Team finds drug that helps Huntington's disease-afflicted mice—and their offspring

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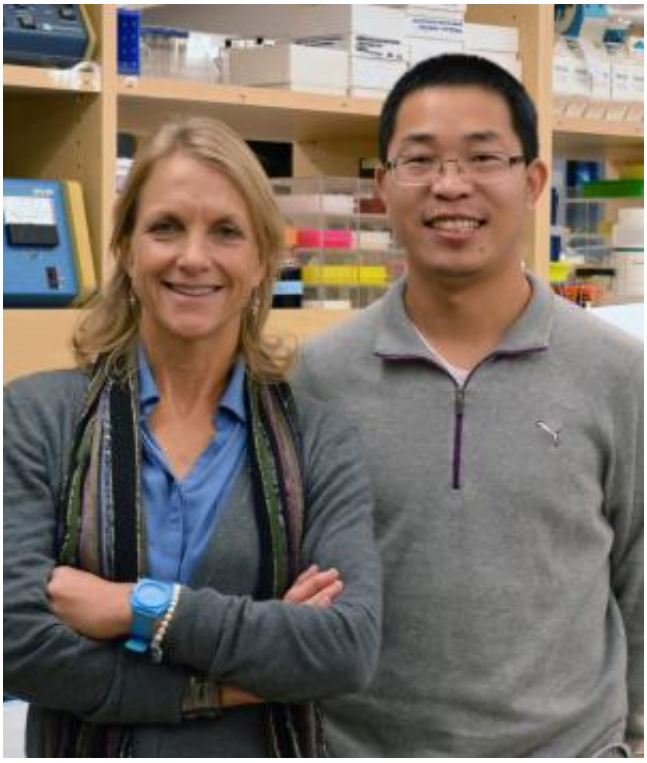

Authors of the new study include (left to right) Elizabeth Thomas, Ph.D., associate professor at the Scripps Research Institute, and Haiqun Jia, first author and professional scientific collaborator. Credit: Photo courtesy of The Scripps Research Institute.

Famine, drug abuse and even stress can "silence" certain genes, causing health problems in generations to come. Now scientists are wondering—could therapies that change gene expression in parents help

their children?

A new study from scientists at The Scripps Research Institute (TSRI) suggests this is possible. The research showed that the offspring of mice treated with a drug also had delayed onset and reduced symptoms of Huntington's disease, an inherited, degenerative disease that causes a loss of motor skills, cognitive impairment and death.

This was the first time scientists have shown that drug compounds that benefit parents can also cause changes in genetic expression that benefit offspring—in this case, improved memory and motor skills.

"One exciting aspect of our study is that the parental drug treatment made the offspring better, not worse, like other compounds known to cause transgenerational effects," said Elizabeth Thomas, associate professor at TSRI who led the new study.

Thomas and her colleagues report their findings online ahead of print in this week's Early Edition of the journal *Proceedings of the National Academy of Sciences*.

Compound Shows Potential

The Huntington's Disease Society of America estimates that more than a quarter of a million Americans have the disease or are at risk of inheriting it from a parent. Thomas began studying Huntington's disease 15 years ago, when she found out that a close friend's mother had the disease.

"If your mom or dad carries the mutation, you have a 50-50 chance of inheriting the disease," said Thomas. Although there is a test to see if a person will develop Huntington's, Thomas said many people don't get tested because there are no good treatments to prevent or reduce

symptoms.

Thomas and other scientists at TSRI have been testing compounds called histone deacetylase (HDAC) inhibitors to see if they can induce "epigenetic" changes to help lessen the severity of diseases such as Huntington's.

Epigenetics refers to changes in gene expression—triggered by diet or toxins in the environment, for example—that are not caused by changes to the genetic code. While the genetic sequence itself remains unchanged, epigenetic changes can be passed to the next generation and have been linked to conditions such as obesity and autism-related disorders. Epigenetic changes are often caused by DNA methylation, a process where a methyl group is attached to DNA, silencing gene expression.

In previous studies, the Thomas lab tested several compounds with the potential to affect Huntington's disease through epigenetic changes. Thomas and her colleagues went on to test one of these compounds, HDACi 4b, which was originally developed by TSRI Professor Joel Gottesfeld. Subsequent studies showed that HDACi 4b worked to reduce symptoms and delay disease onset in mice, and the researchers were curious whether these benefits could be passed on to offspring through epigenetics.

In the first part of the new experiment, the researchers tested the effects of HDACi 4b on gene expression in mouse brain and muscle samples. They found that HDACi 4b changed the expression of genes related to DNA methylation. Next, they showed that HDACi 4b treatment of human patient fibroblast cells altered DNA methylation of more genes on the male-carried Y chromosome than other chromosomes.

The researchers then administered the compound to a group of male

mice with a human Huntington's disease gene. Another group of similar mice did not receive the treatment. After one month of treatment, the mice were bred, and their offspring were tested for symptoms of the disease.

As expected, the female offspring showed no differences, but the male offspring from the drug-treated mice showed a delay in disease onset and a reduction of motor and cognitive symptoms that included improved performance in tests of balance, speed and memory.

Looking Ahead

With the new results from mouse models, Thomas is curious whether the effects of HDAC inhibitors could be passed down through the female germline, and whether the beneficial effects could persist in generations of grandchildren or great-grandchildren.

The scientists are also interested in the effects of other types of HDAC inhibitors already approved to treat certain cancers and bipolar disorder. "Many patients with these diseases have kids, so a big question is how these treatments might affect their offspring," said Thomas.

More information: HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1415195112

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