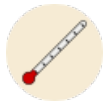


Are there genetic connections between neurodegenerative diseases?



Genetic evidence suggests connections between a polyQ disease and ALS (Lou Gehrig's disease). Why should HD people ca

By Dr Jeff Carroll on December 01, 2010

Edited by Dr Ed Wild

A group of researchers working on ALS (Lou Gehrig's disease) in yeast cells have found an unexpected genetic link between ALS and SCA-2, a disease in the same genetic family as HD. New links between these diseases might reveal new ways of approaching the search for treatments for diseases like HD.

What are polyQ diseases?

HD is one of a family of disorders caused by similar mutations in patients' DNA. DNA is like a recipe written with a very simple alphabet of four letters - A, C, G and T. In DNA, these letters are called 'bases'.

The mutation that causes HD is an abnormally long sequence of C-A-G in the DNA that's the recipe for the huntingtin protein.

Proteins are the molecules that do the work of the cell. They start out a bit like DNA - as long strings of repeating chemicals that we represent as letters. Proteins use a larger alphabet though - 22 letters. One of the protein 'letters' is glutamine, which we abbreviate as Q. The expanded CAG sequence in the HD gene results in a huntingtin protein with too many glutamines at the start of it. Because HD is caused by an increased number of glutamines, scientists call it a polyglutamine, or polyQ, disease.

In all, there are nine polyQ diseases, each caused by a CAG expansion in a different gene. They all result in the death of neurons, but the cells that die are somewhat different in each case. This unique pattern of brain cell death causes different symptoms in each disease.

Six of the nine diseases are called spinocerebellar ataxias, because the neurons that die are in a region of the brain called the cerebellum and the spinal cord. These diseases cause problems in coordinating movement, or 'ataxia' - hence 'spinocerebellar ataxia'.

The more common neurodegenerative diseases, like Alzheimer's, Parkinson's and ALS (Lou Gehrig's disease) are not usually caused by a single mutation. We usually can't tell why a



Neurodegenerative diseases might be more connected than we thought.

person gets one of these diseases - some unknown combination of genetic and environmental factors leads to the disease. Understanding what these factors are, might lead to treatments for these diseases, or at least improved understanding of why they occur.

A connection between SCA2 and ALS?

A group of scientists led by Aaron Gitler at the University of Pennsylvania set out to discover what genetic factors influence the death of cells in ALS. They used yeast cells to model the disease, which allowed them to look at over 5,000 genes to map out which ones caused more or fewer cells to die. Surprisingly, they discovered that a gene called ataxin-2 harmed the yeast model of ALS, by directly interacting with an ALS-related protein called TDP-43.

What has this to do with HD? Well, the ataxin-2 gene can develop an expanded CAG repeat, and when it does, it causes a polyQ disease called spinocerebellar ataxia type 2 (SCA2). This suggests there may be a connection between ALS and ataxin-2 - a gene that can cause polyQ diseases. That sort of connection has never been made before and it might be relevant to HD research.

Some additional experiments in cells confirmed their hunch about the physical interaction between the TDP-43 and SCA2 proteins, but the scientists wondered whether their discovery is applicable to humans, considering they discovered it in yeast cells. How could they test this?

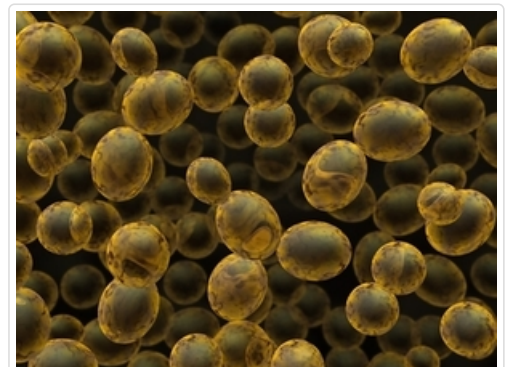
Intermediate alleles

In HD, the length of a person's CAG expansion is a major factor in the age of disease onset. More than 36 CAG repeats in the huntingtin gene will always lead to HD symptoms, if a person lives long enough, and longer CAG repeats tend to produce an earlier age of onset.

Some patients have repeats between 27 and 35 CAGs. These are called intermediate alleles, meaning they won't cause symptoms, but are higher than the norm, which is about 17 CAGs.

In SCA2, there is a similar relationship between CAG repeat length in the ataxin-2 gene and the age of onset of symptoms. Most people have a CAG repeat length of about 22 in their ataxin-2 gene, while SCA2 patients have a repeat of greater than 34. CAG repeats between 24 and 34 in the ataxin-2 gene are considered 'intermediate'.

The researchers looked at whether longer CAG repeats in ataxin-2 made the yeast ALS cells worse, and found that they did. Next, they did a very clever experiment, which was to measure the length of the CAG repeat length in the ataxin-2 gene in **human** patients with ALS. None of these patients had the sorts of symptoms caused by SCA2, but the researchers wondered whether the link between the CAG length of their ataxin-2 gene and ALS was present in humans, too.



Using single cell yeast lets scientists test thousands of genes for their effects on disease.

They found that intermediate CAG repeat lengths in ataxin-2 were much more likely than expected in patients with ALS. This suggests that longer CAG repeats in ataxin-2 are a powerful risk factor for ALS. We don't understand the details of this link, but it suggests there are connections between these diseases that we didn't appreciate before.

Why do we care?

The authors **don't** believe that this same connection exists between the CAG repeat length in the HD gene and ALS. But what they have shown is that unexpected connections might exist between the neurodegenerative diseases, and that studying something as simple as yeast can reveal unexpected features of these diseases. These connections give scientists new targets to explore in trying to understand what causes these devastating conditions. Finding these links between these diseases also gives us hope that therapies discovered for one might help others.

The authors 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.

intermediate alleles HD genes with CAG lengths between 27-35, which do not result in HD symptoms, but are longer than normal. Intermediate alleles are thought to be at risk of expanding in the offspring of people who carry them.

huntingtin protein The protein produced by the HD gene.

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

PolyQ A description of HD and other diseases that are caused by abnormal expansion of stretches of DNA containing the sequence CAG repeated many times. Too many CAGs in a gene results in proteins with too many 'glutamine' building blocks, and glutamine is represented by the symbol Q.

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

glutamine the amino acid building block that is repeated too many times at the beginning of the mutant huntingtin protein

neuron Brain cells that store and transmit information

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

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