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Antisense oligoneucleotide corrects striatal transcriptional abnormalities and protects function in HD mice

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Findings from postmortem studies of the brains of Huntington's Disease (HD) patients suggest that transcriptional dysregulation may be an early step in the pathogenesis of HD before symptoms appear. Other studies report transcriptional alterations in the brains of some mouse models of HD. A new study has found transcriptional changes in mouse striatum which correlate with progressive motor and psychiatric deficits and, most importantly, reports for the first time, that an antisense oligonucleotide (ASO) may be used therapeutically to both correct striatal transcriptional abnormalities and improve motor and behavioral problems. The article is published in the latest issue of the *Journal of Huntington's Disease*.

"Down regulation of the expression of key molecules at the mRNA level could well be one of the underlying mechanisms leading to neuronal dysfunction in HD," says Lisa M. Stanek, PhD, of Genzyme Corporation's Rare Disease Unit, Framingham, MA. "The data presented here provide strong evidence that transcriptional correction has great potential as a novel therapeutic biomarker for HD."

Huntington's disease (HD) is an inherited progressive neurological disorder for which there is presently no cure. It is caused by a dominant mutation in the HD gene leading to expression of mutant huntingtin (HTT) protein. Expression of mutant HTT causes subtle changes in cellular functions, which ultimately results in jerking, uncontrollable

movements, progressive psychiatric difficulties, and loss of mental abilities.

The current study focuses on what is happening early in the disease process before symptoms or even neuropathological changes are apparent. The authors believe that mutant HTT may be disrupting normal transcriptional processes in susceptible neurons. In genetics, transcription refers to the process by which genetic information is copied from DNA to RNA, resulting in formation of a specific protein.

The investigators used the YAC 128 mouse HD model, which mimics many of the pathologic hallmarks of human HD. These include age-related loss of brain mass and a regionally distinct pattern of mutant HTT accumulation.

They found that levels of several striatal mRNAs (DARPP-32, DIR, D2R, Enk and CB1) progressively decreased with age in the YAC128 mice but no age-related changes were seen in the controls. Significant differences between the groups were found at 9 and 12 months. "Transcriptional dysregulation in the YAC128 HD mouse does not appear to be a phenomenon of accelerated aging but likely of the disease process," says Dr. Stanek.

Investigators focused on whether an ASO directed against mutant HTT mRNA could be an effective therapeutic strategy. ASO or saline was administered directly into the CNS via an intraventricular cannula for two weeks using an osmotic mini pump. After a two-week recovery, the mice were tested on an accelerating rotarod apparatus to measure their motor coordination and motor learning, and then on the Porsolt swim test which is used to assess depression in rodents. Two to four months after ASO treatment began, ASO-treated YAC128 mice continued to perform at the same level as saline-treated wild type controls, while age-matched saline-treated YAC128 mice performed significantly worse. In

other words, the ASO treatment prevented a decline in motor coordination. Similarly, the ASO treatment lessened the onset of depressive behavior, as measured by immobility during the swim test, in these HD mutant mice.

When the mouse brains were analyzed, the ASO-treated YAC128 mice showed a 30% reduction in mutant HTT mRNA levels and significant reduction in mutant HTT protein levels four months after the start of ASO treatment. Thus, the study showed a correlation between the correction of transcriptional abnormalities and functional improvement.

Further experimentation focused on the effect of ASO treatment on specific striatal-enriched transcripts in six-month old YAC128 and control mice. These results showed that "decreasing mutant HTT expression using an ASO directed specifically against human mutant HTT in YAC 128 mice significantly corrected the transcriptional profiles of DARPP32, enkephalin and CB1. D1 and D2 receptor levels also showed a trend towards improvement following ASO treatment," says Dr. Stanek.

The authors suggest that monitoring transcriptional changes could serve as a powerful tool for clinicians to follow HD progression and treatment. Since taking samples from human brain is not possible, alternative measures, such as changes in the content of mRNA or proteins in peripheral tissues or visualizing dysregulated receptors in brain using advanced neuroimaging techniques, may be developed as useful transcriptional biomarkers.

More information: Stanek, L. et al. Antisense oligonucleotide-mediated correction of transcriptional dysregulation is correlated with behavioral benefits in the YAC128 mouse model of Huntington's disease, *Journal of Huntington's Disease*, Volume 2/Issue 2. DOI: 10.3233/JHD-130057

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