Genetic modifiers of Huntington's disease

Jong-Min Lee, Ph.D.

Assistant Professor
Center for Genomic Medicine, Massachusetts General Hospital
Department of Neurology, Harvard Medical School

Abstract

Huntington's disease (HD) is a dominantly inherited neurological disorder. A CAG trinucleotide repeat expansion in *HTT* is both necessary and sufficient to cause clinical manifestations. The rate of the pathogenic process that leads to clinical signs is largely determined by CAG repeat size but the remaining variation in age at onset strongly suggested the existence of disease-modifiers. Our international collaborative team performed a genome-wide association (GWA) analysis that identified disease-modifying genetic variants that hasten or delay the clinical onset of HD. Our GeM-HD consortium HD modifier GWA study revealed two genome-wide significant modifier loci. A region on chromosome 15 harbors two independent modifier signals; one hastens age at onset by ~6 years, and the other delays age at onset by ~1.4 years. A region on chromosome 8 carries a locus that delays onset by ~1.6 years. Discovery of significant genetic modifiers of onset from our large international study will provide pre-validated (in humans) targets for drug discovery.