HDBuzz

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

A back-to-front hidden message in the HD gene?

Unzip your genes! A backwards message, hidden in the 'backup DNA' of the Huntington's disease gene... what does it me

By Dr Ed Wild on August 19, 2011
Edited by Dr Jeff Carroll

The double-helix of our DNA contains a backup copy of every gene. Sometimes the backup DNA produces hidden 'messages' that can alter things in our cells. Researchers have now discovered a message in the backup copy of the Huntington's disease gene, which appears to be able to influence how much huntingtin protein is made.

Unzip your genes!

You might have heard of the phrase 'double-helix', used to describe the DNA that our genes are made from. But what exactly does that mean?

Well, each gene is a set of instructions for how to make a protein. The instructions are 'written' in a sequence of 'letters' which we call **bases**. Each base is a small chemical, and the bases are joined together in long strands. The bases are abbreviated as A, C, G and T.

The two strands of DNA like to

A single strand doesn't sound much like a double-helix - and that's because the DNA that contains the instructions

for making proteins is only half the story. The bases in our DNA naturally like to pair up like dance partners - A pairs with T, and C pairs with G.

stick together but can be unzipped when the cell wants to use the DNA

It's this pairing that gives DNA its double-helix structure. Each base on the 'business' strand lines up with a partner, and the partners all join up to form another strand. The two strands wrap around like a spiral staircase - finally, the double-helix. The scientific name for the business strand is the **sense** strand; the other one is called the **anti-sense** strand.

Our DNA is arranged like this for two reasons.

Firstly, it makes copying the DNA easier, when cells want to divide: all the cell has to do is unzip the DNA down the middle so that the strands separate, then throw bases at the two strands. The bases stick to their partners, leaving two exact copies of the original double-helix!

The second reason is that if the DNA gets damaged, the 'spare' anti-sense strand can be used as a backup copy to tell the cell's DNA repair equipment how to fix the sense DNA.

Anti-sense messages

The anti-sense strand clearly has its uses. But until recently it was thought that all the important work of the DNA was done by the sense strand. That all changed a few years ago when scientists realized that some genes have useful DNA hidden in their anti-sense strands.

That's possible because the two strands of our DNA are chemically very similar. The main difference is that the machinery that reads the DNA can only run in one direction along each strand, like cars traveling in opposite directions along the two lanes of a road. The sense and anti-sense strands are read in different directions.

What do we mean by ‘useful DNA’? Well, when a cell reads a gene, the first thing that’s produced is a single-stranded copy of the gene. This copy of the gene is made with chemicals called RNA, which are very similar to those in the original DNA. The RNA copy is used by the protein-building machinery of the cell. Using these copies of genes, rather than constantly using the original gene, means the all-important DNA is protected from constant use.

Historically, scientists thought that the RNA in cells was mostly these copies of genes, or ‘messages’ as they called them. But in the last few years we’ve learned that cells are full of RNA of all different types - not just copies of genes that are going to be made into proteins, but a baffling range of RNA in different sizes and patterns, with functions that we don’t fully understand. Some of these RNAs in the cell were actually made from the anti-sense, rather than the sense strand. In some genetic diseases, an anti-sense message molecule is a cause of damage.

An anti-sense message in the HD gene

> “A few years ago scientists realized that some genes have useful DNA hidden in their anti-sense strands.”

Prof Russell Margolis is a Huntington’s disease researcher at Johns Hopkins University, with an interest in anti-sense messages, so he decided to look at the anti-sense strand of the gene that causes HD. The gene, called HTT, is a recipe for the huntingtin protein. In people with HD, or who are going to get it, a stretch at the beginning of the gene has more than the usual number of repeats of the sequence CAG.

Figuring out the anti-sense sequence for the HTT gene is pretty easy, because we already know the sequence of the sense strand, and we know that the bases of DNA only partner together in specific ways. For example,

where the sense strand reads C-A-G-C-A-G-C-A-G and so on, reading backwards and switching to the opposite partnered bases, the anti-sense strand must read C-T-G-C-T-G-C-T-G.

Using brain tissue donated by Huntington's disease patients, Margolis looked at whether an anti-sense message from the HTT gene was present. He found that it was - and he also found it in brains donated by people without HD.

Margolis called the anti-sense HTT message **HTTAS** - short for huntingtin anti-sense.

Consulting computer databases of all known proteins, Margolis found that HTTAS wasn't a recipe for any known protein. Though we can't be sure, that probably means that the HTTAS message is in cells, but doesn't get as far as causing the cell to make a protein. But as we now know, sometimes anti-sense messages can do stuff on their own. So Margolis set out to find out what, if anything, the HTTAS message molecule does in cells.

What does the message do?

Surprisingly, although the HTTAS message was found in all the brains, the levels were lower in the HD brains, suggesting that something about HD brains reduces the amount of HTTAS message. And the longer the CAG repeat length, the less anti-sense message there was.

What about the other way round? Can the anti-sense message molecule influence the forwards-reading HTT gene? Looks like it can. Working in cells in the lab, Margolis' team used a chemical switch to prevent the cells from producing the HTTAS message. Those cells produced **more** of the forwards-reading huntingtin message.

That all seemed to make sense - in cells with an expanded CAG repeat, there's less HTTAS (the anti-sense message). Because HTTAS has the effect of lowering the levels of HTT, reducing HTTAS increases levels of

HTT.

A spanner in the works

That explanation works in itself, but if it's true we'd expect the brains of people with HD to have more of the HTT message overall. But that's not what we see - all brains have about the same amount of HTT message, regardless of whether their owner had HD.

Clearly - as is often the case - something different is happening in patient brains from what was seen in the lab.

Through more experiments looking at cells with different CAG repeat lengths, Margolis was able to show that, as well as an effect of HTTAS on HTT levels, the HTT gene also has effects on itself - and those effects were the exact opposite from the effects of HTTAS.

The 'sense' and 'anti-sense' strands of DNA are read by the cell in opposite directions. The 'sense' strand contains most of the protein-making instructions.

So in someone with an expanded CAG in the HTT gene, there's less of the HTTAS message, so levels of the HTT message **increase**. But at the same time, the expanded HTT gene acts to **decrease** levels of its own message.

Overall the two effects cancel each other out, and HTT message levels end up the same!

Could the anti-sense message be useful anyway?

That sounds like a complicated way to get back to where we started. So have these discoveries told us anything that might be useful?

Although the two effects Margolis has shown cancel each other out normally, it's still theoretically possible that they could be manipulated separately, to produce benefits.

Since the HTTAS message lowers levels of HTT message, increasing HTTAS levels artificially might reduce production of the harmful huntingtin protein. That could cause beneficial effects similar to what has been seen with 'gene silencing' treatments in animal models of Huntington's disease.

So what this work adds is another possible target: we can add 'increasing huntingtin antisense message' to our list of possible ways of improving the health of cells in Huntington's disease.

This is very early-stage work that's unlikely to lead to treatments any time soon. The more direct approaches of gene silencing, which we've written about before, will certainly be tested in human patients first.

But when it comes to developing treatments for HD, every target helps, and now there's a new potential target: a hidden message, written backwards in our DNA.

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.
anti-sense the half of the DNA double-helix that is mostly used as a backup, but sometimes produces message molecules
gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein
sense strand the half of the DNA double-helix that contains instructions for most proteins. The 'business' strand.
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

HTTAS the anti-sense (backwards) version of the HTT gene

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

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