to the disease itself, and huntingtin refers to the gene and/or protein that causes the disease. Scientists think they're clever and gave the gene/protein name a little twist just to be creative. Just be thankful they didn't get really creative and name it something off the wall like sonic hedgehog, 18 wheeler, or tinman (real gene names, we promise).

And while the word "huntingtin" refers to both a gene and a protein, those are actually quite different. You can think of a gene as a recipe – it provides the written instructions on what to make. And the protein is the product – you can think of it like the product of a recipe, like a pie. So huntingtin the gene is the recipe for huntingtin the protein, which is the product.

The striatum follows a different timeline for development in HD, but other brain areas make stronger connections to compensate. Like if one team mate strays off course, other team members will step up to fill in.

Even though the huntingtin gene was discovered in 1993, there's still a lot we don't know about the function of this protein. One reason for that is because researchers have found that huntingtin actually has many functions – doing a little of this, and a little of that in cells all over the body, and throughout our lifespan. And while some of those functions are beginning to become clear, there's still a lot left to learn.

One of the more recently proposed roles for thehuntingtin protein involves a contribution to development of the brain. Remember – people who inherit the HD mutation have the genetic change that causes the disease from a time before they were even born. But in most HD patients, symptoms don't appear for decades. One of the goals of HD researchers is to understand the very earliest changes caused by the HD mutation, to try and help map these changes and the later dysfunction that leads to HD symptoms.

To study very early changes in development, scientists have used mouse and cell models to identify functions for the huntingtin protein. Increasing evidence suggests that there are subtle changes in brain development in cells and mice that express the mutant HD gene. We recently wrote about development-related changes described in a mini-brain, 3D cell model of HD that you can read about here.

But, as you're all aware, mice aren't humans and models that look at cells grown in a dish can't tell us the whole story of what HD is doing in humans. As we often say, only humans get Huntington's disease. And the reason researchers are studying HD is to find a treatment for humans with HD. So the best samples to use to look at this process are, well, from humans.

> **"The take home message is that this study showed that cells in a certain area of the brain at a specific time point had differences in development because of the mutation that causes HD. "**

The right place at the right time – is it critical?

To determine if HD causes cellular changes during very early stages of human brain development, researchers led by Dr. Humbert examined the developing brain in human fetuses that were at 13 weeks of gestation. This provides researchers with information on what's happening at a very specific point in time during early development – like a photograph of a specific moment.

They specifically looked at the developing cortex – the wrinkly outer bit of brain that executes many of our sophisticated behaviors. In the human fetal tissue carrying the HD mutation, the rate at which cells divided was slower and their location within the brain was altered. This was also seen in a mouse model, suggesting that these effects are definitely related to the HD mutation.

As a cell matures into a neuron, it physically moves in the brain. So at this time point in development, some cells aren't in the right place at the right time, tipping the balance in the developing brain.

The take home message is that this study showed that cells in a certain area of the brain at a specific time point had differences in development because of the mutation that causes HD. However, it's important to know that making brain cells as an adult is a very different process than when brain cells are first made during development. So while this study examines how the HD mutation is affecting the development of brain cells, it doesn't look at changes in the formation of adult brain cells or why new cells don't replace them. Those are questions for another study.

Like team members who fill in for slackers, developmental changes in HD may be no big deal early on because other areas of the brain can compensate.

But many other studies in mice have shown us that even with the mutation that causes HD, a fully functional brain ultimately develops. And we certainly know this to be true in people.

Working together

So how can a brain have altered development **and** function normally? Other areas of the brain help out! It's like when you have to do a group project, but one team member is a slacker – the rest of the team does a little bit extra to get the job done.

In fact, we've seen that this is the case in other studies from humans. A recent study – the ChANGE-HD study – used MRI to look at the sizes of various brain areas in kids (ages 6 to 18) who have inherited the HD mutation, but are many years from symptom onset. With consent from their parents, these kids participated in this study, aimed at understanding the earliest detectible changes in people carrying the HD mutation.

Compared to kids who don't inherit the HD mutation, kids who do initially have a slightly larger striatum (an area of the brain that eventually experiences heavy cell loss due to HD) that decreased in size with age. But the kids who inherited the HD mutation also had **more** connections between other areas of their brains and this same brain region.

> **"Even though HD may cause subtle changes in brain development that appear to be present from before birth, other studies show us that changes in development don't appear to cause symptoms that we can measure. "**

This suggests that the kids who inherit the HD mutation have faster development in certain brain areas affected by HD early on, and that this same brain region eventually shrinks over time. But other areas of the brain appear to be reaching out to help compensate for this altered developmental timeline. So the other areas of the brain pick up the slack for the brain region not pulling its own weight.

Structure doesn't immediately determine function

Never underestimate a team that works well together. While each member might not be performing their function exactly how they're assigned, they get used to working together. And it might take a very long time before cracks begin to appear in their way of doing things.

We learned recently from the HD Young Adult Study (HD-YAS) that even 24 years from predicted symptom onset, people carrying the HD mutation showed no decline in thinking or mood. (You can read more about the HD-YAS study here.) Even though HD may cause subtle changes in brain development that appear to be present from before birth, other studies show us that changes in development don't appear to cause symptoms that we can measure. So it's likely that the brain is able to compensate for these early changes.

With this new study, we have more evidence that huntingtin is involved in brain development, adding to the growing list of functions performed by this protein. Understanding exactly how huntingtin is involved in this process will help reveal things about human development overall. And it gives us a peak at some really cool development-related science!

Findings from this new study also beg the questions – what exactly are the mechanisms that compensate to keep HD brains healthy for so long? And can we identify them to extend that process as a therapeutic strategy? We still have a lot to learn about that area of HD research, but future studies are likely to follow up.

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

GLOSSARY

huntingtin protein The protein produced by the HD gene.

neuron Brain cells that store and transmit information

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

---