Study discovers novel therapeutic targets for Huntington's disease

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A study led by researchers at Boston University School of Medicine (BUSM) provides novel insight into the impact that genes may have on Huntington's disease (HD). The study, published online in *PLOS Genetics*, identified specific small segments of RNA (called micro RNA or miRNA) encoded in DNA in the human genome that are highly expressed in HD. Micro RNAs are important because they regulate the expression of genes. The researchers showed that these miRNAs are present in higher quantities in patients with HD and may act as a mitigating factor in the neurologic decline associated with the disease, making them a possible therapeutic target.

HD is an inherited and fatal neurological disorder that is usually diagnosed when a person is between 30 and 50 years old. Huntingtin, the single gene mutation responsible for the disease, was identified in 1993.

The investigators examined 21 autopsy brain samples: 12 with HD and nine without. Genetic sequencing analyses were performed on these brain tissues, including quantifying the amount of all the microRNAs present in the brain and their corresponding gene or messenger RNA (mRNA) counterparts. This information was combined with a genetic study to characterize variations in the HD gene. The researchers also gathered the clinical neurological information on the patients' age when HD symptoms presented and how long the patient survived with the disease.

Based on this analysis, the investigators discovered increased amounts of four miRNAs were expressed in the brains of HD patients and that the amount of miRNA was highly correlated with disease status. An increased amount of miRNA in brain cells was correlated with a younger age at disease onset and an earlier age at death of the patients.

"The genes which these miRNAs regulate also had increased levels, indicating that these gene expression, indicating that these gene products were likely targeted for storage and for possible future use within the brain cell, rather than for destruction. When we experimentally increased the expression of the microRNAs in model nerve cells designed to replicate the conditions of HD, the cells lived longer, indicating that these miRNAs may promote cell survival," explained lead author Richard Myers, PhD, professor of neurology at BUSM. The authors conclude that these genes may represent new therapeutic targets for HD.

According to the researchers, these miRNA sequences were found to be present in much higher levels in patients with HD (some were undetectable in the brain cells of normal patients), which would also make them excellent targets as biomarkers for HD expression. "If this miRNA were also found outside of brain tissue, for example in the blood, it could be used as an inexpensive, non-invasive assessment of the severity of the disease and perhaps for evaluating the effectiveness of treatments in clinical trials for HD. If the amount of miRNA were quantified in an HD patient, the amount could provide insight into the likely age of disease onset or life expectancy of the patient which current genetic testing in HD does not provide," added Myers.

Provided by Boston University Medical Center