Ultra-rare mutations highlight the importance of the HD gene in brain development

New technology enables researchers to find ultra-rare mutations in the HD gene, distinct from the one causing HD

By Megan Krench  August 29, 2016  Edited by Dr Jeff Carroll

A relatively new technology called exome sequencing has identified a few families with novel mutations in their HD genes. These are different than the mutation that causes HD, but allow researchers to better understand the normal role of the HD gene.

Normal HD gene function

The mutation that causes HD instructs brain cells to make an abnormal, mutant protein scientists call huntingtin. We’ve long known about the many ways mutant huntingtin protein can interfere with cells’ normal processes. For example, mutant huntingtin can interfere with brain cells’ ability to move cargo from one end of the cell to the other and impair cells’ abilities to produce energy.

With whole exome sequencing, scientists can reduce how far they have to search for rare mutations - from the whole field to focusing only on the bales

Image credit: By foxypar4 - originally posted to Flickr as Harvest Time, Alness (Ross-Shire), CC BY 2.0

What we’re less sure about is: what exactly is healthy huntingtin supposed to be doing in the cell in the first place, and what happens when it’s not around to do its job? (You can read more about the “Hunt for the Function of Huntingtin” here: http://en.hdbuzz.net/221.) Two recent discoveries highlight how healthy huntingtin may play critical roles in the development of our brains and nervous systems, giving us new information to keep in mind as we develop treatments for HD.

Before we go into the findings, here’s a quick crash course on the technique that made it all possible: whole exome sequencing.
Our DNA is comprised of over 3 billion letters. But surprisingly, the cell only reads about 1.5% of that genetic blueprint to make proteins. The 1.5% of our DNA that codes for proteins are called **exons**.

Sequencing technologies, which allow scientists to read the information coded in DNA, have advanced very rapidly over the past decade or so. It’s now possible for researchers to read all 3 billion letters to get a person’s complete genetic code. Researchers call this **whole genome sequencing**. But, sequencing all 3-billion letters to look for a tiny mutation is like looking for a needle in a haystack. To make the haystack smaller, researchers instead can sequence only a subset of the **genome** - often just the subset of a person’s DNA that codes for proteins, the **exons**.

This process of sequencing only the protein-coding regions is called **whole exome sequencing**, and results in a haystack about 1.5% as big as a whole **genome**. Two different research groups using **whole exome sequencing** incidentally made important new insights about the normal function of the HD gene.

### Rare HD gene mutations discovered

“**We aren’t certain what impact the new, non-HD genetic mutations are having on the huntingtin protein. But, based on the genetic region where the mutations occur and what we know about the protein’s structure, it is likely that the mutations are dramatically reducing the amount of huntingtin protein in the cell**”

The first group of researchers was searching for genetic mutations in a group of nineteen people with severe developmental disorders. Their symptoms, including intellectual disability, limited speech and motor abilities, and repetitive motions such as hand wringing, were characteristic of a disease called Rett syndrome. But, like HD, Rett syndrome is caused by a mutation in a specific gene—and these people did not have the mutation known to cause Rett syndrome.

To try and solve this mystery, researchers used **whole exome sequencing** to search for the mutations in every gene that might explain these symptoms. They identified several new mutations in these individuals, but one person in particular is relevant to our story here at HDBuzz: a woman with mutations in both copies of her HD genes. The woman didn’t have HD because her HD gene mutations were different than the type that causes HD. And, while most carriers of HD only have the mutation in one huntingtin gene, both copies of this woman’s huntingtin genes carried these novel mutations.

At the same time this study was happening, another group of researchers were searching for the cause of a developmental disorder in an Ecuadorian family. The family was comprised of two healthy parents, one healthy child, and three children with severe developmental delays. The affected children’s symptoms included little or no language skills, dramatically impaired motor abilities, and repetitive motions like hand wringing. None had a mutation in the gene that causes Rett syndrome.

To try to discover the underlying mutation, these researchers performed **whole exome sequencing** on the Ecuadorian family. They discovered that the developmentally delayed children had mutations in both copies of their HD genes. Again, they were new mutations—not the specific mutation that causes HD.

In both of these studies, researchers also performed **whole exome sequencing** on the healthy parents of the people with developmental disorders. In both sets of parents the mother and father each carried one mutated HD gene. However, their other copy of huntingtin was healthy. In the Ecuadorian family, the sibling that didn’t have developmental delays also carried one copy of mutated HD gene and one healthy copy. The only people that experienced developmental disorders were those that inherited two mutated HD genes.

Researchers finally identified previously unknown mutations causing severe developmental delays in the HD gene

Image credit: *[Pixabay](https://pixabay.com)*

We aren’t certain what impact the new, non-HD genetic mutations are having on the **huntingtin protein**. But, based on the genetic region where the mutations occur and what we know about the protein’s structure, it is likely that the mutations are dramatically reducing the amount of **huntingtin protein** in the cell. This type of mutation (called loss of function) is different than the type of mutation that causes HD. In HD, the mutation leads to production of a toxic, abnormal **huntingtin protein**—but it does not affect the amount of **huntingtin protein** that’s being made.

So - just to be clear - these mutations are not the same as the mutations which case HD. But by random chance they happened to occur in the HD gene, and so help us better understand what the HD gene does, beyond being mutated in people who develop Huntington’s Disease.

### What do we learn?

These studies have taught us several important things about huntingtin. First, they show that just a single copy of “healthy” huntingtin is sufficient for the brain to develop and function normally. We know this because parents and siblings that had one “healthy” huntingtin gene were fine, even though their other copy was mutated.

This finding also supports what we’ve observed in two other people with rare huntingtin mutations that caused one copy of the gene to be inactivated, or turned off. People with one inactivating mutation were healthy as long as their other copy of huntingtin was ok. We have also seen the same type of outcomes when we study huntingtin in mice. Mice missing one copy of the huntingtin gene are healthy, as long as their other copy of huntingtin is still intact. Together, these findings suggest just one copy of functional huntingtin is enough to carry out most of its essential functions.

“**These discoveries have taught us that there is a critical role for huntingtin in brain development. Each of the people with loss-of-function mutations in both copies of their huntingtin genes were diagnosed with severe developmental disorders.**”
Next, these discoveries have taught us that there is a critical role for huntingtin in brain development. Each of the people with loss-of-function mutations in both copies of their huntingtin genes were diagnosed with severe developmental disorders. Whole exome sequencing did not reveal any other mutations that were likely to be the culprit. Hence, these rare, unfortunate cases have given us a glimpse into the normal function of huntingtin and what happens to the brain when there’s insufficient huntingtin to support normal brain development.

**Gene silencing for HD - still OK?**

Understanding the normal functions of huntingtin has long been a focus of the HD research community. Knowing what huntingtin is doing in the cell may lead to new insights about HD or spark ideas to develop treatments. Importantly, the normal function of huntingtin is relevant to an investigational HD treatment called gene silencing. (You can read more about gene silencing in this post: [http://en.hdbuzz.net/204](http://en.hdbuzz.net/204).)

Gene silencing turns down the levels of the HD gene to prevent the production of mutant, toxic huntingtin protein. Given what now know about the critical role of huntingtin in brain development, it will be important to carefully monitor HD patients receiving gene-silencing treatment. It also means we will have to strategically evaluate the age of HD carriers undergoing huntingtin gene silencing - attempting to silence the HD gene in the brains of very young people would raise serious safety concerns.

But, since the vast majority of HD patients are adults whose brains are already fully developed, it’s unlikely that gene silencing will lead to the problems seen in these patients who had low huntingtin levels throughout development. Researchers and physicians will be sure to keep all of this in mind during clinical trials with gene silencing drugs.

And of course, none of these insights would have been possible if it wasn’t for whole exome sequencing. This powerful technique allowed researchers to identify for ultra rare mutations that advance our understanding of many diseases—including HD. This new research shines a light onto huntingtin’s critical role in brain development, adds to our knowledge about HD, and helps us plan gene silencing studies which are safer for participants.

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

---

Learn more

Original paper from Rodan and colleagues describing two patients with novel mutations in their HD gene leading to severe developmental disorders (full article requires payment or subscription) Original paper from Lopes and colleagues describing their work investigating patients who resemble Rett syndrome patients (full article requires payment or subscription)

Topics
human genetics huntingtin-function huntingtin-location huntington's gene

More...

Related articles

---

**When interrupting is good: genetic hiccups that protect against Huntington's disease**

March 14, 2019

**Huntington's disease therapeutics conference 2019 - Day 3**

March 05, 2019

**HDSA FAQ on the Roche/Genentech RG6042 program**

October 19, 2018
• Glossary
• Whole genome sequencing Decoding every one of the approximately 3 billion 'letters' of an individual's DNA
• Whole Exome Sequencing Decoding exons, the ~1.5% of a person's DNA which contains instructions for directly building proteins
• huntingtin protein The protein produced by the HD gene.
• gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein
• genome The name given to all the genes that contain the complete instructions for making a person or other organism
• Exons The small fraction of our DNA that is directly used to instruct cells how to make proteins

Read more definitions in the glossary

Huntington's disease research news.
In plain language. Written by scientists.
For the global HD community.

HDBuzz

News
Previously featured
About
HDBuzz funding partners
Sites featuring HDBuzz content
New to research

People

Meet the team
Help us translate

Follow HDBuzz

Sign up to our monthly email summary by entering your email address below or get more options on our mailing list page

Follow