Highlighting a link between brain disorders on Ataxia Awareness Day

September 25th is Ataxia Awareness Day, so HDBuzz is highlighting the connections between HD and Ataxia research. Learn about how these fields have historically grown in parallel and informed one another.

By Dr Leora Fox | September 25, 2024 | Edited by Dr Sarah Hernandez

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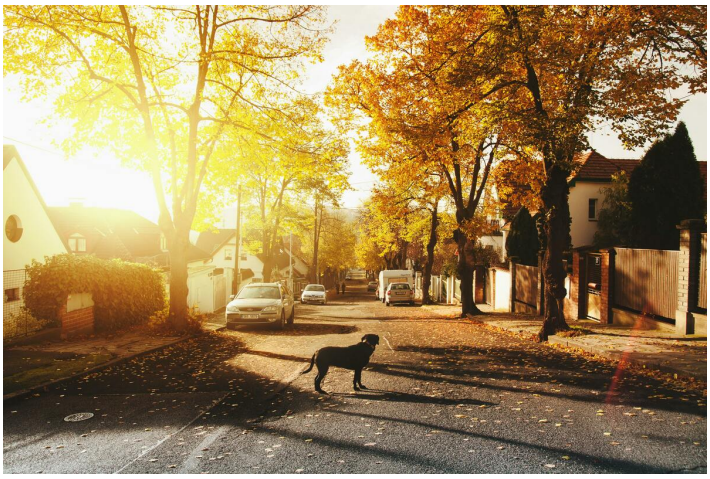
Today, on International Ataxia Awareness Day, we're bringing awareness to a group of brain disorders known as Ataxia, which can take many forms. Like Huntington's disease (HD), Ataxia is degenerative; it damages brain cells, causes changes in movement, and involves complex symptoms that worsen over time. HD and some forms of Ataxia have a shared genetic origin, and we'll talk about medical and research overlap.

What is Ataxia?

Like HD, Ataxia is a rare form of neurological disease. It can lead to a variety of symptoms including lack of coordination, slurred speech, and difficulty walking - this can appear similar to the effects of alcohol. Ataxia is usually caused by damage to a part of the brain that coordinates movement, known as the cerebellum, which is located at the back of the head right above the neck.



There were parallel efforts in the 1980s and 1990s to narrow down the "neighborhood" followed by the exact location of the genes that led to SCAs and HD.

Image credit: Daniel Frank

The symptoms of ataxia can vary a lot by the person, and they can also vary by the type of Ataxia. Some forms are passed down from one parent, as with HD - just one copy of the faulty gene causes disease. This is known as autosomal dominant inheritance. Other forms of Ataxia are passed down only when a person inherits two copies of a faulty gene - the parents don't have ataxia, but they are each a "carrier" of the gene. Ataxia can also be caused by a brain injury or infection (acquired), or have unknown causes (idiopathic/sporadic).

Why should the HD community be aware of Ataxia?

Ataxia can refer to a group of disorders, but it can also simply refer to uncoordinated movements. If you've ever had too much to drink, you've likely experienced alcoholic ataxia. And many people with HD experience ataxia at some point over the course of their disease. Ask many healthcare workers with HD expertise, and they'll tell you that when you've seen one person with Huntington's disease, you've seen one person with Huntington's disease. We all know that HD is complex and that symptoms can vary from day to day, let alone between individuals. Symptoms of ataxia can affect people with HD, especially in later stages.

HD affects the part of the brain that is important for voluntary movements, and it is more likely to cause chorea, which can appear jerky and dance-like. Ataxia affects the part of the brain that coordinates movement, and it is more likely to cause movements that appear unstable or slow. Both diseases worsen over time and cause people to have difficulties with speech, walking, and day-to-day tasks. There are even case reports where a person with HD was misdiagnosed with ataxia because their early symptoms involved difficulties with balance and coordination.

> **"The shared nature of the CAG repeat in HD and several hereditary ataxias means that researchers can continue to learn from one another, working together and in parallel "**

The genetics of HD and Ataxia

The greatest area of overlap in HD and Ataxia research is within a group of Ataxias that is caused by the same genetic error. We know that HD is inherited dominantly (from one parent), and that it is always caused by the expansion of CAG repeats within a gene called huntingtin. Some ataxias are also inherited dominantly, including a group of disorders known as spinocerebellar ataxia (SCA), and several of these are also caused by the expansion of CAG repeats.

In HD, the extra CAGs are found within the huntingtin gene, whereas SCA is caused by CAG repeats within other genes. Some examples are ataxin-1, ataxin-3, and ataxin-7, but there are a whole family of genes with CAG repeat expansions that are known to cause rare Ataxias (among other diseases). We recently heard about research into SCA from Dr. Harry Orr at the Hereditary Disease Foundation conference, which we covered.

New genetic causes of Ataxia have been discovered very recently, including ones caused by triplet repeats. In fact, in 2024 a new 5-letter DNA repeat was revealed as the cause of many hereditary Ataxia cases. Like the discovery of the gene that causes HD in 1993, this is a huge step forward for folks who have this type of Ataxia! Bill Nye the Science Guy, a well-known science communicator (and source of inspiration to us at HDBuzz) has family members who have this form of Ataxia, known as SCA27B. He has partnered with the National Ataxia Foundation in the USA to create several videos about this condition.

Researchers who study similar diseases, like HD and Ataxias, can learn from one another. Working together and learning from each other could help get us to treatments for several diseases faster.

Image credit: Tima Miroshnichenko

Historical research overlap

Historically, genetic research in HD and Ataxia has followed a similar path. There were initial efforts in the 1980s and 1990s to narrow down the "neighborhood" followed by the exact location of the genes that led to disease. There followed the creation of animal models in the 1990s and 2000s allowing scientists to study the development, progression, and treatment of HD and hereditary Ataxias. These paths involved similar laboratory techniques that built upon one another across fields.

Importantly, research developments in the HD and Ataxia fields involved similar collaborative efforts between researchers and family members who agreed to donate their time, samples, and brain tissue for the benefit of future generations.

Research today

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The shared nature of the CAG repeat in HD and several hereditary Ataxias means that researchers can continue to learn from one another, working together and in parallel, and employing a shared set of tools and ideas. Bi-annual international conferences continue to gather global scientists studying CAG repeat disorders, and many labs work on HD in addition to hereditary Ataxias like SCA. The phenomenon of CAG repeats getting longer in some cells (somatic expansion) holds true for these Ataxias in addition to HD, knowledge that can be leveraged towards treatments.

What's more, we're already reaping the benefits of shared insights in drug research. The development of ASOs for huntingtin-lowering has led to similar efforts in the Ataxia field, which also involves an extra-long, clumpy protein. Similarities between diseases in how CAGs repeat themselves has even led to the development of a drug by VICO Therapeutics that may be used to treat people with Huntington's disease, SCA1, or SCA3. Stay tuned for a deeper dive into the recent positive momentum of that human trial, which involves participants with all three disorders.

The takeaway

Ataxia and HD share many similarities. It's productive for researchers to gain insights from one another across disease fields, especially those with common genetic features. And it's gratifying to know that other families challenged with an inherited disease have built their own supportive networks whose parallel efforts drive clinical research and advocacy.

HDBuzz is proud to acknowledge the Ataxia community on Ataxia Awareness Day. We'd also like to give a shout-out to Dr. Celeste Suart at the National Ataxia Foundation (NAF) for her input. The NAF hosts SCAsource, a site similar to HDBuzz which provides plain-language research news written by scientists. If you're interested in learning more, SCAsource is a great place to start.

Leora Fox and Sarah Hernandez have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

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.

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

dominant A genetic condition that only requires one copy of a mutation to occur

somatic relating to the body

chorea Involuntary, irregular 'fidgety' movements that are common in HD

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

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

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