Association between Age and Striatal Volume Stratified by CAG Repeat Length in Prodromal Huntington Disease

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Abstract
Background: Longer CAG repeat length is associated with faster clinical progression in Huntington disease, although the effect of higher repeat length on brain atrophy is not well documented. Method: Striatal volumes were obtained from MRI scans of 720 individuals with prodromal Huntington disease. Striatal volume was plotted against age separately for groups with CAG repeat lengths of 38-39, 40, 41, 42, 43, 44, 45, 46, and 47-54. Results: Slopes representing the association between age and striatal volume were significantly steeper as CAG repeat length increased. Discussion: Although cross-sectional, these data suggest that striatal atrophy, like clinical progression, may occur faster with higher CAG repeat lengths.

Introduction
It has long been known that greater CAG repeat lengths are associated with earlier onset of illness, especially for individuals with particularly high repeat number. More recent evidence demonstrates that higher CAG repeat lengths are also associated with faster clinical progression. Rosenblatt et al. [1] demonstrated that CAG repeat number is a small but significant predictor of progression rates of HD in four different measures: overall neurologic signs, motor impairment, cognition, and daily function. Evidence for faster progression of striatal atrophy with higher CAG repeat length is not as clear. Cross-sectional and longitudinal studies have yielded conflicting results, with some suggesting that brain atrophy progresses more rapidly for individuals with higher CAG repeat length and others showing no relationship [2] [3] [4] [5] [6] [7] [8].

Materials and Methods
The analyses presented here are based on baseline MRI data from participants of PREDICT-HD, a multi-site, longitudinal study of prodromal HD. The sample included 720 participants who tested positive for the HD gene mutation (CAG repeat lengths ranging from 38 to 54), but had not been diagnosed with the motor signs of HD at the time of study enrollment (“prodromal HD”). An additional 206 participants were offspring of a parent with HD but who themselves had tested negative for the HD gene mutation (“controls”). All aspects of the study were approved by the Institutional Review Board at each participating institution, they were in compliance with the code of Ethics of the World Medical Association Declaration of Helsinki, and all participants gave written informed consent.

All MRI scans were obtained using a standard multi-modal protocol that included a 3D volumetric spoiled gradient echo series and a dual echo proton density/T2 series. Scans were processed at The University of Iowa using an automated procedure implemented in BRAINS [9] and artificial neural networks [10]. Caudate, putamen, total striatum (caudate + putamen), and total intracranial volumes were obtained.

Analyses were performed to examine the association between age and striatal volume in each of nine groups defined by CAG repeat length (38-39, 40, 41, 42, 43, 44, 45, 46, 47-54). Each CAG group had at least 34 participants. Table 1 presents demographics and clinical scores for participants in each CAG group. Within each group, a linear regression was performed to examine the association between age and striatal volume (corrected for intracranial volume). The slopes resulting from each of these nine regressions were then correlated with CAG group (using Spearman correlation). This analysis was designed to determine whether the slope of the regressions for age and striatal volume became steeper with increasing CAG repeat length. For each CAG repeat group, a separate linear regression was also performed that included age (centered by group mean to avoid potential multicollinearity issues) and the quadratic term of age as predictors to explore the possibility of a curvilinear relationship between age and striatal volume.

Table 1. Sample description and $R^2$ of regression between age and striatal volume for each CAG group.
Results

Figure 1 shows the regression for each group depicting the association between age and striatal volume (corrected for intracranial volume). These regressions were all highly significant ($R^2$ s ranging from 0.14 to 0.51, all $p$ values < 0.005) but variable, with lower $R^2$ s generally observed for the lowest CAG repeat lengths. The slope for each group (representing association between striatal volume and age) was highly associated with CAG group (Spearman $r = -0.98$, $p < 0.0001$; see Figure 2), with higher CAG repeat numbers associated with steeper slope, at least up through CAG = 44.

The quadratic effect of age in the linear regression model was statistically significant for CAG = 46 group ($t = 2.85$, $p = 0.008$), although this was due to a single outlier. When this outlier was removed, the addition of the $age^2$ factor did not result in an increased significance in the model that was based on age alone ($t = 0.21$, $p = 0.83$ for $age^2$, after accounting for age).

Although not quite reaching significance ($t = -1.85$, $p = 0.07$), the curve for the CAG = 38-39 group suggested a slightly steeper decline for older subjects than younger subjects. A significant effect of $age^2$ was not observed in any other groups ($p$ values all > 0.20).

Fig. 1: Regressions for age and striatal volume (corrected for ICV) for each CAG group.

The solid portion of each line represents actual data (based on age range of participants in each CAG group). Heavy dashed line represents correlation for control participants.
Discussion

Although based on cross-sectional data, our analyses suggest that increased CAG repeat length is associated with faster progression of striatal atrophy in prodromal HD, at least up through CAG = 44. Although it is clearly established that CAG repeat length has an effect on age at onset of HD [1] [11], few studies have examined the effect of CAG repeat length on rate of brain atrophy, and these have all been done on relatively small samples and most have examined brain regions other than the striatum. In a longitudinal study of 37 affected patients, Ruocco et al. [7] found that higher repeat length (> 45) was associated with faster rate of atrophy in frontal, occipital, parietal, and cerebellar regions. In a small sample (n = 13) including both affected and prodromal individuals, Henley et al. [5] found no significant association between rate of whole brain atrophy and CAG repeat length. In a larger sample (n = 62), the same group found that an increase of CAG repeat length by one was associated with an increase in whole-brain atrophy rate of 0.12% per year [6]. In small samples that included both prodromal and affected subjects, Squitieri et al. [8] found a significant correlation between CAG repeat length and increased CSF volume change, and Aylward et al. [2] found that repeat length correlated significantly with rate of change in caudate, globus pallidus, and total basal ganglia, but not putamen. One cross-sectional MRI study with a small sample also demonstrated a significant correlation between CAG repeat length and striatal volume loss (difference between HD subject’s volume and control volume [4]), while a neuropathological study of established HD found a correlation between CAG and cortical, but not subcortical atrophy [3].

Our results are consistent with analyses of longitudinal data from a subsample of the current cross-sectional sample (n = 211 [12]) that revealed a significant association between CAG repeat length and rate of change for caudate (t = ?2.32, p = 0.009) and total striatum (t = ?2.32, p = 0.02), with a trend toward a significant association for putamen (t = ?1.80, p = 0.07). No significant associations were observed for any other regions (cortical gray matter, white matter, CSF, thalamus). Taken together with results from the current study, these findings yield evidence suggesting that rate of striatal atrophy is faster in individuals with higher CAG repeat lengths. Our results are not surprising, given previous research in affected patients with HD demonstrating that (a) faster rate of clinical progression is associated with higher CAG repeat number [1] and (b) smaller striatal volumes are associated with more severe clinical manifestations [13].

A major strength of the current study is its large sample size. Although the findings presented here are based on cross-sectional baseline data, it is expected that longitudinal results would be similar, as the regression between age and striatal volume for a given CAG repeat length can be assumed to be a good estimate of the trajectory of atrophy for the average participant within that CAG group. Lack of very young participants (< 18 years) may skew the data somewhat, especially for the longer CAG groups, where the y-intercept is below that of the other CAG groups (see Figure 1). There is also a lack of cases with very high CAG repeat lengths, as these individuals usually have childhood onset and would not, therefore, qualify for a study of adult prodromal HD. If it were possible to include prodromal individuals younger than 18 years, striatal volumes for those with large CAG repeat lengths might be higher than those in the current study, resulting in even steeper slopes for these groups. Thus, our finding of similar association between age and striatal volume in the groups with CAG > 44 may not be valid across the entire age range.

It is also noteworthy that the slope for the group with CAG = 38-39 is basically the same as for the control group, although absolute values for striatal volumes are lower. The age range for the two groups is similar and the results were not biased by any obvious outliers. The trend for a curvilinear relationship between age and striatal volume (p = 0.07) suggests that striatal atrophy remains fairly normal for prodromal individuals with relatively low CAG repeat lengths until they are older adults, at which time atrophy increases. This would be consistent with the fact that these individuals are usually not diagnosed until fairly late in life.

Evidence that individuals with longer CAG repeat lengths show faster striatal atrophy may be important in the design of future clinical trials in prodromal HD. By selecting participants with relatively longer CAG repeat lengths and faster rate of atrophy, clinical trials might be able to be conducted with smaller sample sizes or shorter duration than selecting those with relatively shorter CAG repeat lengths and slower rate of atrophy.

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Competing Interests

The authors have declared that no competing interests exist.

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**References**


