At Risk for Huntington Disease

The PHAROS (Prospective Huntington At Risk Observational Study) Cohort Enrolled

*The Huntington Study Group PHAROS Investigators**

Objective: To identify the emerging clinical precursors that indicate the early onset of Huntington disease (HD) in a reliable and gene-specific manner. This information is critical for the development of therapeutic trials aimed at postponing clinical onset in HD gene carriers.

Methods: Between July 1999 and January 2004, 1001 adults at 50-50 risk for HD agreed to provide longitudinal clinical data and a blood DNA sample under consent provisions that require their individual clinical and genetic information to never be revealed.

Results: The Prospective Huntington At Risk Observational Study (PHAROS) cohort is characterized by a 2:1 predominance of women to men, high educational attainment, and gainful employment. Despite the gender disparity, the demographic, hereditary, and clinical characteristics of the female and male participants were similar. Investigators, who are unaware of individual gene status, characterized the baseline cohort to be highly functional with minimal motor or cognitive impairment; 92.3% of participants were judged to have no or nonspecific motor abnormalities; 6.7%, to have possible or probable motor signs; and only 1.0%, to have unequivocal HD.

Conclusion: The baseline characteristics of the PHAROS cohort make it well suited to generate objective and prospective data about gene-specific clinical precursors that can be used as outcomes in controlled trials aimed at postponing the onset of HD.

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Authors/Group Information: The authors and members of the Huntington Study Group PHAROS Investigators are listed on pages 997 and 998.

HUNTINGTON DISEASE (HD) is an adult-onset, progressively disabling, and fatal neurodegenerative disorder that is inherited in an autosomal dominant pattern, owing to an expanded trinucleotide repeat mutation of cytosine-adenine-guanine (CAG_n) in the 5′-translated region of the *IT-15* gene on chromosome 4p16.3.[1,2] The extent of the CAG_n expansion is inversely correlated with the age when HD becomes clinically manifest and is estimated to account for at least half of the variance in determining age at clinical onset.[2,3] Individuals who inherit the HD gene spend on average about two thirds of their shortened life in a healthy-appearing state before gradually emerging motor, cognitive, and behavioral signs and symptoms are recognized as manifest illness.[4,5]

Some 30 000 individuals in the United States and Canada have HD. Although an additional 150 000 are at 50-50 risk of having inherited the HD gene,[4-6] only a small proportion of at-risk individuals have chosen to undergo presymptomatic predictive DNA testing to learn whether they have the HD gene.[7,8] Important information has emerged about individuals who have been tested.[8] In contrast, relatively little is known about the larger numbers of individuals at risk to develop HD who are unaware of or have chosen not to undergo predictive DNA testing. This group of individuals provides a unique research opportunity to define prospectively and objectively the earliest and most specific signs and symptoms of HD as a critical prelude to examining experimental treatments aimed at postponing the onset of illness.

The Prospective Huntington At Risk Observational Study (PHAROS) is a noninterventional, longitudinal investigation of the HD gene–specific features that are predictive of manifest disease, defined by prespecified criteria and using strict measures to conceal individual genetic data. Our major aim is to identify the clinical features that reliably indicate the

Figure 1. Confidence rating of Huntington disease (HD) motor abnormalities (item 17 of Unified Huntington's Disease Rating Scale[12] 1999).

earliest onset of illness, with high specificity for the HD gene. This knowledge will better inform the design of clinical trials aimed at postponing onset. We herein report the baseline clinical features of the fully enrolled PHAROS cohort.

METHODS

STUDY ELIGIBILITY, CONSENT, AND CONFIDENTIALITY

Beginning in 1999, investigators at 43 research sites of the Huntington Study Group (www.huntington-study-group.org) in the United States and Canada participated in the screening, enrollment, and evaluation of research participants. Institutional review boards at all participating sites approved the research protocols and consent procedures.

The PHAROS participants included unaffected adults, aged 26 to 55 years, who were at nominal 50-50 risk for having inherited the HD gene by virtue of having an affected parent or sibling, who had chosen not to undergo predictive DNA testing for the HD gene, and who wished to remain unaware of their gene status. Subjects consented to participate in this longitudinal research study with the provision that privacy was maintained and individual clinical and genetic data would never be disclosed. The eligibility of 26 to 55 years of age was chosen because this age group has the highest actuarial risk for developing HD during the planned period of prospective evaluation.[4,5,9]

No experimental treatments were assigned in this observational study. Prescribed, over-the-counter, and natural remedies were not restricted, except that neuroleptic or atypical antipsychotic medication could not be taken within 6 months of enrollment. Potential participants were excluded if they had been previously diagnosed with HD or had clinical evidence of psychosis or severe depression.

Consenting research participants agreed to be evaluated at approximately 9-month intervals at their enrolling site for a minimum of 4 years of observation. Our goal was to enroll individuals who were not clinically affected with HD while honoring a condition of consent that participants would not be informed of clinical status. Accordingly, protocol contingencies were also provided to enroll a small number of clinically affected, otherwise eligible individuals without informing them of their clinical status. We estimated that up to 5% of the baseline cohort would represent such individuals.[10] In the event that participants request information about their clinical status, they are referred to health care professionals and seen outside of formal research visits.

A blood sample was obtained at baseline from each research participant to measure CAG_n of the HD gene under an arrangement stipulating that no party, including research participants and investigators, would ever be informed of identifiable genetic data. A confidentiality certificate from the National Institutes of Health Office of Research Management[11] provided an additional assurance that genetic or diagnostic information is protected from legal action. A bar-code system deidentified the samples, thereby preventing researchers from gaining access to or linking identifiable genetic and clinical data. In the event that PHAROS research participants decide to undergo clinical DNA testing, they are referred to established testing sites for comprehensive genetic counseling and asked not to reveal their CAG_n status to PHAROS researchers.

ASSESSMENT OF CLINICAL FEATURES

At the baseline evaluation, a site coordinator and site investigator obtained a comprehensive medical history and performed a physical examination, including the Unified Huntington's Disease Rating Scale (UHDRS), version 1999,[12] and the Beck Depression Inventory (BDI).[13] An independent rater at each site served strictly as a motor examiner, interacting with research participants only to perform the motor component of the UHDRS. Site coordinators, site investigators, and independent raters underwent annual reliability training for the UHDRS motor examination using videotapes of research participants in the US-Venezuela HD Project.[3,14] A key item on the motor examination required the rater to assign a level of "diagnostic confidence of HD" (**Figure 1**). The rating of a 4 (clinically definite HD) has been found to have good reliability among independent raters.[14]

GENOTYPE ASSESSMENT

Coded venous blood samples from research participants were sent to the DNA laboratory of the Molecular Neurogenetics Unit at Massachusetts General Hospital where CAG_n analysis was performed under the direction of Marcy MacDonald, PhD, using previously described techniques.[15]

SAMPLE SIZE CONSIDERATIONS AND STATISTICAL ANALYSIS

A sample size of 1000 PHAROS participants was estimated to consist of about 400 individuals with expanded CAG_n.[4,5,16] Assuming 20% of participants with expanded CAG_n develop an HD gene–specific clinical sign, the projected sample of 400 HD gene–positive individuals and 600 gene-negative individuals provides 80% power, at a significance level of .05, to detect a difference of 7% in the prevalence of a specific clinical precursor of HD among participants with and without the CAG_n expansion.[17] Based on data from Brinkman et al,[18] we estimated the annual incidence rate of manifesting HD to be 6%, defined by the first diagnostic rating of "definite HD" (Figure 1). Thus, 400 individuals with expanded CAG_n, followed up for an average of 4 years, will yield approximately $(4) \times (400) \times (0.06) = 96$ individuals who manifest HD. Allowing for an annual withdrawal rate of 5%, about 77 research participants are projected to manifest HD during an observation period of 4 years.

Using survivorship analysis and a proportional hazard model for the risk of manifesting HD,[17] we estimated that a total of 77 individuals will provide 80% power to detect the influence of a dichotomous risk factor corresponding to a hazard ratio of 2.0, provided the prevalence of this risk factor in the population of individuals with expanded CAG_n lies between 30% and 70%. To maintain the objectivity of ongoing clinical assessments and the integrity of future phenotype-genotype analyses, the protocol specified that the effect of
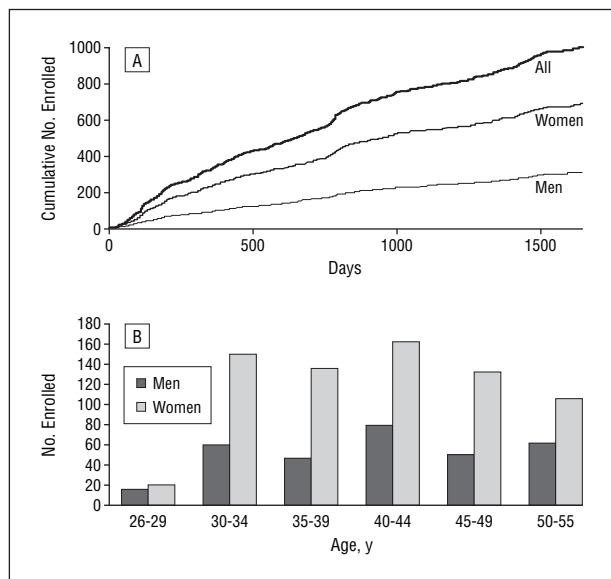
Figure 2. A, Cumulative accrual of the Prospective Huntington At Risk Observational Study (PHAROS) cohort for women, men, and all participants. B, Age distributions of PHAROS cohort for women and men.

*Values are expressed as mean ± SD unless otherwise indicated. Height and weight differ significantly (*P*<.01) for men and women.

CAG$_n$ on study outcomes will not be determined until 77 participants are judged by the independent rater to have developed unequivocal motor signs of HD (Figure 1).

Statistical analyses were performed on the baseline data, which included demographic variables, medical histories, UHDRS scores, and BDI scores. Baseline characteristics were compared for men and women, using either χ^2 test or *t* test as appropriate. The present results report accrued data for baseline characteristics as of January 31, 2004, and entered into the database as of July 13, 2004. Data pertaining to a detailed analysis of baseline UHDRS data and the prospective follow-up of the cohort[19] will be reported separately.

RESULTS

ACCRUAL

Between July 9, 1999, and January 31, 2004, 1001 research participants were enrolled at 43 research sites in the United States and Canada, with a mean ± SD of 23 ± 11.9 participants per site (range, 3-58). The pace of accrual was largely linear, but about a 2:1 ratio of enrolled women to men among all age groups persisted throughout the approximately 4.5 years of enrollment with a final representation of 689 women and 312 men (**Figure 2**A). The disproportionate representation of women to men was not appreciably influenced by special recruitment efforts that began in 2001 to attract more male research participants.

BASELINE CHARACTERISTICS

Table 1 presents the baseline characteristics of the research participants. The mean ± SD age of research participants at enrollment was 41.8 ± 7.3 years. Racial distribution was 98% Caucasian, 1% African American, and 1% Asian or Native American. Ethnic representation included 2.5% Hispanic participants. Marital status was dis-

tributed as 70% married, 18% single, and 12% divorced, similar for men and women. Forty percent of the women and 29% of the men reported that they were naturally or surgically sterile.

Both female and male research participants were highly educated, with mean ± SD 14.9 ± 2.6 years of formal education (range, 6-28 years); 45% reported at least 16 years of education (comparable with 4 years of college) and 96%, at least 12 years of education (comparable with 4 years of high school). Nearly all PHAROS participants (96%; 94% of women, 99% of men) were active in the labor force in roles self-reported as professional (45%; 44% of women, 48% of men), managerial (36%; 40% of women, 26% of men), service (8%; 8% of women, 8% of men), craftsperson (5%; 1% of women, 14% of men), or laborer (1%; 1% of women, 3% of men).

Only 6% of research participants reported symptoms that concerned them as possibly related to HD (44% motor, 32% cognitive, 23% psychiatric, 2% mixed). A self-reported history of psychiatric illness at baseline was common (29% depression, 9% suicidal ideation, 4% suicide attempt), significantly more so in women than men (depression, 33% vs 18%; suicidal ideation, 11% vs 6%; and suicide attempt, 5% vs 2%, respectively). However, the overall severity of the baseline BDI scores[13] was modest; only 6.5% of participants had BDI scores considered to be in a depressed range. Distribution of BDI scores was similar for women and men.

Except for antidepressant medication, which 14% of participants reported taking at enrollment (16% women, 9% men), there was little reported use of medications commonly used to treat patients with HD. Only 2.7% of participants were taking coenzyme Q$_{10}$ at a mean ± SD daily dosage of 100 ± 59.4 mg, and no participants were taking a dosage exceeding 300 mg/d. Only 1.8% reported taking anxiolytics; 1%, fish oil supplements; 0.6%, minocycline; and 0.3%, creatine.

BASELINE UHDRS SCORES

The baseline UHDRS scores, including motor, cognitive, and behavioral component scores, are summarized in **Table 2**. The total motor UHDRS score of 2.8 ± 4.3 units (mean ± SD) was near the floor of the 31-item scale

Table 2. Baseline UHDRS Characteristics*

Characteristic	All (N = 1001)	Women (n = 689)	Men (n = 312)
Motor assessments			
Total UHDRS motor assessment score (range, 0-124)	2.8 ± 4.3	2.6 ± 3.9	3.3 ± 4.9
Total maximal chorea score (range, 0-28)	0.5 ± 1.5	0.4 ± 1.2	0.7 ± 1.9†
Total maximal dystonia score (range, 0-20)	0.1 ± 0.5	0.1 ± 0.3	0.1 ± 0.6
Composite bradykinesia + gait + tandem walk + retropulsion pull test score (range, 0-16)	0.3 ± 0.8	0.3 ± 0.8	0.3 ± 0.7
Total rigidity arms score (range, 0-8)	0.2 ± 0.6	0.2 ± 0.5	0.3 ± 0.7
Composite finger taps + pronate/supinate hands score (range, 0-16)	0.5 ± 1.1	0.5 ± 1.0	0.5 ± 1.1
Composite saccade velocity + initiation score (range, 0-16)	0.6 ± 1.3	0.6 ± 1.3	0.6 ± 1.3
Luria score (range, 0-4)	0.3 ± 0.7	0.2 ± 0.6	0.4 ± 0.8
Dysarthria score (range, 0-4)	0 ± 0.1	0 ± 0.1	0 ± 0.1
Cognitive assessments			
Verbal fluency test score (observed range, 8-82)	38.6 ± 11.7	39.1 ± 11.5	37.4 ± 12.0
Symbol Digit Modalities Test score (observed range, 19-96)	52.9 ± 10.1	53.6 ± 10.2	51.4 ± 9.8‡
Stroop color naming score (observed range, 25-150)	79.9 ± 14.2	80.6 ± 13.9	78.5 ± 14.9
Stroop word reading score (observed range, 10-160)	95.0 ± 13.2	95.4 ± 12.8	94.0 ± 14.0
Stroop interference score (observed range, 11-120)	46.1 ± 11.8	46.2 ± 11.1	45.8 ± 13.2
Behavioral assessments			
Behavioral assessment: frequency (range, 0-44)	4.1 ± 4.3	4.2 ± 4.2	3.9 ± 4.3
Behavioral assessment: severity (range, 0-44)	4.2 ± 4.4	4.3 ± 4.4	3.9 ± 4.4

Abbreviation: UHDRS, Unified Huntington's Disease Rating Scale.
*Values are expressed as mean ± SD. Gender differences are tested excluding the 10 subjects with unequivocal HD.
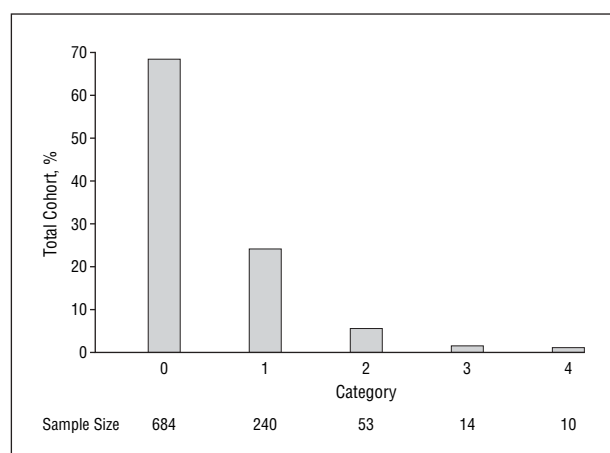†$P<.05$.
‡$P<.01$.

Figure 3. Diagnostic confidence ratings (Figure 1) of the Prospective Huntington At Risk Observational Study (PHAROS) cohort by site investigator.

(4 possible units for each item) that ranges from 0 to 124 units of severity. Overall cognitive performance was high; verbal fluency, symbol digit scores, and Stroop scores were within the reported scores for a normal age-appropriate population.[20] Behavioral UHDRS assessment also showed minimal impairment; composite behavioral frequency (mean ± SD, 4.1 ± 4.3) and severity (mean ± SD, 4.2 ± 4.4) scores were at the floor of these 11-item scales that ranged from 0 to 44 units of severity. The cohort was highly functional and at the maximum scores for total functional capacity (13 units), independence scale (100%), and the functional checklist assessment (25 units). There were no significant gender differences in these baseline UHDRS characteristics.

BASELINE DIAGNOSTIC CONFIDENCE

The distribution of diagnostic confidence categories (Figure 1) at baseline, as reported by the site investigator, is illustrated in **Figure 3**; 92.3% of participants were judged to have ratings of 0 or 1; 6.7%, to have ratings of 2 or 3; and only 1.0% (3 women, 7 men), to have a rating of 4 (unequivocal HD). There were no major gender differences in the distribution of the diagnostic confidence categories for ratings 0, 1, 2, or 3.

Analysis of 6-month epochs during the 4.5-year accrual phase showed no change in the time-related distribution of unequivocal (rating 4) or likely (rating 3) signs of HD at baseline. However, there was a time-related trend for increased severity of diagnostic judgments for the categories of possible (rating 2) and nonspecific (rating 1) signs, paralleling the repeated annual training sessions that the investigators underwent during the 4.5 years of enrollment.

COMMENT

The PHAROS cohort of 1001 adults at risk for HD, accrued over 4.5 years at 43 specialized research sites in the United States and Canada, consists of eligible research participants who are predominantly women, highly educated, and gainfully employed. While such individuals are more likely to participate in clinical trials,[21] the disproportionate participation by women in this observational study is not indicative of the gender parity observed in interventional clinical trials involving research participants who have manifest signs of HD.[22]

The reasons for the gender imbalance in PHAROS are not obvious. Although we attempted to enhance recruitment of men by emphasizing the importance of their participation, the 2:1 representation of women to men was steady throughout the period of accrual. This imbalance was foreshadowed by a planning survey to assess interest and feasibility in PHAROS that yielded 2:1 women to men respondents.[23] In an earlier cross-sectional study of 585 individuals at risk for HD, 69% of the participants were women.[24] Data from the National Institutes of Health–supported National Research Roster for Huntington Disease Patients and Families (NS 82396) indicate that 1295 (69.1%) of the 1873 respondents who were at 50-50 risk for HD were women (P. M. Conneally, PhD, oral communication, February 2002). Similarly, about 65% of adults worldwide who seek predictive DNA testing for HD are women.[8]

These patterns suggest that unaffected women at risk for HD are twice as likely as their male counterparts to participate in observational clinical research as well as predictive DNA testing. We have not been able to identify aspects of PHAROS particularly aversive to men. Rather, it seems that women are more willing than men to contribute to observational clinical research that is unlikely to provide any direct benefits, a finding perhaps related to a greater interest by women in their reproductive fate. This gender disparity in observational studies of individuals at risk for HD should be considered in planning therapeutic trials where the availability of experimental treatments and potential direct benefits are expected to produce greater gender parity. The underrepresentation of minorities in PHAROS is similar to prior studies involving individuals with manifest HD[22] but may be related to the nearly exclusive use of English-language materials and the geographic distribution of study sites with limited access to a broader sampling of ethnic and racial groups.

The demographic and clinical characteristics of the female and male participants in PHAROS were similar despite the gender disparity. The more common baseline reports by women of symptoms of depression are in keeping with reports of a higher incidence of self-reported depression in women than men in general[25,26] and may also reflect the greater willingness of women than men to participate in this observational study. Nonetheless, we remain vigilant to the risk of suicide[27] because of the high occurrence of attempted and completed suicide among patients with HD and individuals at risk for HD.[28]

Our enrolled research participants reported infrequent use of putative disease-modifying treatments such as coenzyme Q_{10}, creatine, and minocycline.[29] This finding seems surprising in view of the relative availability of these potential remedies and the generally well-educated background of this cohort. However, the uncertainty of benefits and dosage, the risks of long-term adverse effects, and the cost of taking these unproven treatments might also be viewed as consistent with educated and informed decision making.

Distribution of baseline diagnostic confidence levels was consistent with the research aims and design of PHAROS to enroll an unaffected cohort of adults at risk
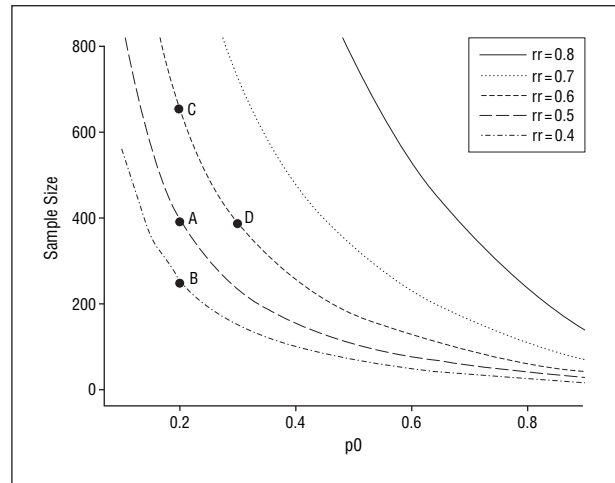

Figure 4. Relationship between phenoconversion rate (p0) in the placebo group, the effect size or ratio of the phenoconversion rate between treatment and placebo groups (rr), and the total sample size requirements for a preventive randomized trial in preclinical Huntington disease, assuming a significance level = .05, power = 0.80, and 1:1 allocation of placebo and active treatments. For example, p0 of 0.2 for a given period of assessment requires a total sample size of 400 participants (point A). For the same p0, greater (point B) or smaller (point C) effects require correspondingly smaller or larger sample sizes. However, if p0 increases with longer duration of prospective evaluation, smaller effects can be detected (point D) with the same sample size (point A).

for HD. Despite our projection that we would enroll about 5% individuals already affected by HD, only about 1% of our cohort at baseline was judged to have unequivocal motor features of HD. This low level of manifest HD at baseline should enhance longitudinal detection of the early, specific features marking the onset of HD.

The low prevalence of unequivocal HD findings among PHAROS participants is in keeping with that found in previous studies of at-risk individuals. In a cross-sectional analysis of 657 subjects at risk for HD, 4.9% were diagnosed with manifest HD on initial examination,[24] and subsequent genetic analyses showed that 3 of the 20 individuals clinically classified as having manifest HD did not have an expanded CAG repeat.[10] Similarly, in a group of 124 subjects at risk for HD, 2.4% were diagnosed with manifest disease, and 3 subjects classified as having "unequivocal" HD were found not to carry a CAG expansion.[30] Whether these classifications are false-positive diagnoses or whether these subjects have other autosomal dominant choreic disorders would require more extensive follow-up evaluations. When prospective evaluation of the PHAROS cohort is completed and genetic data are analyzed, we will have a clearer estimate of the extent of false-positive clinical diagnosis for HD.

The PHAROS genotype data have not yet been analyzed because of concerns about biasing the ongoing and blinded longitudinal evaluations of phenotype. The planned prospective observation of at least 4 years and high participant retention will enhance identification of the early HD gene–specific precursors and more accurately estimate the rate of "phenoconversion." In turn, this knowledge will help inform the sample size, power, and effect size for experimental treatments aimed at postponing the onset of HD (**Figure 4**). The PHAROS co-

hort at enrollment, largely unaffected clinically and with a range of diagnostic confidence, is well suited to generate objective data, comparing participants who do and do not carry the CAG_n expansion, as well as those who do and do not manifest HD.

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Authors

The following members of the Huntington Study Group are investigators in PHAROS (Prospective Huntington At-Risk Observational Study) and authors of this report.

Steering Committee

University of Rochester, Rochester, NY: Ira Shoulson, MD (principal investigator), Karl Kieburtz, MD, MPH (director, Clinical Trials Coordination Center), David Oakes (chief biostatistician), Elise Kayson, MS, RNC (project coordinator), Hongwei Zhao, PhD, M. Aileen Shinaman, JD (Huntington Study Group executive director), Megan Romer, MS; *Massachusetts General Hospital, Charleston*: Anne Young, MD, PhD (co–principal investigator), Steven Hersch, MD, PhD, Jack Penney, MD†; *Johns Hopkins University, Baltimore, Md*: Kevin Biglan, MD (medical monitor); *Columbia University Medical Center, New York, NY*: Karen Marder, MD; *University of Iowa, Iowa City*: Jane Paulsen, PhD; *Indiana University School of Medicine, Indianapolis*: Kimberly Quaid, PhD; *Lily Corporate Center, Indianapolis*: Eric Siemers, MD; *The Parkinson's Institute, Sunnyvale, Calif*: Caroline Tanner, MD.

Participating Investigators and Coordinators

Hereditary Neurological Disease Centre, Wichita, Kan: William Mallonee, MD, David Palmer, MD,† Greg Suter, BA; *University of Kansas Medical Center, Kansas City*: Richard Dubinsky, MD, Gary Gronseth, MD, R. Neil Schimke, MD, Carolyn Gray, RN; *Hennepin County Medical Center/Minneapolis, Minneapolis, Minn*: Martha Nance, MD, Scott Bundlie, MD, Dawn Radtke, RN; *Ohio State University, Columbus*: Sandra Kostyk, MD, PhD, George W. Paulson, MD, Karen Thomas, DO, Nonna Stepanov, MD, Corrine Baic, BS; *Wake Forest University School of Medicine, Winston-Salem, NC*: James Caress, MD, Francis Walker, MD, Vicki Hunt, RN; *Hotel-Dieu Hospital–CHUM, Montreal, Quebec*: Sylvain Chouinard, MD, Guy Rouleau, MD, PhD, Hubert Poiffaut, RN, Brigitte Rioux†; *Emory University School of Medicine, Atlanta, Ga*: Claudia Testa, MD, PhD, Timothy Greenamyre, MD, PhD, Joan Harrison, RN; *University of California, San Diego, LaJolla*: Jody Corey-Bloom, MD, PhD, David Song, MD, Guerry Peavy, PhD, Jody Goldstein, BS; *University of Iowa, Iowa City*: Jane Paulsen, PhD, Henry Paulson, MD, Robert L. Rodnitzky, MD, Ania Mikos, BA, Becky Reese, BS, Laura Stierman, BS, Katie Williams, BA, Lynn Vining, RN, MSN; *Columbia University Medical Center*: Karen Marder, MD, PhD, Carol Moskowitz, RN; *Indiana University School of Medicine*: Kimberly Quaid, PhD, Joanne Wojcieszek, MD, Melissa Wesson, MS; *University of Washington and VA Puget Sound Health Care System, Seattle*: Ali Samii, MD, Thomas Bird, MD, Hillary Lipe, ARNP; *Medical College of Wisconsin, Milwaukee*: Norman Reynolds, MD, Karen Blindauer, MD, Jeannine Petit, ANP; *University of Rochester*: Peter Como, PhD, Frederick Marshall, MD, Timothy Counihan, MD, Kevin Biglan, MD, Carol Zimmerman, RN; *Oregon Health and Science University, Portland*: Penelope Hogarth, MD, John Nutt, MD, Pamela Andrews, BS, CCRC; *Massachusetts General Hospital*: Steven Hersch, MD, PhD, Leslie Shinobu, MD, PhD, Diana Rosas, MD, Yoshio Kaneko, BA, Sona Gevorkian, MS, Paula Sexton, BA, CCRA; *Mayo Clinic Scottsdale, Scottsdale, Ariz*: John Caviness, MD, Charles Adler, MD, PhD; *University of California, Davis, Sacramento*: Vicki Wheelock, MD, David Richman, MD, Teresa Tempkin, RNC, MSN; *Brown University (Memorial Hospital of Rhode Island), Pawtucket*: Chuang-Kuo Wu, MD, PhD, Hubert Fernandez, MD, Joseph H. Friedman, MD, Margaret Lannon, RN, MS; *Colorado Neurological Institute, Englewood*: Lauren Seeberger, MD, Christopher O'Brien, MD, Sherrie Montellano, MA; *University of Michigan, Ann Arbor*: Ninith Kartha, MD, Sharin Sakurai, MD, PhD, Susan Hickenbottom, MD, PhD, Roger Albin, MD, PhD, Kristine Wernette, RN, MS; *Washington University, St Louis, Mo*: Brad Racette, MD, Joel S. Perlmutter, MD, Laura Good, BA; *University of California Los Angeles Medical Center, Los Angeles*: George Jackson, MD, PhD, Susan Perlman, MD, Shelley Segal, MD, Russell Carroll, MA, Laurie Carr, BS; *University of Alberta, Edmonton*: Wayne Martin, MD, Ted Roberts, MD, Marguerite Wieler, BSC, PT; *University of British Columbia, Vancouver*: Blair Leavitt, MD, Lorne Clarke, MD, CM, Lynn Raymond, MD, PhD, Joji Decolongon, MSC, Vesna Popovska, MD, Elisabeth Almqvist, RN, PhD; *Baylor College of Medicine, Houston, Tex*: William Ondo, MD, Madhavi Thomas, MD, Tetsuo Ashizawa, MD, Joseph Jankovic, MD; *University of South Florida, Tampa*: Robert Hauser, MD, Juan Sanchez-Ramos, MD, PhD, Karen Price, MA, Holly Delgado, RN; *University of Calgary, Calgary, Alberta*: Sarah Furtado, MD, PhD, Anne Louise LaFontaine, MD, Oksana Suchowersky, MD, Mary Lou Klimek, RN, MA; *Centre for Addiction and Mental Health, Markham, Ontario*: Rustom Sethna, MD, Mark Guttman, MD, Sandra Russell, BSW, RSW, Sheryl Elliott, RN; *North Shore University Hospital, Manhasset, NY*: Marc Mentis, MB, CHB, Andrew Feigin, MD, Marie Cox, RN, BSN, Barbara Shannon, RN; *University of Alabama at Birmingham*: Alan Percy, MD, Leon Dure, MD, Donna Pendley, RN, Jane Lane, RN, BSN; *University of Virginia, Charlottesville*: Madaline Harrison, MD, Elke Rost-Ruffner, RN, BSN; *University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical Center, Stratford*: William Johnson, MD; *University of Pennsylvania, Philadelphia*: Amy Colcher, MD, Andrew Siderowf, MD, Mary Matthews, RN; *Institute for Neurodegenerative Disorders, New Haven, Conn*: Danna Jennings, MD, Kenneth Marek, MD, Karen Caplan, MSW;

(*continued*)

Albany Medical College, Albany, NY: Stewart Factor, DO, Donald Higgins, MD, Eric Molho, MD, Constance Nickerson, LPN, Sharon Evans, LPN; *Winnipeg Clinic, Winnipeg, Manitoba*: Douglas Hobson, MD, Paul Shelton, MD, Shaun Hobson, RN; *University of Miami, Miami, Fla*: Carlos Singer, MD, Nestor Galvez-Jimenez, MD, William Koller, MD,† Doris Martin, DDS, Kelly Lyons, PhD, Dinorah Rodriguez, RN; *Rush Presbyterian-St Luke's Medical Center, Chicago, Ill*: Kathleen Shannon, MD, Cynthia Comella, MD, Jean Jaglin, RN, CCRC; *University of Maryland School of Medicine, Baltimore*: Karen Anderson, MD, William Weiner, MD, Kelly Dustin, RN, BSN; *Johns Hopkins University*: Adam Rosenblatt, MD, Christopher Ross, MD, PhD, Deborah Pollard; *Boston University, Boston, Mass*: Marie H. Saint-Hilaire, MD, Peter Novak, MD, J. Stephen Fink, MD, PhD,† Bonnie Hersh, MD, Melissa Diggin, MS, RN, Leslie Vickers, RN, MS; *University of Connecticut, Hartford*: Wallace Deckel, PhD, James Duffy, MD, Mary Jane Fitzpatrick, APRN.

Participating National Institutes of Health Authors
National Human Genome Research Institute, Bethesda, Md: Elizabeth Thomson, PhD; *National Institute of Neurological Disorders and Stroke, Bethesda.*

Event Monitoring Committee
Massachusetts General Hospital: Steven Hersch, MD, PhD (co-chair); *Indiana University*: Julie Stout, PhD (co-chair), James Calhoun; *University of Iowa*: William Coryell, MD, Cheryl Erwin, JD, PhD; *Wake Forest University School of Medicine*: Vicki Hunt, RN; *Johns Hopkins University*: Christopher Ross, MD, PhD; *Minnesota Center for Health Care Ethics, Minneapolis*: Dorothy Vawter, PhD.

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Chicago-Kent College of Law, Chicago, Ill: Lori Andrews, JD, Debbie Bury, James Calhoun; *Massachusetts General Hospital*: Steven Hersch, MD, PhD (chair); *Wake Forest University School of Medicine*: Vicki Hunt, RN, Carl Leventhal, MD; *Indiana University School of Medicine*: Kimberly Quaid, PhD; *University of Rochester*: Aileen Shinaman, JD; *Minnesota Center for Health Care Ethics*: Dorothy Vawter, PhD; *Columbia University*: Nancy Wexler, PhD.

Biostatistics and Clinical Trials Coordination Center
University of Rochester: Alicia Brocht, BA, Susan Daigneault, Karen Gerwitz, BS, Connie Orme, BA, Ruth Nobel, Victoria Ross, MA, Mary Slough, Arthur Watts, BS, Joe Weber, BS, Christine Weaver, Elaine Julian-Baros.

Genetic/Environmental Modifiers Committee
Massachusetts General Hospital: Anne Young, MD, PhD (chair); *Columbia University Medical Center*: Karen Marder, MD (co-chair); *Indiana University School of Medicine*: Tatiana Foroud, PhD; *Massachusetts General Hospital*: James Gusella, PhD, Rudolph Tanzi, PhD; *Massachusetts Institute of Technology, Cambridge*: David Housman, PhD; *Massachusetts General Hospital*: Marcy MacDonald, PhD; *Boston University*: Richard Myers, PhD; *The Parkinson's Institute*: Caroline Tanner, MD.

Independent Monitoring Committee
Columbia University: Stanley Fahn, MD, Weiu-Yann Tsai, PhD; *Indiana University*: Michael Conneally, PhD.

Scientific Advisory Committee
New York Hospital Department of Neurology, New York: Flint Beal, MD; *Massachusetts Institute of Technology*: David Housman, PhD; *Johns Hopkins University*: Christopher Ross, MD, PhD; *Massachusetts General Hospital*: Rudolph Tanzi, PhD, Anne Young, MD, PhD; *University of California, Irvine*: Claudia Kawas, MD; *University of California, Los Angeles*: Marie Francoise-Chesselet, MD, PhD

DNA Oversight Committee
Indiana University Medical Center: Michael Conneally, PhD; *University of Minnesota/Minnesota VA Medical Center, Minneapolis*: Martha Nance, MD; *University of California, San Diego*: Clifford Shults, MD; *The Parkinson's Institute*: Caroline Tanner, MD.

Independent Rater Video Committee
Oregon Health and Science University: Penelope Hogarth, MD; *Massachusetts General Hospital*: Diana Rosas, MD; *University of Rochester*: Hongwei Zhao, PhD.

†Deceased.