Novel mouse model provides insight into rare neurodegenerative disease

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New research sheds light on common pathogenic mechanisms shared by Huntington's disease (HD) and HD-like disorders. The study, published by Cell Press in the May 12, 2011, issue of the journal *Neuron,* uses a new transgenic mouse model for an HD-like disorder to unravel complex molecular events that drive disease pathology.

Huntington's disease like-2 (HDL2) is a rare neurodegenerative disorder that is similar to HD. However, HDL2 patients do not have the HD-causing mutation: a repeating CAG sequence in the huntingtin gene that codes for the amino acid glutamine. This mutation results in the production of a chain of glutamines called a polyglutamine (or polyQ) tract within the mutant huntingtin protein. Instead, HDL2 is caused by a CTG/CAG repeat within a region of the Junctophilin-3 (JPH3) gene.

"Both HD and HDL2 brains contain a pathological hallmark called 'intranuclear inclusions' (NIs) that have a similar but not identical distribution pattern in the brain," says senior study author, Dr. X. William Yang, from the Semel Institute at the University of California, Los Angeles. "The NIs in HD contain mutant huntingtin protein, but those in HDL2 do not. Therefore, the pathogenic origins of NIs in HDL2 and the mechanisms underlying HDL2 pathogenesis remain to be uncovered."

To gain new insight into HDL2, Dr. Yang and colleagues at UCLA, and collaborators led by Dr. Russell Margolis at Johns Hopkins University, developed a series of bacterial artificial chromosome (BAC)-mediated

transgenic mouse models of HDL2 (BAC-HDL2) that contain an expanded CTG/CAG repeat in the human JPH3 gene, as well as control BAC mice with a nonexpanded CTG/CAG repeat. BACs have been shown to be useful for modeling genetic diseases because they allow introduction of a large piece of human DNA carrying the disease mutation into the mouse genome, thereby permitting the accurate expression of the disease gene similar to that in the patient.

The researchers found that the BAC-HDL2 mice exhibited several key characteristics found in HDL2 patients, including age-dependent motor deficits, selective forebrain atrophy, and brain region-specific distribution of NIs. Molecular analysis revealed that a novel promoter was driving expression of an unexpected section of DNA which encoded a polyQ protein. Importantly, BAC-HDL2, but not control BAC mice, accumulated polyQ-containing NIs in a pattern that was remarkably similar to that seen in HDL2 patients.

The findings point to overlapping polyQ-mediated pathogenic mechanisms in HD and HDL2. "We have generated and characterized the first BAC transgenic mouse models of an HD-like disorder, HDL2," concludes Dr. Yang. "Our analysis suggests that expression of a novel expanded polyQ protein could play a critical role in HDL2 pathogenesis and provides experimental evidence to suggest that HD and HDL2 may have overlapping polyQ-mediated disease mechanisms. Further elucidation of such mechanisms may provide therapeutic targets for both disorders."

More information: Wilburn et al.: “An Antisense CAG Repeat Transcript at JPH3 Locus Mediates Expanded Polyglutamine Protein Toxicity in Huntington’s Disease-like 2 Mice.” *Neuron* May 12, 2011

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