Tracking Motor Impairments in the Progression of Huntington's Disease

Jeffery D. Long, PhD[1,2], **Jane S. Paulsen, PhD**[1,3,4,*], **Karen Marder, MD, MPH**[5], **Ying Zhang, PhD**[2], **Ji-In Kim, PhD**[1], **James A. Mills, MS**[1], and **the Researchers of the PREDICT-HD Huntington's Study Group**

[1]Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA

[2]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa, USA

[3]Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA

[4]Department of Psychology, College of Liberal Arts and Sciences, University of Iowa, Iowa City, Iowa, USA

[5]Departments of Neurology and Psychiatry, Sergievsky Center and Taub Institute, College of Physicians and Surgeons, Columbia University, New York, New York, USA

Abstract

The Unified Huntington's Disease Rating Scale is used to characterize motor impairments and establish motor diagnosis. Little is known about the timing of diagnostic confidence level categories and the trajectory of motor impairments during the prodromal phase. Goals of this study were to estimate the timing of categories, model the prodromal trajectory of motor impairments, estimate the rate of motor impairment change by category, and provide required sample size estimates for a test of efficacy in clinical trials. In total, 1010 gene-expanded participants from the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) trial were analyzed. Accelerated failure time models were used to predict the timing of categories. Linear mixed effects regression was used to model the longitudinal motor trajectories. Age and length of gene expansion were incorporated into all models. The timing of categories varied significantly by gene expansion, with faster progression associated with greater expansion. For the median expansion, the third diagnostic confidence level category was estimated to have a first occurrence 1.5 years before diagnosis, and the second and first categories were estimated to occur 6.75 years and 19.75 years before diagnosis, respectively. Motor impairments displayed a nonlinear prodromal course. The motor impairment rate of change increased as the diagnostic confidence level increased, with added acceleration for higher progression scores. Motor items can detect changes in motor impairments before diagnosis. Given a sufficiently high progression score, there is evidence that

*Correspondence to: Dr. Jane S. Paulsen, The University of Iowa College of Medicine, 1–305 Medical Education Building, Iowa City, IA 52242; predict-publications@uiowa.edu.

the diagnostic confidence level can be used for prodromal staging. Implications for Huntington's disease research and the planning of clinical trials of efficacy are discussed.

Keywords

movement disorders; Huntington's disease; neurodegenerative disease; predictive testing; cohort studies

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by the trinucleotide expansion of cytosine-adenine-guanine (CAG) in exon 1 of the huntingtin (*HTT*) gene.[1] HD is associated with severe motor, cognitive, and psychiatric impairments that typically develop in adulthood.[2]

Although HD onset is characterized by a tripartite of symptoms and signs, diagnosis is based on motor impairments, and endpoints for clinical trials focus mainly on motor signs.[3,4] The main measure of motor impairments is the motor assessment section of the Unified Huntington's Disease Rating Scale (UHDRS),[5] which is administered by a trained examiner. The first part of the motor section consists of 31 items in 15 domains of motor impairment, each rated on a 5-point scale ranging from 0 (normal) to 4 (severest impairment). The motor items are distributed among oculomotor functioning (6 items), chorea (7 items), dystonia (5 items), bradykinesia (11 items), and rigidity (2 items).[6] In many studies of HD, interest is in the sum of all 31 items, which is referred to as the total motor score (TMS).[2,7-9]

The second part of the motor assessment section consists of the diagnostic confidence level (DCL), which is a single item with a 5-category ordinal rating scale. The examiner selects a response to the question, "To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (eg, chorea, dystonia, bradykinesia, rigidity) in a subject at risk for Huntington's disease?" The rating categories are 0 (normal; no abnormalities), 1 (nonspecific motor abnormalities; < 50% confidence), 2 (motor abnormalities that may be signs of HD; 50%-89% confidence), 3 (motor abnormalities that are likely signs of HD; 90%-98% confidence), and 4 (motor abnormalities that are unequivocal signs of HD; ≥ 99% confidence).

Despite widespread use of the DCL and the TMS, many questions remain regarding their ability to track progression, especially in the prodromal period of HD (ie, in the years before DCL = 4). The response format of the DCL suggests that the item can be used as a type of progression staging, but little is known about the timing of the occurrences of the categories. The trajectory of the TMS is well characterized for later stages of HD (ie, the years after first DCL = 4)[10-13]; however, the nature of the prodromal TMS trajectory is unclear. There is also lack of information regarding the relation between the DCL and the TMS. For example, given a cross-section of progression, there is scarce information regarding what constitutes typical TMS levels for DCL categories. Furthermore, it is possible that individuals remain for a time within a DCL category, and it is of interest to examine how the TMS changes during this time.

The issues raised above can be addressed with longitudinal data that span the prodromal phase of HD. Such data are provided by the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) study.[2,14] Using the PREDICT-HD database, the current study had the following aims: First, examine the timing of DCL categories in progression. Second, examine change in motor impairment (TMS and the motor factors) from the prodromal period (DCL < 4) through the manifest period (DCL = 4). Third, estimate typical mean levels of rates of annual change in motor impairments for DCL categories. Fourth, compute estimated required sample sizes for a hypothetical clinical trial of efficacy examining change in TMS. Age and CAG length are important factors in motor onset and are incorporated into the methods used to address the goals.

Participants and Methods

Participants

Participants were N = 1010 individuals who voluntarily underwent genetic testing and were found to have a CAG repeat length > 36 (mean = 42.35, median = 42, minimum = 37, maximum = 62). A subset of N = 21 participants were diagnosed at study entry. Another subset of N = 204 "converters" received a diagnosis at some point after study entry.

Enrollment was at sites in the United States, Australia, the United Kingdom, Canada, Germany, and Spain. Institutional review boards at each participating site approved the study, and each participant signed an informed consent. At study enrollment, participants were required to be at least 18 years old. Exclusion criteria included history of a significant developmental cognitive disorder, other central nervous system disease or injury, evidence of an unstable medical or psychiatric illness (including substance abuse), a pacemaker or metallic implants, prescribed antipsychotic medication in the last 6 months, or phenothiazine derivative antiemetic medication in the last 3 months. For additional details, see Paulsen et al.[2]

Clinical Assessments

Participants underwent detailed motor, cognitive, psychiatric, and functional evaluations at baseline and annually thereafter. Participants had data for the TMS and DCL for at least one visit up to a maximum of 10 visits. There was a small amount of missing data (approximately 1%), consisting of unanswered TMS items, which were assigned a value of zero ("normal"). Preliminary analysis (not presented) indicated that missing values did not appear to cause outliers or other unexpected values. There were 88 motor examiners, and the mean number of examinations per examiner was 49.43 (standard deviation = 61.99); and the quartiles (Q) were $Q_1 = 2$, $Q_2 = 16$, and $Q_3 = 76$. In addition, 60.83% of participants had the same rater throughout, 23.64% had two raters, and 15.53% had three or more raters. Findings did not change based on the number of raters or examinations. At study entry, the site coordinator responded to question 81 of the UHDRS: "Does the motor rater know the participant's gene status? (0 = no, 1 = yes)." Gene mutation status was reported as be known (UHDRS question 81 = "yes") for 69% of participants. The findings did not vary based on blinding.

Statistical Methods

The first goal of estimating the timing of the DCL categories was addressed by using a Weibull accelerated failure time (AFT) model.[15] The same AFT model was used with four different events: first occurrence of DCL = 1, 2, 3, or 4. The log time to each DCL category was predicted separately, with age as the time metric and with CAG and CAG-squared as the predictors. CAG-squared was included because of evidence that the relation between time of onset and CAG is nonlinear.[16,17] The outcome for each participant was treated as left-censored, right-censored, or interval-censored. The age at first occurrence for each category was the predicted value from the fitted model stratified by CAG, and the distance between the predicted values was computed for the different categories. The standard error of prediction was used to compute 95% confidence intervals (CIs).

The second aim of examining motor impairment trajectories was addressed using only the converters. For each converter, time in the study (in years) was anchored to the first occurrence of a DCL = 4 (diagnosis). This was accomplished by subtracting the year at first occurrence from each year (zero indicated the time of diagnosis). The trajectory of the TMS and motor factors was estimated using cubic splines in linear mixed effects regression (LMER).[18,19] The TMS and each motor factor were modeled separately. Time predictors were cubic splines with the quartiles of time as the knots, and a random effect was included for each spline term plus the intercept. Age and CAG were incorporated into the analysis using the age-CAG product (CAP)[20] as a predictor. The CAP is computed as CAP = (age at study entry) × (CAG – 33.66) and is similar to the burden score reported by Penney et al.[21] The CAP is a purported index of the cumulative toxicity of mutant huntingtin at the time of study entry. For reference, CAP ≥ 368 denotes a "high" probability of converting in the near future after study entry, 290 < CAP < 368 denotes a "medium" probability, and CAP ≤ 290 denotes a "low" probability.

The third aim concerned estimating the level and slope of motor impairments for DCL categories. All gene-expanded participants were included, except for those with a baseline diagnosis (21 excluded patients). LMER was used again, with predictors being dummy variables for time-varying DCL categories and CAP. To help inform future clinical trials, the zero point of time was anchored to study entry, so that time represented years in the study. All possible interactions among CAP, the dummy variables, and time were included as predictors. Six correlated random effects were specified, one for each DCL category dummy variable and time. Because of the relevance for planning clinical trials of efficacy, emphasis was on the hypothesis test of zero slope. Efficacy trials require a detectible change in the untreated group to have the potential for demonstrating a treatment effect. Detectible change was defined as a slope significantly different from zero.

Finally, the required sample size for clinical trials of efficacy was computed based on LMER models. Single-arm sample size was computed for the test of equal TMS slopes for hypothetical placebo and treatment groups. Additional details are presented in the Appendix.

Results

Table 1 provides demographic information for the larger sample and subsamples of converters and non-converters. Converters had substantially higher mean CAP than non-converters.

The results of the DCL timing analysis are illustrated in Figure 1, which depicts the predicted year before diagnosis of a DCL category (color-coded) as a function of CAG, with 95% CIs. Although the entire CAG distribution was used for the analysis, the quartiles of the gene-positive CAG distribution were used for graphing, which were $Q_1 = 41$, $Q_2 = 42$, and $Q_3 = 44$. The horizontal axis indicates the years to diagnosis, with diagnosis occurring at year zero (marked by a solid vertical line). CAG-squared was statistically significant in the prediction of all DCL categories, but its effect was greatest for DCL = 4 ($P < 0.001$). For the median CAG = 42, DCL = 3 was predicted to occur 1.50 years before diagnosis (95% CI, 0.23-2.77), DCL = 2 was predicted to occur 6.75 years before diagnosis (95% CI, 5.62-7.88), and DCL = 1 was predicted to occur 19.74 years before diagnosis (95% CI, 18.65-20.83). Figure 1 reflects the significance of CAG on the timing of the categories. For CAG = 41, the predicted occurrence of the categories was further from diagnosis. For CAG = 44, the predicted occurrence of the categories was closer to diagnosis, and the 95% CI for DCL = 3 overlapped with DCL = 4 (the vertical line at zero is contained in the CI).

Converter trajectories of motor impairments are indicated in Figure 2. Individual empirical curves are the jagged gray lines, and the fitted spline curves stratified by CAP are the smooth colored lines. The data thinned over time because the study is ongoing, and many of the individuals depicted in the graphs do not yet have many follow-up visits. The data thinning is reflected in the decreasing acceleration at the extreme right-hand side of each graph. Intercept (starting level) varied significantly by CAP for all motor outcomes (all $P < 0.001$). The motor trajectories were not statistically different by CAP strata for chorea and rigidity, but they were significantly different for the remaining variables in Figure 2 (all remaining $P < 0.001$). Although the entire CAP distribution was used in the analysis, curves for the quartiles of the converters were used for graphing ($Q_1 = 360$, $Q_2 = 405$, and $Q_3 = 450$). Negative values on the horizontal axis indicate years to diagnosis, and positive values indicate years after diagnosis (0 = time of diagnosis). The top left graph depicts the TMS trajectory, and the remaining graphs illustrate the trajectories of the motor factors.

Table 2 lists the LMER results from the analysis examining change in motor impairments by CAP and DCL category. The results are presented only for TMS, but the motor factors had similar patterns. The column headed "Slope" in Table 2 lists the estimated mean rate of annual change for the TMS (along with the standard error). The column headed "Mean TMS at year 2" lists the predicted mean TMS after 2 years in the study. The 2-year point corresponds with the power analysis discussed in the Appendix. Although the entire CAP distribution was used in the analysis, Table 2 shows results only for limited values, including the quartiles ($Q_1 = 285$, $Q_2 = 350$, and $Q_3 = 400$). The rate of change was statistically greater than zero for DCL = 3 or 4, regardless of CAP. CAP = 290 was the minimum that produced slope significance for DCL = 2 at the $P < 0.05$ level, and CAP =

310 was the minimum for the $P < 0.01$ level. As indicated in the "Mean TMS at year 2" column, all mean estimates were statistically greater than zero at the $P < 0.001$ level.

Table 3 indicates the estimated required sample size (in boldface) for a hypothetical 2-year clinical trial of efficacy with measurements every 6 months. The single-arm sizes are for testing the null hypothesis of equal TMS rate of change over time for placebo and treatment groups (see Appendix). Minimum CAP indicates sampling all available participants with CAP   minimum CAP, and dropout refers to the rate in each group (see Appendix).

Discussion

The results of this analysis provide information concerning the timing of DCL categories in HD progression and the nature of change in motor impairments. There is evidence the DCL and the UHDRS motor items can detect changes in motor impairments during the HD prodromal period. Age and CAG repeat length were significant both for the timing of DCL categories and for change in motor impairments. Greater CAG length was associated with more rapid DCL progression, and higher CAP was associated with faster change in motor impairments.

Trajectories of motor impairments were characterized by nonlinear change in the prodromal phase (see Fig. 2). The more targeted analysis of TMS change while in the same DCL category provides an indication of how annual rates of change in motor impairments vary by DCL and CAP (see Table 2). There was no significant change associated with DCL = 0 (normal) or DCL = 1 (nonspecific motor abnormalities) regardless of CAP. DCL = 2 (possible signs of HD; 50%-89% confidence) showed significance for a minimum CAP = 290 or 300, depending on the desired level of significance. DCL = 3 (likely signs of HD; 90%-98% confidence) and DCL = 4 (unequivocal signs of HD;   99% confidence) showed significance regardless of CAP, suggesting that a clinical examination with corroborative history of HD may be a sufficient entry criterion.

The finding that motor impairment slopes increased with DCL provides evidence that the stage of disease is related to the rate of progression, even during prodromal HD. The pattern of progression for our results is consistent with a long-term slow build-up of impairments that ultimately gives rise to an accelerated trajectory of deterioration that varies by CAP (see Fig. 2). This pattern has been verified in other cohorts of HD patients.[5,10,11,13,22] For example, Mahant and colleagues observed that motor impairments did not increase at a constant rate in their longitudinal study of diagnosed patients with early through late HD.[12] Individuals were stratified based on initial TMS, and it was found that the rate of yearly TMS change increased with initial TMS for ranges of values similar to those observed in our study (ie, TMS $\in$ [0,77]). Similar results have been found using CAG length rather than TMS,[23-25] and there is evidence that other domains, such as cognitive impairments, also may change as a function of stage.[26]

The results have implications for the classification of progression at study entry. In HD research, it is common to use DCL = 4 as the definition of diagnosis or manifest HD. By complement, DCL < 4 defines the prodromal, pre-diagnosis, or pre-manifest phase. In some

studies, a different DCL cutoff is used; for example, DCL < 2 for pre-manifest HD and DCL 2 for manifest HD.[27] In other studies, several values are used to define multiple groups, such as manifest (DCL = 4), pre-manifest with abnormalities (DCL = 2 or 3), and pre-manifest with minimal signs (DCL = 0 or 1).[26,28,29]

If the goal of classification is to distinguish individuals who are actively deteriorating from those who are not, then our results suggest that DCL = 4 is assigned relatively late. Figure 2 and Table 2 provide evidence of active and meaningful motor decline for DCL = 3 and perhaps even for DCL = 2, provided the CAP is sufficiently large. Cutoffs for phases of activity might be DCL 2 versus DCL 3 when the entire CAP range is considered, or DCL 1 versus DCL 2 when CAP 290 is considered (see Table 2).

The findings have implications for the planning of clinical trials of efficacy, with the outcome variable being motor impairments and the TMS in particular. The slope results from Table 2 indicate a possible minimum CAP that might be considered should a researcher want to recruit patients with the greatest likelihood of active motor decline. Recruitment based on DCL might be problematic because of the unreliability of the rating at the individual level. In ancillary analysis (results not presented), we have observed that progression through the DCL categories is not necessarily monotonic, with some patients even dropping over time after an initial value of DCL = 4. In contrast, the CAP can be highly reliable provided that age is accurately reported and CAG length is laboratory-verified.[20] Therefore, we recommend using CAP as the primary consideration in recruitment. Table 3 is a resource for planning clinical trials of efficacy if the CAP of recruits can be computed. Sample sizes are provided for comparing the rate of change (slope) of the treatment and placebo groups under various non-informative dropout scenarios. Graphical evidence (not presented) suggests that non-informative dropout is a reasonable assumption for the planning of a clinical trial based on the PREDICT-HD database.[30]

Finally, the sensitivity to change of the TMS has been questioned for use with prodromal individuals.[31,32] Our results indicate that the TMS is sensitive in the prodromal period in that it can detect statistically and substantively significant change.

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Appendix

Required sample size for slope difference

Estimates of sample size required for a randomized clinical trial of efficacy were based on power formulas for LMER[33,34]. Sample size was calculated for the endpoint of TMS rate of change (slope) over a 2 year study with observations every 6 months (baseline, 6, 12, 28, and 24 months). The design was a two-arm Placebo (P) and Treatment (T) group study, and dropout was assumed to be non-informative (or ignorable). The evaluation of efficacy is defined as the test of the null hypothesis that the TMS rates of change in the P and T groups are equal. The null hypothesis can be evaluated based on parameter estimates in LMER.

Suppose Y_{ij} is the TMS value for the ith participant ($i = 1, …, N$) at the jth month ($j = 1, …, n_i$), and t_{ij} denotes time in months. Assuming linear change over time, the LMER model can be written as the following,

$$Y_{ij} = \beta_I + \beta_s t_{ij} + \beta_{\Delta I} g_i + \beta_{\Delta s} g_i t_{ij} + (b_{Ii} + b_{si} t_{ij} + e_{ij}) \quad \text{(A1)}$$

where g_i is a dummy variable for group ($g_i = 1$ if the participant is in the T group, and 0 otherwise). In Equation A1, the βs are the fixed effects, with β_I being the P group intercept and β_S being the P group slope; β_I is the difference in the intercepts among the groups, and β_I is the difference among the slopes. The bs are random effects, and e is random error. We make the typical assumptions, $[b_{Ii} \quad b_{Si}]^T \sim N(0, G) \perp e_{ij} \sim N(0, \sigma_e^2 I_i)$. The prime object of inference is β_S, as this is the difference in TMS longitudinal change of the T and P groups. The null hypothesis of equality of T and P slopes is H_0: $\beta_S = 0$, and can be

evaluated with a Z-test. The Z statistic is $Z = \dfrac{\widehat{\beta}_{\Delta s}}{SE\left(\widehat{\beta}_{\Delta s}\right)}$ and leads to the rejection of H_0 when $|Z| > Z_{1-\alpha}$, with the latter being the $100(1-\alpha)$th quantile of the standard normal distribution (single tailed).

The LMER model of A1 can be written more generally as

$$Y_i = X_i \beta + Z_i b + e_i$$

where X_i is the design matrix of the fixed effects, β is the vector of fixed effects, Z_i is the design matrix of the random effects, b is the vector of random effects, and e_i is the vector of random errors. In this context, X_i for a person with no dropout has dimensions 5×4 with the first column being a vector of 1s, the second column a vector of time values (0, 6, 12, 18, 24), the third column a vector of g_i values, and the last column a vector of $g_i \times$ time values. An individual is defined as a dropout if their row dimension is less than 5.

TABLE A1

Dropout proportions (π) for computing required sample size.

	Dropout Condition		
Missing Visits	**0%**	**10%**	**20%**
0	1.00	0.90	0.80
1	0	0.04	0.08
2	0	0.03	0.06
3	0	0.02	0.04
4	0	0.01	0.02

The required sample size for the Z-test depends on the variance of the responses,

$$V_i = Z_i G Z_i^T + \sigma_e^2 I_i$$

V_i is 5×5 for no dropout, but has reduced dimension under dropout similar to X_i. Suppose α is the type I error rate (set to 0.05 or 0.10), and $1 - \gamma$ is power (set to 0.80). Then the required sample size for a single arm (half the total sample size) is

$$\frac{N}{2} = \frac{(\boldsymbol{Z}_{1-\alpha} + \boldsymbol{Z}_{1-\gamma})^2 \left(\sum_k^2 \sum_l^L \boldsymbol{X}_{kl}^T \boldsymbol{V}_{kl}^{-1} \boldsymbol{X}_{kl} \pi_{kl} \right)_{4,4}^{-1}}{\beta_{\Delta S}^2} \quad \text{(A2)}$$

where l refers to a specific dropout pattern, $\boldsymbol{X}_{kl}$ is the design matrix for the kth group with the lth dropout pattern, and π_{kl} is the proportion of participants with the lth missing pattern in the kth group, and the π_{kl} sum to one among the dropout patterns within a group. The 4,4 subscript indicates the element in the 4th row and 4th column of the resulting matrix. When there is no dropout, $\pi_{11} = \pi_{21} = 1$, and the right hand expression in the numerator is $\left(X_1^T V^{-1} X_1 + X_2^T V^{-1} X_2 \right)_{4,4}^{-1}$, where the subscripts 1 and 2 represent the P and T groups.

Three dropout scenarios were considered: no dropout (0%), 10%, and 20%. The values pertain to the percentage of participants who dropped out in each group, not the total missing data. Dropout was identical for the P and T groups ($\pi_{1l} = \pi_{2l} = \pi_l$), and the dropout proportions, π_l, tapered to create a scenario in which dropout was slight very earlier in the hypothetical study, but increased over time. Five dropout patterns were considered, no dropout, missing last visit, missing last two visits, missing last three visit, and missing last four visits. Table A1 shows the π_l used for the three dropout conditions.

The variance components of Equation A2 can be estimated using the PREDICT-HD database. However, PREDICT-HD is not a treatment study and all geneexpanded patients are considered as members of the untreated placebo group in this context (not to be confused with gene-negative patients), with mean slope β_S. The object of inference, β_S, can be estimated as the proportion reduction of the placebo group slope under a hypothetical treatment, expressed as $\beta_S = \psi \beta_S$, where ψ is the proportion reduction in the placebo slope.

Sample size was estimated for $\psi = 0.30, 0.40, 0.50, 0.60, 0.70$. The last value, representing a 70% improvement by treatment, was the approximate percentage group difference in change over 12 weeks in a HD randomized clinical trial of tetrabenazine,[34,35] which is one of the few studies to show statistically significant efficacy.[36] The range of effects is also consistent with clinical trials of other neurodegenerative diseases, such as Multiple Sclerosis.[37] Table 3 presents parameter estimate for β_S, the unique elements of G (g_{11}, g_{12}, g_{22}), and σ^2_e. These values can be used along with different design matrices, dropout proportions, etc., to provide estimates for a wide variety of clinical trial scenarios.

We assumed a single-tailed statistical test, 80% power, and a 2-year study with measurements taken at baseline and every half-year, $t = 0, 6, 12, 18, 24$ months. The variance components were estimated using the PREDICT-HD participants in the range of CAP = [minimum CAP, 846], with the latter value being the maximum value in the sample. Different dropout scenarios, including differential dropout by group, can be created by altering the design matrices of Equation A2.

PREDICT-HD Investigators, Coordinators, Motor Raters, Cognitive Raters

Stephen Cross, Patricia Ryan, Eric A. Epping, and Stacie Vik (University of Iowa, Iowa City, Iowa, USA); Edmond Chiu, Joy Preston, Anita Goh, Stephanie Antonopoulos, and Samantha Loi (St. Vincent's Hospital, The University of Melbourne, Kew, Victoria, Australia); Phyllis Chua and Angela Komiti (The University of Melbourne, Royal Melbourne Hospital, Melbourne, Australia); Lynn Raymond, Joji Decolongon, Mannie Fan, and Allison Coleman (University of British Columbia, Vancouver, British Columbia, Canada); Christopher A. Ross, Mark Varvaris, and Nadine Yoritomo (John Hopkins University, Baltimore, Maryland, USA); William M. Mallonee and Greg Suter (Hereditary Neurological Disease Centre, Wichita, Kansas, USA); Ali Samii and Alma Macaraeg (University of Washington and VA Puget Sound Health Care System, Seattle, Washington, USA); Randi Jones, Cathy Wood-Siverio, and Stewart A. Factor (Emory University School of Medicine, Atlanta, Georgia, USA); Roger A. Barker, Sarah Mason, and Natalie Valle Guzman (Cambridge Centre for Brain Repair, Cambridge, UK); Elizabeth McCusker, Jane Griffith, Clement Loy, and David Gunn (Westmead Hospital, Sydney, Australia); Michael Orth, Sigurd Süβmuth, Katrin Barth, Sonja Trautmann, Daniela Schwenk, and Carolin Eschenbach (University of Ulm, Ulm, Germany); Kimberly Quaid, Melissa Wesson, and Joanne Wojcieszek (Indiana University School of Medicine, Indianapolis, IN); Mark Guttman, Alanna Sheinberg, and Albie Law (Centre for Addiction and Mental Health, University of Toronto, Markham, Ontario, Canada); Susan Perlman and Brian Clemente (UCLA Medical Center, Los Angeles, California, USA); Michael D. Geschwind, Sharon Sha, and Gabriela Satris (University of California San Francisco, California, USA); Tom Warner and Maggie Burrows (National Hospital for Neurology and Neurosurgery, London, UK); Anne Rosser, Kathy Price, and Sarah Hunt (Cardiff University, Cardiff, Wales, UK); Frederick Marshall, Amy Chesire, Mary Wodarski, and Charlyne Hickey (University of Rochester, Rochester, New York, USA); Peter Panegyres, Joseph Lee, Maria Tedesco, and Brenton Maxwell (Neurosciences Unit, Graylands, Selby-Lemnos & Special Care Health Services, Perth, Australia); Joel Perlmutter, Stacey Barton, and Shineeka Smith (Washington University, St. Louis, Missouri, USA); Zosia Miedzybrodzka, Daniela Rae, and Mariella

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Executive Committee

Jane S. Paulsen, Principal Investigator; Eric A. Epping, Jeffrey D. Long, Hans J. Johnson, Jeremy H. Bockholt, and Kelsey Montross.

Scientific Consultants

Brain: Jean Paul Vonsattel and Carol Moskowitz (Columbia University Medical Center).

Cognitive: Deborah Harrington (University of California, San Diego); Tamara Hershey (Washington University); Holly Westervelt (Rhode Island Hospital/Alpert Medical School of Brown University); Megan M. Smith, and David J. Moser (University of Iowa).

Functional: Janet Williams and Nancy Downing (University of Iowa).

Imaging: Hans J. Johnson (University of Iowa); Elizabeth Aylward (Seattle Children's Research Institute); Christopher A. Ross (Johns Hopkins University); Vincent A. Magnotta (University of Iowa); and Stephen Rao (Cleveland Clinic, Cleveland, OH.).

Psychiatric: Eric A. Epping (University of Iowa); David Craufurd (University of Manchester).

Core Sections

Biostatistics: Jeffrey D. Long, Ji-In Kim, James A. Mills, Ying Zhang, Dawei Liu, Wenjing Lu, and Spencer Lourens (University of Iowa).

Ethics: Cheryl Erwin (McGovern Center for Health, Humanities and the Human Spirit); Eric A. Epping and Janet Williams (University of Iowa); Martha Nance (University of Minnesota).

Biomedical Informatics: Jeremy H. Bockholt and Ryan Wyse (University of Iowa).

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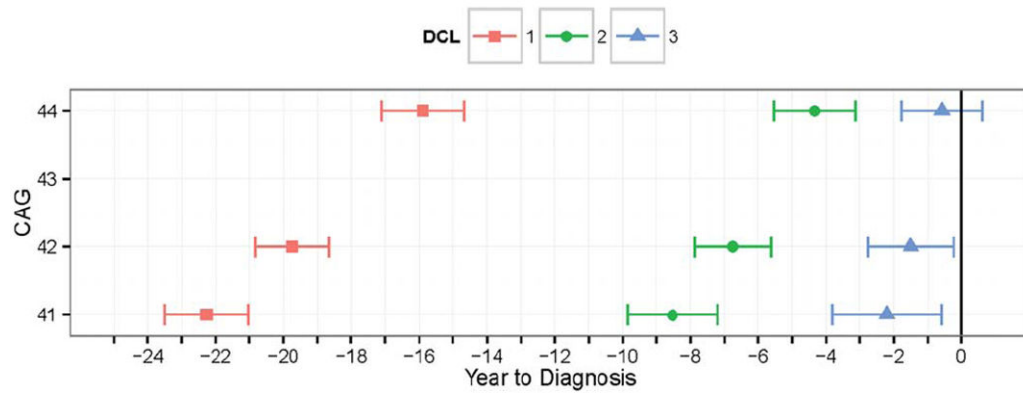
FIG. 1.
The predicted year of diagnostic confidence level (DCL) category occurrence is illustrated with 95% confidence interval as a function of cytosine-adenine-guanine (CAG) repeat length. A vertical line denotes the time of motor diagnosis (DCL=4).
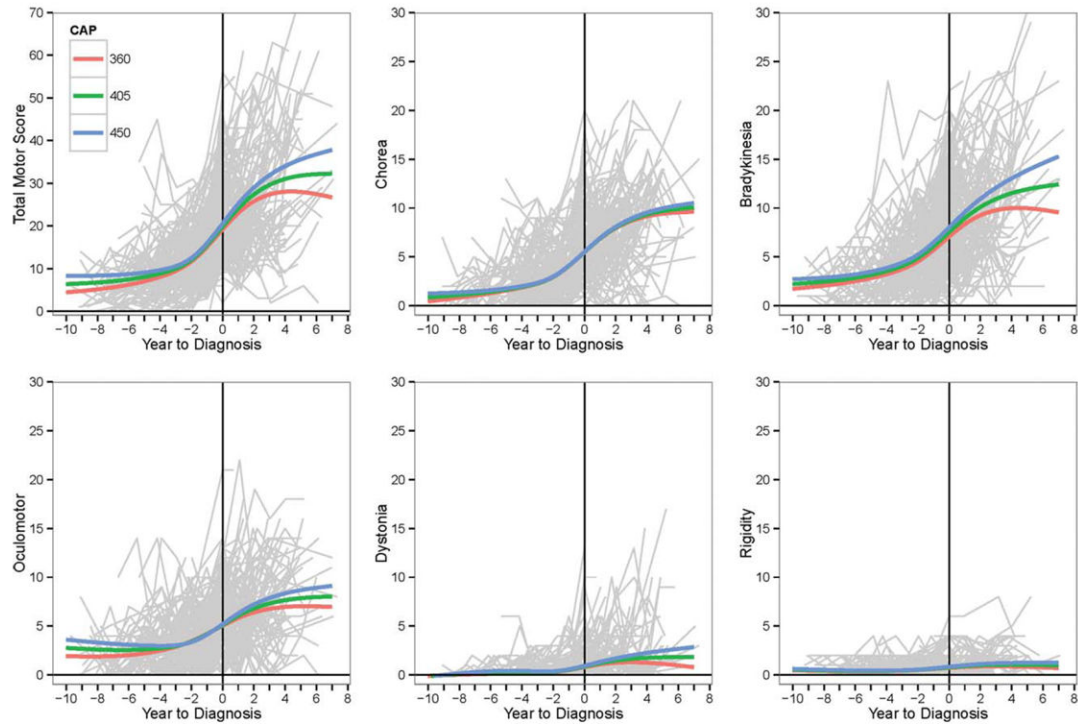
FIG. 2.
Trajectories of motor impairments for converters are illustrated as a function of age-CAG product (CAP). Light gray lines are the empirical trajectories of the participants, and colored lines are the fitted spline model curves. A vertical line denotes the time of motor diagnosis (diagnostic confidence level=4).

TABLE 1

Demographic information for the sample

Variable	Converters, N = 204		Non-converters, N = 806		Combined, N = 1010	
	Mean	SD	Mean	SD	Mean	SD
Age[a]	43.99	10.26	40.13	9.94	41.17	10.17
Education	14.14	2.59	14.58	2.63	14.46	2.63
CAG repeat length	43.24	2.78	42.01	2.30	42.34	2.50
CAP[b]	402.14	76.58	322.58	72.55	343.70	81.59
Women[c]	0.66	0.47	0.61	0.49	0.63	0.48

[a] The age indicated is the age at study entry.

[b] Age–CAG product (CAP) is computed as: CAP = (age at study entry) × (CAG − 33.66).

[c] Values indicate the proportion of women.

Abbreviations: SD, standard deviation; CAG, cytosine–adenine–guanine.

TABLE 2

Linear mixed effects regression results: total motor score slopes and mean at year 2 by age-CAG product and diagnostic confidence level

		Mean (standard error)	
CAP	DCL	Slope	Mean TMS at year 2
285	0	0.0381 (0.0485)	1.0632 (0.1023)[a]
285	1	0.0919 (0.0494)	4.8179 (0.135)[a]
285	2	0.1638 (0.0902)	8.4232 (0.3209)[a]
285	3	0.5396 (0.1567)[a]	11.213 (0.6121)[a]
285	4	1.227 (0.1897)[a]	13.4854 (1.1873)[a]
290	0	0.0414 (0.0475)	1.088 (0.1012)[a]
290	1	0.0894 (0.0479)	4.8739 (0.1315)[a]
290	2	0.1732 (0.0871)[b]	8.5255 (0.3112)[a]
290	3	0.5542 (0.1517)[a]	11.3388 (0.5938)[a]
290	4	1.2811 (0.1848)[a]	13.5992 (1.1537)[a]
310	0	0.0544 (0.0459)	1.1876 (0.0996)[a]
310	1	0.0793 (0.0435)	5.0978 (0.1205)[a]
310	2	0.211 (0.0762)[c]	8.9347 (0.2763)[a]
310	3	0.6129 (0.1329)[a]	11.8418 (0.5244)[a]
310	4	1.4974 (0.1655)[a]	14.0545 (1.0242)[a]
350	0	0.0806 (0.0529)	1.3867 (0.1114)[a]
350	1	0.0593 (0.0443)	5.5457 (0.1169)[a]
350	2	0.2865 (0.0663)[a]	9.753 (0.234)[a]
350	3	0.7302 (0.105)[a]	12.848 (0.4117)[a]
350	4	1.9301 (0.1321)[a]	14.9651 (0.8016)[a]
400	0	0.1133 (0.0745)	1.6356 (0.1462)[a]
400	1	0.0342 (0.0607)	6.1055 (0.1462)[a]
400	2	0.3809 (0.0817)[a]	10.776 (0.2531)[a]
400	3	0.8768 (0.1014)[a]	14.1056 (0.3621)[a]
400	4	2.4709 (0.108)[a]	16.1032 (0.6554)[a]

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

Abbreviations: TMS, total motor score; CAP, age-CAG product; DCL, diagnostic confidence level.

TABLE 3

Required sample size (boldface) for a hypothetical clinical trial of efficacy[a]

Dropout, %	Min CAP	Type I error, %	Parameter Estimates					Effect Size				
			β_S	G_{11}	G_{12}	G_{22}	σ^2_e	30%	40%	50%	60%	70%
0	290	5	1.56	21.40	4.45	3.20	16.54	**552**	**310**	**199**	**138**	**101**
0	350	5	2.04	25.96	5.61	3.67	19.39	**377**	**212**	**136**	**94**	**69**
0	400	5	2.81	32.11	6.56	5.26	24.63	**263**	**148**	**95**	**66**	**48**
0	290	10	1.56	21.40	4.45	3.20	16.54	**402**	**226**	**145**	**101**	**74**
0	350	10	2.04	25.96	5.61	3.67	19.39	**275**	**155**	**99**	**69**	**51**
0	400	10	2.81	32.11	6.56	5.26	24.63	**192**	**108**	**69**	**48**	**35**
10	290	5	1.56	21.40	4.45	3.20	16.54	**591**	**332**	**213**	**148**	**109**
10	350	5	2.04	25.96	5.61	3.67	19.39	**404**	**227**	**145**	**101**	**74**
10	400	5	2.81	32.11	6.56	5.26	24.63	**281**	**158**	**101**	**70**	**52**
10	290	10	1.56	21.40	4.45	3.20	16.54	**431**	**242**	**155**	**108**	**79**
10	350	10	2.04	25.96	5.61	3.67	19.39	**295**	**166**	**106**	**74**	**54**
10	400	10	2.81	32.11	6.56	5.26	24.63	**205**	**115**	**74**	**51**	**38**
20	290	5	1.56	21.40	4.45	3.20	16.54	**636**	**358**	**229**	**159**	**117**
20	350	5	2.04	25.96	5.61	3.67	19.39	**435**	**245**	**157**	**109**	**80**
20	400	5	2.81	32.11	6.56	5.26	24.63	**303**	**170**	**109**	**76**	**56**
20	290	10	1.56	21.40	4.45	3.20	16.54	**464**	**261**	**167**	**116**	**85**
20	350	10	2.04	25.96	5.61	3.67	19.39	**317**	**178**	**114**	**79**	**58**
20	400	10	2.81	32.11	6.56	5.26	24.63	**221**	**124**	**79**	**55**	**41**

[a]The single-arm sample size is for a treatment–placebo slope difference analyzed with linear mixed effects regression. Sample size is listed as a function of percentage of dropout, minimum CAP, Type I error rate, estimated parameters, and effect size. Details are provided in the Appendix.

Abbreviations: Min, minimum; CAP, age-CAG product.