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Overlap between age-at-onset and disease-progression determinants in Huntington disease

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Study question

Is disease progression in Huntington disease (HD) determined by the same factors that determine age-at-onset?

Summary answer

Approximately two-thirds of the disease progression determinants are also age-at-onset determinants.

What is known and what this paper adds

The age-at-onset determinants in HD are the size of the CAG repeat expansion in the *HTT* gene, environmental factors, and genes other than *HTT*. This study shows that these factors are also important determinants of disease progression.

Participants and setting

This study reviewed data for 3,411 patients with HD who were registered with Enroll-HD, a worldwide observational study on HD. Online data retrieval was performed on February 17, 2017. Each participant had 40–57 CAG repeats and ≥2 follow-up assessments after disease onset.

Design, size, and duration

For each participant, this study calculated a residual age-at-onset (RAO), which was defined as the difference between the reported age-at-onset and the expected age-at-onset given that person's number of CAG repeats. The RAO was treated as a proxy for age-at-onset determinants other than the number of CAG repeats. This study measured disease progression as annual changes in Unified HD Rating Scale metrics including the total functional capacity, the total motor score, and a cognitive summary score that was based on the Scale's cognitive subdomains.

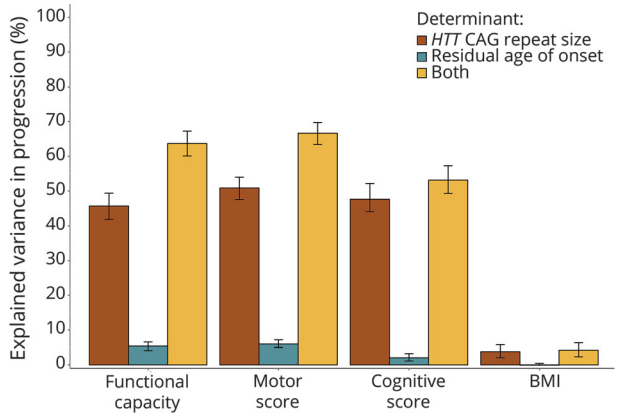
Primary outcomes measures

The primary outcome was the extent to which various factors explained variability in disease progression rates in a linear mixed-effects model.

Main results and the role of chance

CAG repeat sizes alone accounted for approximately half of the variability in disease progression rates. In conjunction with CAG repeat sizes, RAO values accounted for another 5%–20% of the variability. There was a substantial influence of *HTT* CAG repeat size on the average body weight, with each CAG repeat increase associated with 0.55 units lower average BMI. However, RAO was not associated with the average BMI and hardly affected weight loss.

Figure Distribution of the variance in HD progression rates attributable to age-at-onset determinants



Bias, confounding, and other reasons for caution

This study lacked any imaging or biochemical markers for disease progression.

Generalizability to other populations

The study analyzed a large international patient sample, thus favoring the generalizability of the findings.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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