MedicalXpress

Insights on timing of Huntington's disease onset

August 8 2019

Huntington's disease (HD), an inherited and fatal disorder in which nerve cells in the brain break down over time, may become evident at any time in life but typically starts in a person's 30s or 40s. New research results published in the journal *Cell*, call into question an accepted theory about the timing of HD onset.

HD and a number of other neurodegenerative diseases are caused by inheritance of an expanded DNA segment of repeated CAG nucleotides that code for the amino acid glutamine. The age of onset of these diseases is negatively correlated with the length of the expanded CAG repeat and has been thought to result from increasing toxicity of the multiple glutamines—or polyglutamine—encoded by this CAG repeat in the DNA.

When James Gusella, Ph.D., Jong-Min Lee, Ph.D., and Marcy MacDonald, Ph.D., of the Molecular Neurogenetics Unit in the Center for Genomic Medicine at Massachusetts General Hospital (MGH), and their colleagues in the Genetic Modifiers of Huntington's Disease Consortium analyzed information on more than 9,000 individuals with HD, they found that the timing of HD onset was due to a property of the expanded CAG repeat in an individual's DNA, not due to the length of polyglutamine.

In addition, investigators found that multiple genes involved in DNA maintenance and repair can modify the timing of HD onset, making it either earlier or later than expected based upon the length of the

inherited CAG repeat.

"Our data support the hypothesis that the critical property of the CAG repeat is its propensity to expand further as an individual ages, leading to longer and longer repeats in particular brain cells until a critical threshold length is reached and toxicity results," says Gusella, who is also a professor of neurogenetics at Harvard Medical School. "Our findings change the way researchers look at HD and other DNA repeat diseases by focusing attention early in the disease process on the DNA repeat itself rather than on the protein that it codes for. Rather than sharing a pathogenic process based upon polyglutamine toxicity, the 'polyglutamine diseases' instead share a DNA property that can be modified by processes that the cell uses to maintain the DNA."

The results indicate that either the CAG repeat itself or the DNA maintenance processes that modify its expansion in neurons may be potential targets for treatments that could delay or prevent the onset of HD and other repeat disorders. "A number of approaches are already being pursued to alter the length or purity of the HD CAG repeat and to develop drugs that inhibit or activate particular DNA maintenance proteins," says Gusella.

More information: Jong-Min Lee et al, CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset, *Cell* (2019). DOI: 10.1016/j.cell.2019.06.036

Provided by Massachusetts General Hospital