Normal and mutant HTT interact to affect clinical severity and progression in Huntington disease.

OBJECTIVE: Huntington disease (HD) is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion in the HD gene (HTT). We aimed to assess whether interaction between CAG repeat sizes in the mutant and normal allele could affect disease severity and progression. METHODS: Using linear regression and mixed-effects models, the influence of mutant and normal CAG repeat sizes interaction was assessed on 1) age at onset in 921 patients with HD, 2) clinical severity and progression in 512 of these patients with follow-up data available, and 3) basal ganglia volume on magnetic resonance images in 16 premanifest HD mutation carriers. RESULTS: Normal and mutant CAG repeat sizes interacted to influence 1) age at onset (p = 0.001), 2) severity or progression of motor, cognitive, and functional, but not behavioral, symptoms in patients with HD (all p< 0.05), and 3) in premanifest subjects, basal ganglia volumes (p< 0.05). In subjects with mutant CAG expansions in the low range, increasing size of the normal repeat correlated with more severe symptoms and pathology, whereas for those subjects with expansions in the high range, increasing size of the normal repeat correlated with less severe symptoms and pathology. CONCLUSIONS: Increasing CAG repeat size in normal HTT diminishes the association between mutant CAG repeat size and
disease severity and progression in Huntington disease. The underlying mechanism may involve interaction of the polyglutamine domains of normal and mutant huntingtin (fragments) and needs further elucidation. These findings may have predictive value and are essential for the design and interpretation of future therapeutic trials.

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