Confirmation of Subtle Motor Changes Among Presymptomatic Carriers of the Huntington Disease Gene

Sandra Close Kirkwood, PhD; Eric Siemers, MD; Cherie Bond, BS; P. Michael Conneally, PhD; Joe C. Christian, MD, PhD; Tatiana Foroud, PhD

Objective: To confirm that subtle changes in motor function and reaction time are present in presymptomatic individuals carrying the expanded Huntington disease (HD) allele.

Design: A case-control, double-blind study comparing presymptomatic HD gene carriers (PSGCs) and non-gene carriers (NGCs) at risk for HD.

Setting: The Department of Medical and Molecular Genetics at a general clinical research center in a midwestern city.

Participants: Two hundred sixteen individuals at risk for HD who were asymptomatic by self-report and who did not have manifest HD on results of clinical examination, including PSGCs (n=61) and NGCs (n=155).

Measures: Molecular testing was used to determine the number of CAG repeats in the HD gene. A quantified neurologic examination and a battery of physiological measures of central nervous system function measuring speed of movement and reaction time were administered.

Results: On neurologic examination, the PSGCs exhibited significantly more definite or possible abnormalities than NGCs for overall oculomotor function, saccade velocity, optokinetic nystagmus, chorea of the extremities, and dystonia of the extremities (P<.05). The PSGCs also had significantly slower performance for auditory reaction time, visual reaction time, visual reaction time with decision, movement time, movement time with decision, and button-tapping time, compared with the NGCs (P<.05).

Conclusions: Subtle changes in motor function, speed of movement, and reaction time are present in HD gene carriers who do not exhibit definite choreiform movements and who do not have sufficient signs to make a clinical diagnosis of HD. In addition, a trend toward slower speed of movement and reaction time was observed among this population as their neurologic abnormalities increased.

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Huntington disease (HD) is an autosomal dominant, neurodegenerative disorder characterized neuropathologically by the loss of medium-sized spiny neurons in the neostriatum. Huntington disease is caused by an increased number of triplet (CAG) repeats in the HD gene, which is on chromosome 4. Typically, individuals with HD have 38 or more CAG repeats. A negative correlation between age at HD onset and number of CAG repeats has been observed, with patients with juvenile-onset HD having the greatest number of CAG repeats. The clinical implication of an intermediate allele with 32 to 37 repeats is ambiguous, as such an allele may confer variable penetrance or meiotic instability.

Clinically, a triad of progressive motor, cognitive, and emotional symptoms characterizes HD. Great variation has been seen in the age at onset, the initial presentation of symptoms, and the clinical course of disease. The determination of the exact age at symptom onset is frequently difficult, and the categorization of an individual as affected or unaffected uncertain. A clinical diagnosis of HD in at-risk individuals is usually made after the onset of involuntary, choreiform movements. Involuntary movement abnormalities associated with HD that sometimes develop later in the course of disease include myoclonus, dystonia, and tremor. Voluntary movement abnormalities include difficulty with rhythmic and rapid alternating movements, bradykinesia, postural reflex instability, decreased fine motor control, dysarthria, and dysphagia. Changes in extraocular movements, mild chorea, brisk muscle stretch reflexes, and diminished rapid alternating movements are the most consistent early findings in manifest disease.

Conflicting results have been found regarding motor impairment and decline...
PARTICIPANTS AND METHODS

PARTICIPANTS

As in the original study, a sample of individuals at risk for HD was recruited through the National Research Roster for HD Patients and Families at Indiana University, Indianapolis. At-risk individuals without a previous diagnosis of HD reporting themselves as asymptomatic were invited to participate. Details regarding participant recruitment can be found in Foroud et al.17 Participants were informed of the risks and benefits involved in the study, and informed consent was obtained (Indiana University Purdue University at Indianapolis Institutional Review Board study 8806-02).

Samples of DNA were analyzed after the participants’ visit by means of a polymerase chain reaction–based diagnostic screen to determine the number of CAG repeats.16 None of the participants were informed of their gene testing results. Of the 238 participants genotyped, 22 were eliminated before data analyses because of a lack of a molecular test result (n = 7); having an allele in the inconclusive, intermediate size range (32–37 CAG repeats) (n = 3); or having sufficient neurologic symptoms to warrant a clinical diagnosis of manifest HD (n = 12). The remaining participants were categorized into one of 2 groups: PSGCs (n = 61), defined as those individuals with an expanded HD gene (≥38 CAG repeats) but who did not have sufficient neurologic symptoms to warrant a clinical diagnosis of manifest HD, and NGCs (n = 155), defined as those individuals with 2 unexpanded HD alleles (<32 CAG repeats).

Demographic information from the 216 study participants used in the statistical analyses is summarized in Table 1. Not surprisingly, the PSGCs were significantly younger than the NGCs, since the sample consists only of individuals who reported themselves as presymptomatic and who did not have manifest HD on results of clinical examination. Older individuals with the expanded allele are more likely to have disease symptoms and thus would not be included in our sample.

EXAMINATIONS

Quantified Neurologic Examination

A quantified neurologic examination adapted from previously described protocols18 was administered by a board-certified neurologist (E.S.) with a specialization in movement disorders who was unaware of the other test results. Since the participants reported themselves as presymptomatic, it was expected that only a few individuals would have features consistent with a diagnosis of HD. Consequently, a prominent portion of the neurologic examination was designed for detection of early motor features of HD to determine whether gene carriers had a consistent pattern of early clinical findings before the onset of the characteristic chorea. The examination encompassed extraocular movements, gait and stability, chorea, dystonia, parkinsonism, tremor, muscle stretch reflexes, and cerebellar function. Results of the neurologic examination were not discussed with the study participants.

Ratings were 0 (normal), 1 (possibly abnormal), or 2 (abnormal) for 29 individual neurologic tests.19 Because the purpose of the study was to identify the earliest changes in individuals at risk for HD, clinical ratings were given to maximize sensitivity, even at the expense of some specificity. After the clinical examination, the neurologist assigned an overall score from 0 to 3. A score of 0 indicated a normal result of a clinical examination; 1, minor soft signs consistent with HD (eg, brisk reflexes); 2, major soft signs consistent with HD (eg, possible chorea); and 3, individuals who in the neurologist’s perception had manifest HD. An overall score of 3 was made using criteria designed to approximate that used in clinical practice to diagnose HD. Only those individuals with definite chorea, in the absence of other possible causes (ie, hyperthyroidism) or other

RESULTS

The PSGCs had higher rates of minor or major soft signs of HD on results of clinical examination as measured by their overall at-risk score for HD (P < .001). Post-hoc testing of the 7 neurologic variables with more than 5 PSGCs demonstrating abnormalities found significantly (P < .05) higher rates of probable or definite abnormality among the PSGCs when compared with the NGCs for optokinetic nystagmus, saccade velocity, overall ocular function, chorea of the extremities, and dystonia of the extremities (Table 2). In addition, the PSGCs tended

in individuals without definite chorea. A study in a Venezuelan HD population noted that disease was more likely to develop in the next few years in individuals with abnormalities in fine motor movement and rapid saccades when compared with individuals without these signs, suggesting that these motor abnormalities may be the earliest evidence of HD. Other studies report that oculomotor deficits, including slowed horizontal saccades, may be indicative of an increased risk of development of HD,11 however, these findings have not been consistently demonstrated.12,13 In a study of motor function in individuals at risk for HD, reaction-time tasks differentiated between symptomatic and presymptomatic gene carriers (PSGCs) and between symptomatic gene carriers and non-gene carriers (NGCs), although no differences were found between PSGCs and NGCs. In another study of 20 individuals at risk for HD, tapping and simple-choice reaction time were not statistically different between gene carriers and NGCs.

In a previous study from our laboratory of individuals at risk for HD, significant differences in oculomotor and functional motor performance were found between the PSGCs and the NGCs. The PSGCs demonstrated abnormal saccade velocity and muscle stretch reflexes. Small but significant differences in physiological measures of speed of movement and reaction time, including movement time, movement time with decision, and auditory reaction time, were found between the PSGCs and the NGCs. The purpose of our study is to confirm and expand on these findings in a second sample of at-risk individuals recruited and undergoing evaluation using the same protocol as in the previous study.16

Continued on next page
unequivocal abnormalities consistent with HD and not explained by other conditions were assigned a score of 3. The 12 participants in this sample with an overall at-risk score of 3 all had definite chorea on results of neurologic examination. These individuals, who received a clinical diagnosis of manifest HD, were not included in the statistical analyses, as this study was intended to assess clinical changes in PSGCs.

**Physiological Measures**

To complement the analysis of motor function as assessed by the neurologic examination, 6 physiological measures of central nervous system function were obtained. The battery of tests was administered with an automated computer-driven program that included a keyboard, a panel with 6 lamps with corresponding buttons below each lamp, and headphones for the auditory stimuli program (H-Scan; Hoch Co, Corona Del Mar, Calif).28 These tests measured reaction time and speed of movement by alternating button tapping, movement time, movement time with decision, auditory reaction time, visual reaction time, and visual reaction time with decision. In the previous study,16 12 physiological tests were measured, with 5 demonstrating significantly slower responses among gene carriers compared with NGCs. Therefore, the current statistical analyses included these 5 physiological variables as well as the variable visual reaction time. Visual reaction time was included in the analyses because of its high correlation with the other 5 physiological measures, despite the lack of significant difference between the gene carriers and NGCs in the previous study.16

With the use of regression coefficient estimates from a large, independent sample of 2462 control individuals, an individual test age was calculated for each physiological measure.24 A relative test age was then computed by dividing the participant’s computed test age by their chronological age. If individuals performed at the mean for their chronological age, the ratio (or relative test-age) would be 1, whereas a score of greater than 1 implied a test performance worse than that expected for chronological age.

**STATISTICAL ANALYSES**

The Fisher exact test (1-tailed) was used to compare the overall at-risk score from the neurologic examination of the PSGCs with that of the NGCs. Post hoc testing was then performed to identify those specific neurologic variables contributing to the significantly greater rate of abnormality observed among the PSGCs. To decrease the number of comparisons, only those variables for which at least 5 PSGCs had 1 questionably abnormal or definitely abnormal result were used in the statistical analyses (n = 7). These 7 tests were saccade accuracy and velocity, optokinetic nystagmus, overall ocular movements, muscle stretch reflexes, chorea of the extremities, and dystonia of the extremities. The Fisher exact test was used to determine whether the PSGCs had a higher frequency of possible or definite abnormalities (score of 1 or 2) than the NGCs for each of these 7 tests.

The relative test age scores for the 6 physiological measures were transformed to minimize skewness by means of the optimum Box Cox transformation.29 Because of the previously16,21 observed sex and age effects on the physiological variables, partial R² values were calculated to estimate the amount of variability accounted for by these covariates. A significant effect (P ≤ 0.05) of age and sex was adjusted for in all subsequent analyses of the physiological variables. These variables were then standardized to a mean of 0.0 with an SD of 1.0.21 Multivariate analysis of variance (1-tailed) was used to examine the hypothesis that overall PSGCs performed worse than NGCs on the physiological measures. Post hoc analyses of the 6 individual tests were used to determine which measures contributed to the significantly higher relative test age for the PSGCs by means of 1-way analysis of variance.

**Table 1. Demographic Data for the 216 Study Participants With DNA Results**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>PSGCs (n = 61)</th>
<th>NGCs (n = 155)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34.1 ± 8.3</td>
<td>40.4 ± 10.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.6 ± 2.8</td>
<td>15.5 ± 2.9</td>
<td>.86</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>18:43</td>
<td>46:109</td>
<td>.98</td>
</tr>
<tr>
<td>Size of non-HD allele (n = 61)</td>
<td>18.5 ± 3.5</td>
<td>18.1 ± 2.2</td>
<td>.34</td>
</tr>
<tr>
<td>Size of larger allele (n = 155)</td>
<td>43.0 ± 2.0</td>
<td>19.8 ± 2.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SD and compared using t test. PSGCs indicates presymptomatic gene carriers; NGCs, nongene carriers, and HD, Huntington disease.
†Evaluated using χ² test statistic.
‡Average allele size used for NGCs.

(P > .05 through P < .10) to perform worse on the measure of saccade accuracy compared with the NGCs.

No definite chorea or dystonia of the extremities (a score of 2) was exhibited by the PSGCs or NGCs; the positive ratings for chorea and dystonia were only for possible abnormality (a score of 1). The percentages of possible chorea (25.8%) and dystonia (5.2%) exhibited by the NGCs (Table 2) are consistent with the strategy of attempting to maximize sensitivity during the neurologic examination, even at the expense of some specificity. These possible abnormalities observed among the
NGCs indicate that some irregular adventitial movements were in fact classified as possible abnormalities for all participants.

Multivariate analysis of the 6 physiological test results simultaneously detected significantly worse performance for the PSGCs compared with the NGCs (Wilks $\lambda = 0.88; F = 3.88; P = .001$). Post hoc analyses found significantly higher relative test ages for PSGCs compared with NGCs ($P<.05$) for all 6 tests (Figure). When categorized by their overall score derived from their neurologic examination results, a nonsignificant trend toward increasing relative test age for the physiological variables was observed among PSGCs as their neurologic abnormalities increased (Table 3). Even those PSGCs with an overall at-risk score for HD of 0 performed worse than the NGCs on 4 of the 6 tests. The PSGCs with an overall at-risk score of 1 or 2 had a mean relative test age for all 6 physiological test scores that was greater than that of the NGCs.

**COMMENT**

Analyses of this sample of at-risk individuals confirm previous results$^{8,9,11,16}$ that suggested that individuals with an expanded HD gene have subtle oculomotor and functional motor deficits that precede the onset of unequivocally abnormal neurologic function. Results in our sample confirm such subtle abnormalities in a sample of gene carriers who are presymptomatic on results of clinical examination. Specifically, abnormalities in overall oculomotor function, optokinetic nystagmus, saccade velocity, chorea of the extremities, and dystonia of the extremities were observed. Also, as expected in this population of presymptomatic participants, findings more likely to occur in advanced disease, eg, bradykinesia, rigidity, paratonia, and tremor, were absent.

Although the PSGCs demonstrated a tendency toward a higher rate of neurologic abnormalities than the NGCs, none of the PSGCs exhibited definite chorea or had sufficient neurologic signs on results of clinical examination to warrant a diagnosis of HD. Of primary importance in a study such as this are the criteria used to differentiate individuals with manifest HD from those with possible abnormalities that are not of sufficient magnitude to warrant a clinical diagnosis. A high degree of sensitivity, even at the expense of specificity, was critical in a study of this type. The fact that more than 25% of NGC subjects were believed to have possible (but not definite) chorea suggests that some irregular adventitial movements were in fact classified as possible abnormality for all participants and, therefore, would not be of sufficient severity to warrant a diagnosis of manifest HD.

In addition to the subtle changes found on results of neurologic examination, this PSGC sample and the previously reported sample$^{16}$ demonstrated lower performance for several physiological measures of central nervous system function. In both samples, movement time, movement time with decision, and auditory reaction time were significantly slower for the PSGCs. In addition, the tendency toward slower performance of the PSGCs for visual reaction time, visual reaction time with decision, and button-tapping time were statistically confirmed in the present sample.

In this new sample, when the results of the PSGCs were grouped by their overall at-risk score derived from their neurologic examination (Table 3), there was a trend for worsening performance on the physiological tests, as measured by an increase in relative test age, when the neurologic findings increased. Interestingly, substantial variability was observed between individuals on their physiological measures, even as their neurologic perfor-

### Table 3. Physiological Examination Relative Test Ages

<table>
<thead>
<tr>
<th>Physiological Test</th>
<th>HD Gene Carriers, Overall At-Risk Score†</th>
<th>Nongene Carriers (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 21)</td>
<td>1 (n = 27)</td>
</tr>
<tr>
<td>Movement time</td>
<td>1.35 ± 0.67</td>
<td>1.16 ± 0.75</td>
</tr>
<tr>
<td>Movement time with decision</td>
<td>1.13 ± 0.63</td>
<td>1.62 ± 0.85</td>
</tr>
<tr>
<td>Auditory reaction time</td>
<td>1.20 ± 0.85</td>
<td>1.46 ± 1.09</td>
</tr>
<tr>
<td>Visual reaction time</td>
<td>1.79 ± 1.35</td>
<td>2.51 ± 0.89</td>
</tr>
<tr>
<td>Visual reaction time with decision</td>
<td>1.86 ± 0.85</td>
<td>2.13 ± 1.17</td>
</tr>
<tr>
<td>Button-tapping time</td>
<td>1.30 ± 0.78</td>
<td>1.44 ± 0.88</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. HD indicates Huntington disease.
†Zero indicates normal; 1, minor soft signs; 2, major soft signs; and 3, definite HD.
mance became consistently worse, suggesting that global abnormalities do not occur simultaneously among PSGCs as they approach manifest HD. Longitudinal data are necessary to determine whether changes in physiological function are progressive before the onset of manifest HD, or whether they are static and present early in life, worsening only as overt disease begins.

Our study avoided some of the difficulties that plagued other studies of at-risk individuals and contributed to the conflicting literature regarding early abnormalities among PSGCs. Many of the previous studies were completed before the HD gene was identified, which led to misclassification of some participants. In addition, the total number of participants in other studies was often small (<50), whereas the present sample contains a large number of gene (n = 61) and nongene carriers (n = 155). Further, since all individuals participating in our study were adult, presymptomatic individuals, we would not have expected, nor did we have, any participants with a very large number of CAG repeats (>50). Rather, our restricted range of expanded CAG repeats (38-48) suggests that this is a representative sample of patients with adult-onset HD, and that the deficits that we detected before disease onset may be the typical HD prorome.

These findings confirm those of previous analyses16 showing that subtle changes in motor function are present in individuals at risk for HD who are considered to be presymptomatic on results of clinical examination. In addition to abnormalities that were present even among PSGCs with an overall score of 0, we noted a trend toward more extensive physiological abnormalities as neurologic symptoms increase. Taken together, this suggests that some essentially static abnormalities may be present from birth, with the degree of abnormality accelerating at about the time of clinical onset of the disease. Given the subtlety of these findings, a longitudinal study using serial assessment of a large, well-characterized sample of at-risk individuals, such as ours, will be necessary to provide important data regarding symptom variability and progression. A more complete understanding of the subtle changes that occur early in the course of HD will lead to a better definition of the disease process and may allow earlier diagnosis and intervention. In addition, a better understanding of the early signs and symptoms of HD will help identify relevant outcome measures for use in controlled clinical trials of new therapies.

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Reprints: Tatiana Foroud, PhD, Department of Medical and Molecular Genetics, Indiana University School of Medicine, 975 W Walnut St, Indianapolis, IN 46202 (e-mail: tforoud@iupui.edu).

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