Possible role for Huntington's gene discovered

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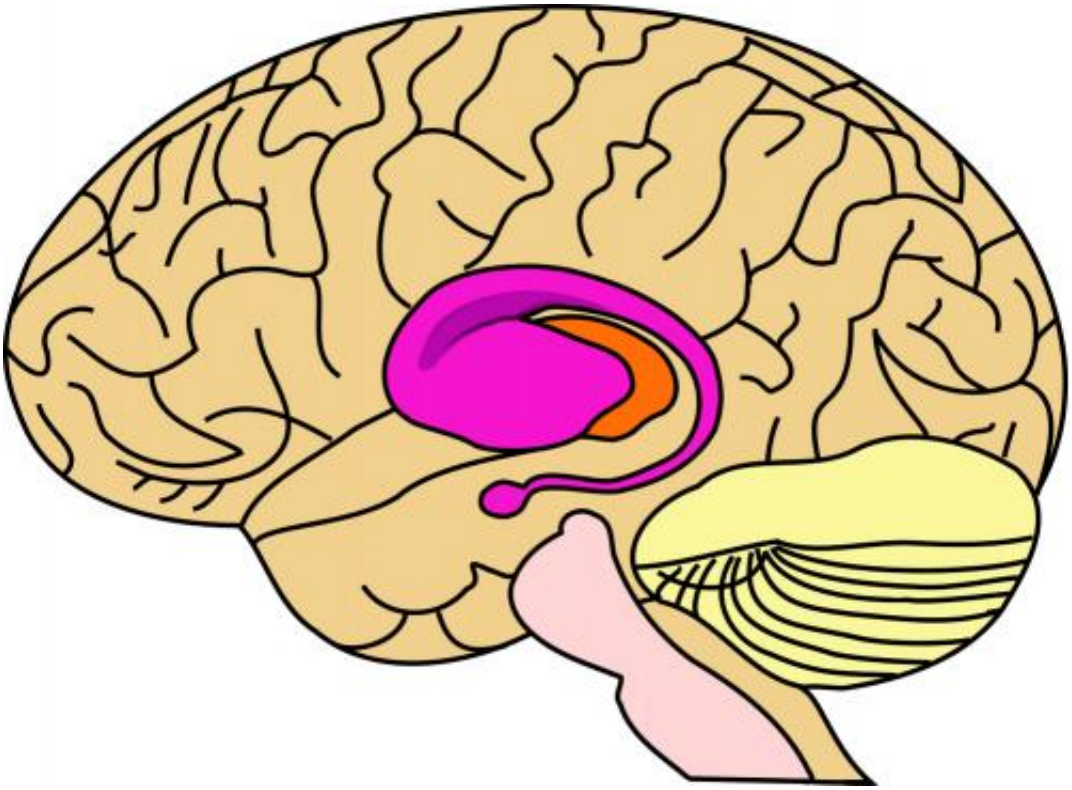

The gene that causes Huntington's disease does most of its damage in the basal ganglia, shown in pink. The basal ganglia are responsible for many functions, including voluntary motor control and habit formation. Credit: U.S. Food and Drug Administration

About 20 years ago, scientists discovered the gene that causes Huntington's disease, a fatal neurodegenerative disorder that affects

about 30,000 Americans. The mutant form of the gene has many extra DNA repeats in the middle of the gene, but scientists have yet to determine how that extra length produces Huntington's symptoms.

In a new step toward answering that question, MIT biological engineers have found that the protein encoded by this mutant gene alters patterns of chemical modifications of DNA. This type of modification, known as methylation, controls whether genes are turned on or off at any given time.

The mutant form of this protein, dubbed "huntingtin," appears to specifically target genes involved in brain cell function. Disruptions in the expression of these genes could account for the neurodegenerative symptoms seen in Huntington's disease, including early changes in cognition, says Ernest Fraenkel, an associate professor of biological engineering at MIT.

Fraenkel's lab is now investigating the details of how methylation might drive those symptoms, with an eye toward developing potential new treatments. "One could imagine that if we can figure out, in more mechanistic detail, what's causing these changes in methylation, we might be able to block this process and restore normal levels of transcription early on in the patients," says Fraenkel, senior author of a paper describing the findings in this week's issue of the Proceedings of the National Academy of Sciences.

Unexpected patterns

DNA methylation has a major impact on genetic expression: Genes that are methylated at particular sites are usually dormant, because the methyl groups deny access to the proteins needed to copy DNA's instructions and carry them to the rest of the cell. For a long time, scientists believed that DNA methylation patterns changed during embryonic development

and then remained constant in adulthood. However, DNA methylation is emerging as important to a wide range of normal cell activity.

In the new study, the MIT team measured changes in methylation patterns during early stages of Huntington's disease in cells derived from a brain region called the striatum in mouse embryos. This region, where planning of movement occurs, is severely affected by Huntington's disease.

"We're very interested in the earliest phases, because that's when there's the most hope that you could either slow down or stop progression of the disease, and allow people to live healthy lives much longer," Fraenkel says. "By the time there is much more severe neurodegeneration, it's unlikely that you're going to be able to reverse the damage."

Fraenkel and Ng were surprised to find a dramatic difference in methylation patterns between cells with normal and mutant forms of the huntingtin protein. Some genomic sites gained methylation, while others lost it. Many of the affected sites were in regions that regulate the expression of nearby genes necessary for neuron growth and survival.

Turning genes off and on

After observing the changing methylation patterns, the MIT team identified many proteins that tend to bind to the DNA sites where those changes take place. These proteins include Sox2 and others known to regulate genes involved in neuronal activity, including growth of the neurons.

The new findings go a long way toward explaining how the extra DNA repeats in the mutant form of the huntingtin gene might bring about disease, says Mark Mehler, a professor of neurology at the Albert Einstein College of Medicine. "People have not had a good sense, until

this paper, of what these repeats might be doing," says Mehler, who was not part of the research team. "What this study has done is demonstrated a mechanism by which expanded repeats can alter gene expression."

The researchers are now studying whether huntingtin affects other modifications of DNA and histones, the proteins around which DNA is wound. Together, these might cause genes to be turned on or off inappropriately, Fraenkel says.

The researchers are also working with mouse models at different stages of Huntington's disease to track how the methylation patterns change as the disease progresses. "That also gives us an opportunity to do interventions and test whether affecting particular proteins influences the progression of the disease," Fraenkel says.

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