Trinucleotide repeat length and progression of illness in Huntington's disease

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Abstract

The genetic defect causing Huntington's disease (HD) has been identified as an unstable expansion of a trinucleotide (CAG) repeat sequence within the coding region of the IT15 gene on chromosome 4. In 50 patients with manifest HD who were evaluated prospectively and uniformly, we examined the relationship between the extent of the DNA expansion and the rate of illness progression. Although the length of CAG repeats showed a strong inverse correlation with the age at onset of HD, there was no such relationship between the number of CAG repeats and the rate of clinical decline. These findings suggest that the CAG repeat length may influence or trigger the onset of HD, but other genetic, neurobiological, or environmental factors contribute to the progression of illness and the underlying pace of neuronal degeneration.

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An unstable expansion of trinucleotide (CAG) repeats in the IT15 gene has been identified as the genetic defect underlying the inheritance of Huntington's disease (HD).[1] While the number of CAG repeats in IT15 ranges normally from nine to 37, the number of repeats in affected HD persons ranges from 37 to 102.[2-7] A strong inverse correlation between the number of trinucleotide repeats and the age at onset of HD has been shown; however, no apparent relationship has been found between the number of repeats and clinical manifestations of illness.[4 8]

Early age at onset of HD has been considered a harbinger of more rapid progression of illness, but a recent analysis of 1000 patients with HD failed to confirm such a relationship.[9] The HD Functional Capacity Scale (HDFCS), as reflected by its aggregate score of total functional capacity (TFC), has been found to be a valid and reliable measure of the severity of HD.[10 11] Using TFC as an index of illness progression, we similarly found no correlation between the age at onset of HD and the rate of illness progression.[12]

A reliable biological marker or predictor of the rate of illness progression would be useful for evaluating potential therapies for HD as well as for caring for patients and families. The extent of the underlying genetic defect, as measured by the number of CAG repeats, is a potential marker of illness progression. We therefore examined the relationship between the number of CAG trinucleotide repeats in the IT15 gene and the onset and prospective course of HD.

Methods

We studied patients with manifest HD to determine the rate of illness progression and attendant clinical features. A single examiner (IS) prospectively evaluated each patient using the HDFCS scale. The total functional capacity (TFC) score, ranging from 13 (normal) to 0 (severely incapacitated) units, assesses a patient's capacity in relevant functional domains including employability, financial tasks, domestic capacities, and self-care skills. Patients were evaluated on at least two occasions separated by at least six months in the setting of continuing clinical care, while participating in a controlled clinical trial,[13] or both. All clinical assessments were made independent of any information regarding DNA analysis and CAG repeat length.

Prospectively derived information, including family history, demographic data, and medications, was also obtained from all patients. Age of onset was determined by a single examiner (IS) on the basis of the first reported onset of motor features. After obtaining consent from the patient or guardian, blood samples were obtained from 54 HD patients.

DNA was prepared from frozen blood samples as described previously.[2] The length of the CAG trinucleotide repeat was determined using the polymerase chain reaction (PCR) to amplify either the CAG and polymorphic CCG stretch as originally described[1] or with oligonucleotide primers 5'ATGAAGGCCTTC-GAGTCCCTCAAGTCCTTC3' and 5'GG-CGGTGGCGGCTGTTGCTGCTGCTGC-TGC3' to amplify just the CAG stretch, as described by Warner *et al*.[14] The sizes of the PCR products were determined by comparison with signed products generated in the PCR assay using sequencing cosmid DNAs. The two methods yielded similar results, and only data from the method described by Warner *et al*[14] are presented.

The rate of TFC change for each patient was calculated from the slope of the least squares fitted line, using individual plots of the patient's TFC score over time. Correlations were tested by Pearson coefficients comparing the rate of TFC change, the number of CAG repeats, and the natural log of the age at onset of HD.

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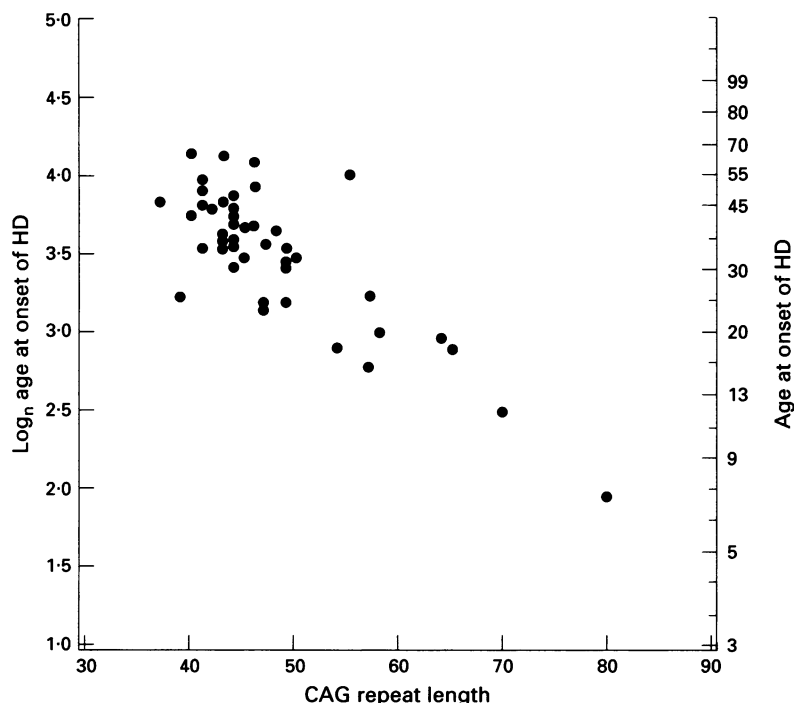J Srinidhi
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Figure 1   Relationship between age at onset of HD and CAG repeat length.
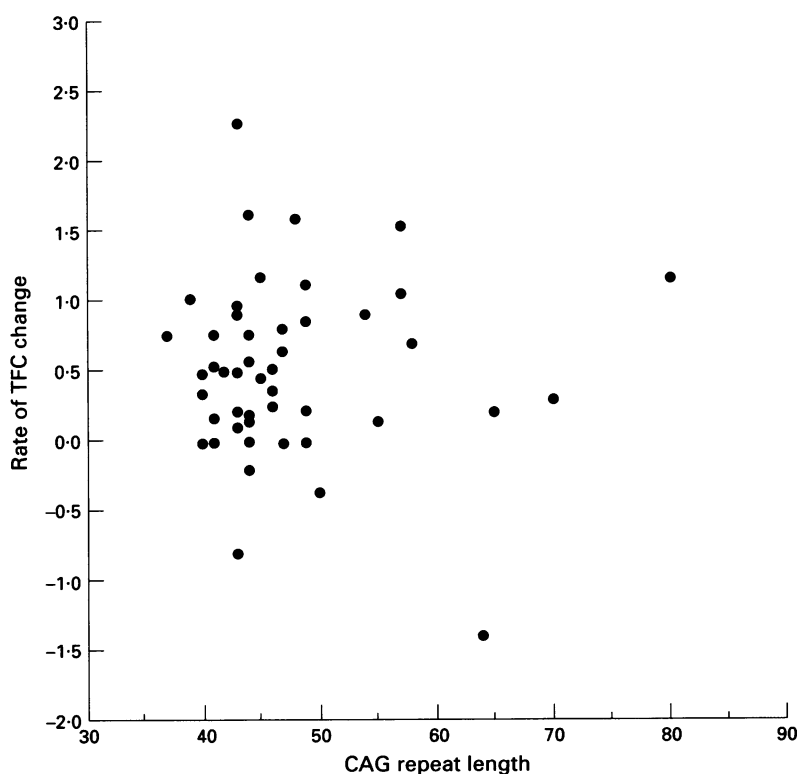

Figure 2   Relationship between annual rate of TFC change (units/year) and CAG repeat length.

Results

Of the 54 blood samples obtained, DNA analysis produced reliable CAG results from 50 patients, consisting of 24 men and 26 women with a mean age of 50·9 (SD 14·3) years (range 15 to 77 years) at the time of sampling. Features of HD had been present for 13·8 (SD 5·5) years (range 4 to 27), with a mean duration of HD of 37·0 (SD 13·5) years (range 7 to 63).

The patients were evaluated prospectively on 6·3 (SD 3·6) different occasions (range 2 to 16) and were followed for 4·4 (SD 2·9) years (range 0·5 to 13·8). The TFC at initial evaluation was 9·2 (SD 2·1) (range 2 to 13), and the TFC at final evaluation was 6·8 (SD 3·1) (range 0 to 12). The mean rate of TFC decline was 0·5 (SD 0·6) TFC units per year (range −1·4 to 2·3) similar to previous reports of the rate of TFC decline in HD.[10] Only four subjects showed any improvement in TFC scores (negative rate of TFC change) during the period of observation.

The average CAG repeat length was 47·5 (SD 8·3) (range 37 to 80). There was a strong inverse correlation between CAG repeat length and age at onset: $r = -0·82$, $p<0·0001$ (fig 1), similar to that found by other investigators.[23] In contrast, the relationship between CAG repeat length and the rate of TFC decline (fig 2) was virtually a flat line: $r = 0·01$, $p = 0·97$. There was also no relationship between age at onset and the rate of TFC decline (fig 3).

Discussion

In this prospective study, we confirmed the strong relationship between CAG repeat length in the IT15 gene and the age at onset of HD. However, consistent with the report of Roos et al,[9] we found no relationship between age at onset of HD and severity of illness. In a previous study we examined the rate of functional decline in a cohort of 129 prospectively evaluated patients with HD and, contrary to previous reports,[15] found no correlation between functional decline and age at onset, body weight, gender of affected parent, or neuroleptic use.[12]

Our current study failed to establish any relationship between the number of CAG repeats and the rate of functional decline as assessed by the TFC scale. These findings suggest that the range of HD severity is relatively uniform across a large spectrum of age at onset and CAG repeat length. However, we found considerable variability in the rate of decline in our cohort, ranging from relatively stable illness to declining at greater than two TFC units per year (fig 2). Taken together, these observations suggest that the number of CAG repeats is a strong predictor of the age at onset of HD but not of the pace of disease progression. Thus, the CAG repeat length may play an important role in the initiation of the clinical features of HD, but there appear to be other contributing genetic, neurobiological, or environmental factors that modify and influence the subsequent progression of disease.

The lack of association between the number of CAG repeats and the progression of illness limits the use of CAG repeat length as a reliable predictor of the clinical course. Some of our patients with relatively few repeat lengths experienced a rapid clinical decline while some patients with high repeat lengths had a relatively slow clinical course. These findings have implications for genetic counselling and the appropriate interpretation of genetic test results in patients with symptomatic HD. These observations may extend to asymptomatic persons at risk for HD, but need to be confirmed in such a population.
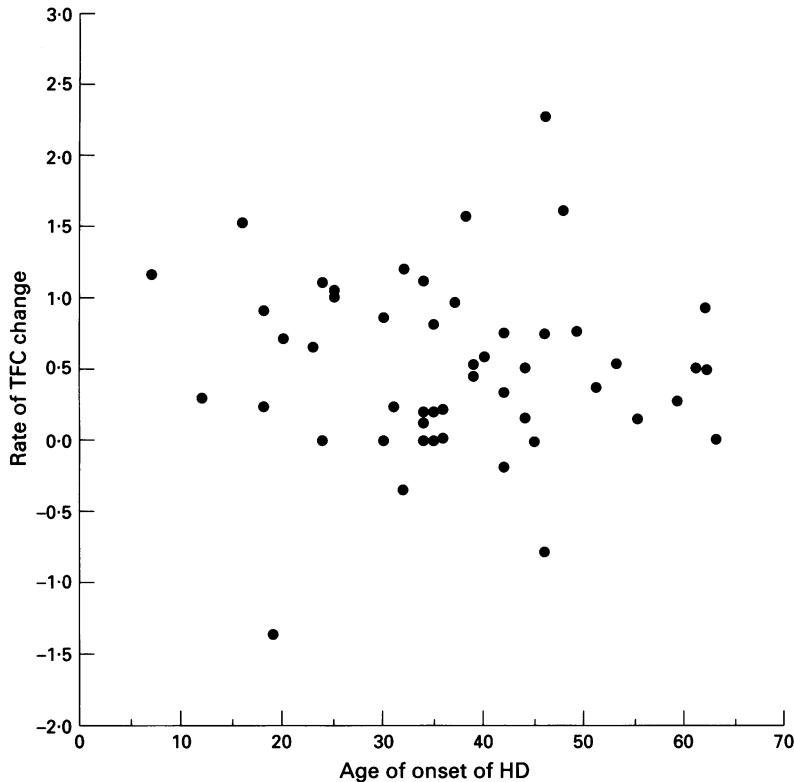
Figure 3   Relationship between annual rate of TFC change and age at onset of HD.

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