Study identifies new biomarkers for Huntington's disease

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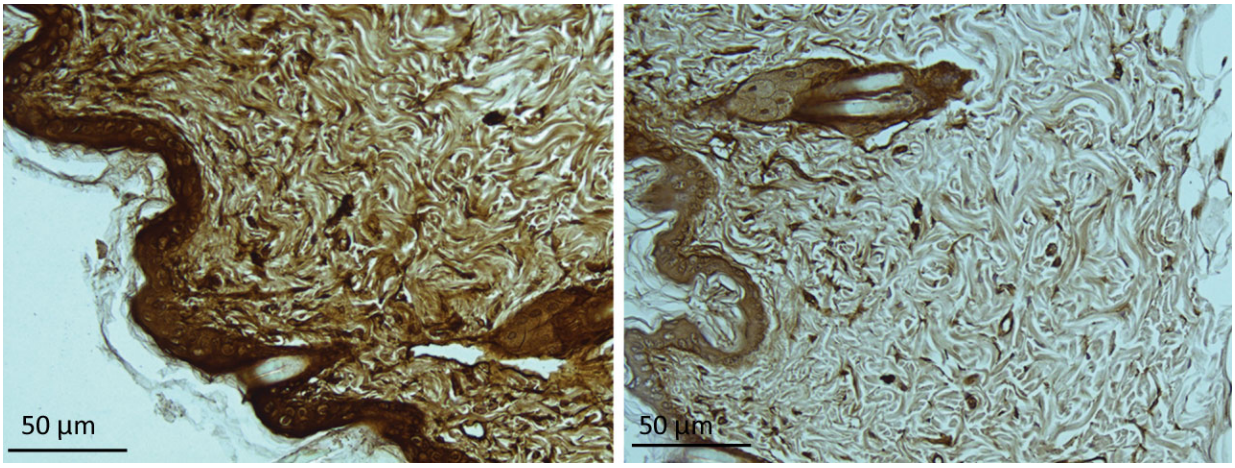

Huntingtin aggregates (brown) are elevated in skin sections from HD model mice (left). Levels are reduced after treatment with P110 (right). Credit: Disatnik et al., 2016

Researchers at Stanford University School of Medicine have identified several new biological markers to measure the progression of the inherited neurodegenerative disorder Huntington's disease (HD). Their findings, which will be published online November 7 ahead of issue in *The Journal of Experimental Medicine*, could benefit clinical trials that test new treatments for the disease.

In HD, an expansion of a trinucleotide repeat sequence in the gene

encoding huntingtin protein results in the production of a mutant form of huntingtin that can aggregate and damage cells, particularly neurons in the striatum and cerebral cortex. Patients display a progressive loss of voluntary and involuntary movements, as well as psychiatric and cognitive disturbances, and usually die 10-15 years after its onset.

Though genetic testing can identify HD patients long before their first symptoms appear in middle age, there are still no pharmacological treatments that can prevent or ameliorate the disease. A few drugs have shown promise in cell culture or animal models, but clinical trials in humans are time consuming because of the slow onset and progression of the disorder's clinical symptoms. Moreover, researchers are unable to take biopsies of the brain to assess the effects of potential therapeutic compounds.

One of the earliest events in HD is that mutant huntingtin aggregates disrupt the function of mitochondria, lowering cellular energy levels and causing oxidative damage. Daria Mochly-Rosen and her team at Stanford have previously identified a molecule, P110, that can restore mitochondrial function and prevent neuronal death in mouse models of HD. Now the researchers set out to identify markers of HD in non-neural tissues that could be used to track the progression of the disease and its response to P110 or other candidate drugs.

The team found that the levels of mitochondrial DNA, presumably released from dying neurons, were increased in the blood plasma of mice that were starting to develop the symptoms of HD. In contrast, mitochondrial DNA levels decreased at later stages of the disease. P110 treatment corrected plasma mitochondrial DNA back to the levels seen in healthy mice.

Mochly-Rosen and colleagues identified several other potential biomarkers that were elevated in HD model mice, including the levels of

8-hydroxy-deoxy-guanosine, a product of oxidative DNA damage, in the urine and the presence of mutant huntingtin aggregates and oxidative damage in muscle and skin cells. The levels of each of these biomarkers were reduced by P110 treatment.

It remains to be seen whether all of these biomarkers are reliable indicators of HD in humans. The Stanford team found, however, that mitochondrial DNA levels were significantly elevated in plasma samples from a small number of HD patients. "We have identified several biomarkers that correlate with disease progression and treatment in mice," says Mochly-Rosen. "We hope that our work will provide the basis for a larger study of patient samples that may ultimately identify biomarkers that can be used as surrogate markers to determine the benefit of therapeutic interventions in diagnosed but asymptomatic HD patients to prevent or delay disease onset."

More information: Disatnik, M.-H., et al. 2016. *J. Exp. Med.* DOI: 10.1084/jem.20160776

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