Huntington's Disease with Small CAG Repeat Expansions

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RESEARCH ARTICLE

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ABSTRACT: Background: Carriers of small cytosine-adenine-guanine (CAG) repeats below 39 in the *HTT* gene are traditionally associated with milder Huntington's disease, but their clinical profile has not been extensively studied.

Objective: To study the phenotype of CAG_{36-38} repeat carriers.

Methods: We included 35 patients and premanifest carriers of CAG_{36-38} repeats. We compared clinical and neuropsychological profiles of 11 CAG_{36-38} patients with 11 matched CAG_{40-42} patients. In addition, we analyzed 243 CAG_{36-38} individuals from the ENROLL study to complete the phenotype description.

Results: Global cognitive efficiency and performance in different cognitive subdomains were similar in small CAG_{36-38} and typically CAG_{40-42} expanded individuals. Chorea as the first symptom was significantly less frequent for CAG_{36-38} patients ($P = 0.04$) despite similar total motor scores at first visit. Total motor score at last visit was significantly lower in CAG_{36-38} carriers ($P = 0.003$). The similar cognitive and different motor profile of CAG_{36-38} ($n = 243$) and CAG_{40-42} ($n = 4675$) carriers was confirmed in the ENROLL database. Additionally, clinicians were significantly less confident in diagnosing Huntington's disease ($P = 2.4e{-}8$) and diagnosis happened significantly later in CAG_{36-38} ($P = 2.2e{-}6$) despite a similar age at symptom onset ($P = 0.29$).

Conclusions: We showed that small CAG_{36-38} expansion carriers had a similar cognitive profile to those with the more common CAG_{40-42} expansions. These individuals may evade molecular diagnosis because of the absence of chorea rather than because of a low penetrance of symptoms. This finding should encourage neurologists to consider Huntington's disease in cognitively impaired elderly patients without typical chorea and anticipate consequences for genetic counseling in their offspring. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: chorea; cognitive decline; Huntington's disease; reduced penetrance; small expansions

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Introduction

Huntington's disease (HD) is an autosomal dominant neurological disorder caused by an unstable expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat in the *HTT* gene. The typical phenotype is characterized by motor, cognitive, and psychiatric symptoms. Diagnosis is made based on the presence of unequivocal motor signs and positive genetic testing.[1] However, cognitive dysfunction and psychiatric symptoms can appear years before motor signs and can be the major source of disability.[2,3] The cognitive profile is characterized by subcortical features including slowed mental processing, executive deficits, and impaired socio-emotional processing.[4]

The heterozygous CAG repeat size determines the age at onset in a fully dominant fashion, with earlier onset in patients with larger expansions.[5] The CAG repeat size is the major determinant of age at onset and accounts for ~60% of its variation. The variance not explained by the repeat size is primarily driven by rare genetic modifiers such as those involved in DNA repair.[6] The threshold for disease is 35, with complete penetrance above 39 and incomplete penetrance for 36, 37, and 38 repeats. Estimated penetrance rate at 70 years is 10%, 17%, and 32% for 36, 37, and 38 CAG repeats, respectively.[7] Repeat size also influences the phenotype. High CAG repeats (>60 CAG) are associated with early onset and a phenotype characterized by bradykinesia, dystonia, severe psychiatric manifestations, and even developmental delay and epilepsy.[8] In contrast, the clinical profile of patients with small expansions below 39 has not been extensively studied. They are rare in HD cohorts, but seem to be more frequent in the general population than previously estimated.[9] Consequently, sufficient knowledge about the clinical profile of these patients is necessary to offer reliable genetic counseling.

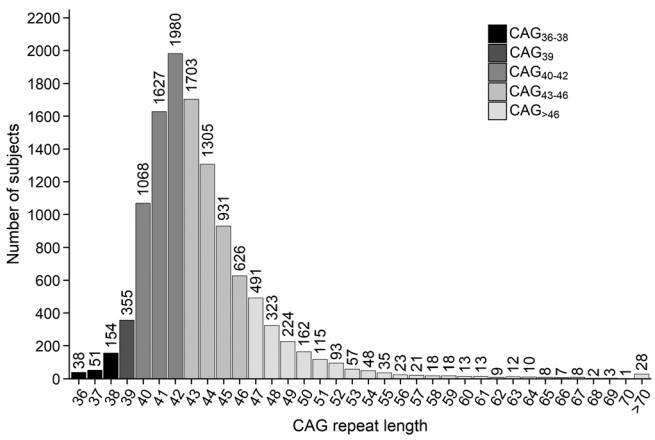

FIG. 1. Distribution of pathological CAG repeats in the ENROLL cohort, indicating the small subgroup of $CAG_{36\text{-}38}$. The overall distribution is not symmetrical for small versus large repeats.

In accordance with the hypothesis that the phenotype of small expansion carriers would be milder, the aim of this study was to gain insight into the clinical presentation of patients in the reduced penetrance range and determine if it is different than that of classical HD.

Methods

French Individuals with CAG_{36-38} Repeats (Flowchart in Supporting Data)

We included 35 patients and asymptomatic carriers of $CAG_{36\text{-}38}$ repeats in *HTT* who had at least one visit in the genetics department Pitié-Salpêtrière University Hospital in Paris or the University Hospital in Toulouse, France. All had genetic testing in the Molecular and Cellular Neurogenetics Department of the Pitié-Salpêtrière Hospital with informed signed consent. The laboratory is certified and performs genetic testing in the usual clinical setting for patients. DNA was extracted from peripheral blood samples using standard methods. Repeat expansions in *HTT* were analyzed by sizing the fragment using two sets of primers (methods described in Losekoot et al).[10] Data collection was approved by local French authorities (Ile de France II ethics committee; RBM 03-48, IRB00001072) for patients seen from 2008 to 2017. Beginning in 2017, subjects were informed of their right to object to the publication of their data, according to local regulations of Assistance Publique-Hôpitaux de Paris (Fig. 1).

Clinical data were collected retrospectively and completed during regular prospective follow-up visits. They included Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), age, sex, family history of HD, psychiatric history, symptoms, and current medications.

A detailed neuropsychological evaluation done by a neuropsychologist was performed for 11 patients including the following tests: the Mini-Mental State Examination (MMSE) or the Dementia Rating Scale (DRS) and Frontal Assessment Battery Score (FAB); assessment of executive functioning included the Stroop Color Word Test, the Verbal Fluency test (semantic: animals and phonemic: letters), the Trail Making Test (TMT) and the Modified Wisconsin Card Sorting Test (mWCST). Social cognition was evaluated by an emotional recognition test (Ekman faces). Attentional skills and working memory were assessed by Bell's test and the digit and spatial span (backward and forward), visuospatial skills by the cube subtest from the Visual Object and Space Perception test (VOSP), visuoconstruction skills by the Rey Complex Figure, episodic memory by the Free and Cued Selective Reminding Test (FCSRT) and recall of the Rey Figure,

and language by the naming test from the GRECO Neuropsychological Semantic Battery. For each test, individual scores were compared with French population norms for age and education level to determine if there was cognitive impairment or not. We determined that cognitive impairment was present when performance was inferior to 1.65 standard deviation below the norm for the general population matched on age and education level.

In accordance with the hypothesis that the phenotype of small expansion carriers would be milder, we compared the cognitive profile of our cohort of 11 $CAG_{36\text{-}38}$ patients to an age and gender matched cohort of 11 patients with $CAG_{40\text{-}42}$, the closest pathological range. CAP-Age-Product (CAP) score as an index of cumulative disease burden was compared for both groups at the age of cognitive assessment.[11]

In addition, 12 participants had partial testing evaluating global cognitive efficiency, executive function, processing speed, and memory.

Cognitive evaluation was performed in a routine clinical setting. A complete evaluation by a neuropsychologist was administered when the patient complained about cognitive deficits or when the clinician suspected cognitive deterioration.

ENROLL Cohort

To study an independent cohort of $CAG_{36\text{-}38}$ repeat carriers and compare them to those with higher CAG repeats, we analyzed the ENROLL database. We had authorized access to the European Huntington's Disease Network database ENROLL-HD (NCT01574053; start date July, 2012, still active) and signed the respective agreements governing access and use of these resources according to EHDN sharing rules. ENROLL-HD is a global clinical research platform. Datasets are collected annually from all research participants. All participating sites acquired institutional review board approval and all participants provided written informed consent.

Subjects were divided into five groups of healthy controls with $CAG_{0\text{-}26}$ (CTRL) and carriers with $CAG_{36\text{-}38}$, CAG_{39}, $CAG_{40\text{-}42}$ and $CAG_{43\text{-}46}$ repeats. Individuals were considered to have manifest HD if they met at least one of the following criteria: diagnostic confidence level (DCL) = 4, Total Motor Score (TMS) of the UHDRS > 5/124 or when the clinician documented the individual to be manifest in the ENROLL database. This combines the conventional criterion (DCL = 4) with the criterion chosen in TRACK-HD (TMS UHDRS > 5), adding the rater's opinion if he considers a subject to have manifest HD or not, regardless of the intensity of motor symptoms.

Descriptive characteristics of the participants at baseline and last follow up visit included demographic and clinical data on sex, education level as determined by the international standard classification of education (ISCED), age at inclusion, CAG repeat length of the Huntingtin *HTT* gene and family history. The primary outcomes for the HD group were age at onset, type of first symptom (motor, psychiatric, cognitive, oculomotor or mixed) (as perceived by the patient, the caregiver, and the clinician), and age at clinical diagnosis. Disease severity was assessed by the UHDRS based on TMS and included information about the DCL, the Total Functional Capacity scale (TFC), and the Independence Scale (IS).

For the cognitive evaluation we used the following tests: executive functioning was assessed by the Verbal Letter Fluency Test (VLFT) (total correct words in 1 minute for three letters and semantic fluency in 1 minute) and the TMT B-A, processing speed by the Symbol Digit Modalities Test (SDMT) and the Stroop Word Reading Test (SWRT). The MMSE (range from 0–30 points) was used to evaluate global cognitive efficiency. Psychiatric symptoms were evaluated based on

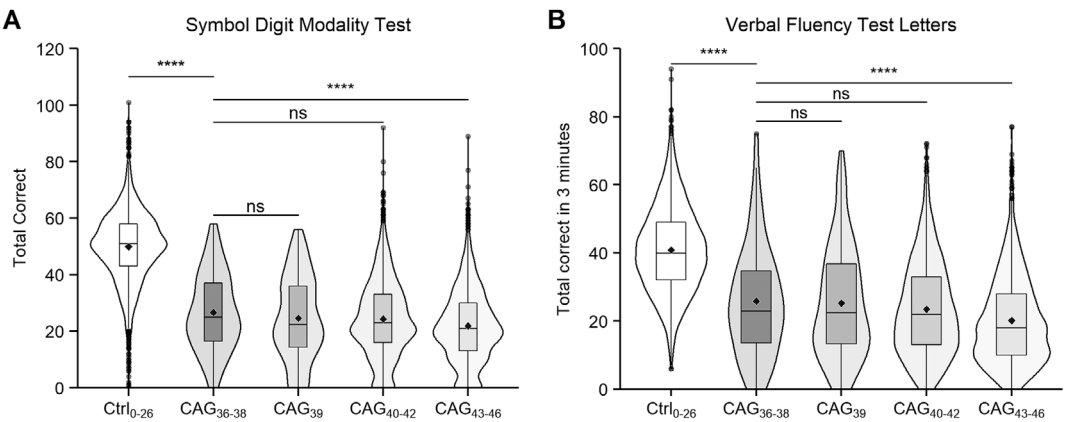

FIG. 2. Cognitive tests in two domains (processing speed: Symbol Digit Modalities Test, executive function: verbal fluency test with letters over 3 minutes) according to CAG repeat sizes and comparison (ENROLL). Type II ANOVA F-test followed by Dunnett's post hoc test for pairwise comparisons between all CAG groups with $CAG_{36\text{-}38}$ (****$P < 0.0001$, ns: not significant). All tests have been adjusted for age, sex, and education.

the presence or absence of psychiatric comorbidities and symptoms as determined and documented by the rater in the ENROLL database (Fig. 2).

Statistical Analyses

Statistical analyses were performed using the software R (version 3.6.1, R Development Core Team, 2019; https://www.R-project.org/), and plots were generated with the ggplot2 R package (v3.3.0).[12] Data were summarized as n (number of available values), mean ± standard deviation (SD) and range (minimum and maximum) for quantitative variables, and as frequency counts and percentages for categorical variables. Group differences for demographic and clinical measures in the French cohort were assessed using two-sample *t*-tests and χ^2 tests. In the ENROLL cohort, five group comparisons were performed using Kruskal-Wallis tests followed by Dunn's pairwise comparisons with Bonferroni correction, and χ^2 tests for proportion comparisons followed by post hoc pairwise testing with Holm correction.

Differences in performance on neuropsychological tests were assessed between healthy controls and manifest subjects in the CAG groups using multivariate linear regression models including sex, age, and education level for covariate adjustment. For each of the tests, including the SWRT, SDMT, TMT B-A, verbal (phonemic and semantic) fluency tasks, and MMSE, a significant effect of the CAG group was tested using a type II analysis of variance (ANOVA) F-test from the car R package (v3.0–7), followed by Dunnett's post hoc pairwise comparisons between all CAG groups with $CAG_{36\text{-}38}$ using the emmeans R package (v1.4.5). The level of statistical significance was set at P or adjusted $P < 0.05$ for all tests.

Results

French Individuals with CAG_{36-38} Repeats

We included 35 individuals with $CAG_{36\text{-}38}$ repeats (Paris, n = 31 and Toulouse, n = 4). Ten had 36, another 10 had 37 CAG repeats (10/35, 28.6%), and 15 had 38 CAG repeats (15/35, 42.9%). Mean age at first visit was 54.0 ± 16.7 years (ranging from 23 to 90 years). As expected, premanifest individuals were significantly younger (43.2 ± 14.3 years, n = 17, 23–64 years) than manifest patients (64.2 ± 11.7 years, n = 18, 46–90 years; $P < 0.0001$). Of the premanifest individuals who had a follow-up visit (n = 9), three came back for genetic counseling, one for research participation, and five because of symptom onset. Five premanifest individuals converted during follow-up resulting in 23 manifest patients in our cohort. Symptoms of the converters were exclusively psychiatric and cognitive for two patients (MHU-2959-001, MHU-TOU-001). Mean age at conversion was 51.2 ± 4.1 years (n = 5, 46–55 years) and not different from mean age at onset of patients who were symptomatic at first visit, which was 54.1 ± 8.4 years (n = 16, 40–66 years; $P = 0.47$).

Mean age at last follow-up was 56.4 ± 15.4 years (n = 18, 24–74 years). There were more women (22/35, 62.9%) than men. Transmission was maternal for 19 (54.3%), paternal for nine (25.7%), and unknown for seven patients (20%). The latter had either no family history of HD and in two cases there was censorship. In three cases, we observed CAG contractions through maternal transmission (from 40 to 36, 39 to 37, and 40 to 38 CAG).

At the first visit, all manifest participants (n = 18) had motor signs with a mean UHDRS score of 24.5 ± 12.6 (n = 6, 11–43, maximum most severe value /124) and at the last visit, 28.5 ± 22.4 (n = 13, 2–84). Interestingly, 30.4% (7/23) manifest individuals (ie, cognitive, psychiatric, or motor onset) presented no chorea. Motor signs were mostly discrete and variable: they included oculomotor signs, coordination difficulties, extrapyramidal features, dystonia, or postural instability.

A total of 51% (18/35) had psychiatric symptoms, a history of psychiatric symptoms, or behavioral disturbances over the entire follow-up period and, as expected, these were more frequent in symptomatic (17/23, 73.9%) than in premanifest individuals (1/12, 8.3%; $P < 0.001$).

Cognitive Evaluation

Cognitive evaluation was performed for 23 patients at a mean age of 62.6 ± 9.8 years (n = 16, 49–82 years). Detailed information about the cognitive profile is listed in Supplementary Table S1.

A total of 21 (91.3%) were cognitively impaired as expected with mostly executive deficits (14/17, 82.4%). Interestingly, 68.8% (11/16) had episodic memory difficulties because of a storage deficit, but only 38.5% (5/13) showed slowed information processing. A total of 80% (4/5) of patients showed impairment in social cognition, characterized by a deficit in emotional identification.

One patient with an atypical cognitive profile for HD (predominant episodic memory disturbances) underwent brain imaging and biomarker assessments to exclude Alzheimer's disease. His cerebral magnetic resonance imaging showed cortico-subcortical atrophy predominantly in the frontoparietal regions and the caudate and hippocampal structures (Scheltens score left: 4, right: 3). ^{18}F-fluordeoxyglucose positron emission tomography showed typical caudate and frontal hypometabolism associated with hypometabolism of the posterior temporal cortex, and normal metabolism of medial temporal lobes. Cerebrospinal fluid biomarker analysis

including Tau, phospho-Tau, β-amyloid were normal, ruling out Alzheimer's disease. We also excluded genetic frontotemporal dementia by analyzing 12 genes involved in Frontotemporal dementia including *C9ORF72*.

Cognitive Phenotyping in 11 Patients with CAG_{36-38} Compared to 11 Age-Matched HD Patients with CAG_{40-42}

Comparison to patients with CAG_{40-42} repeats showed no significant difference in age at onset, age at neuropsychological investigation, or disease duration (Table 1). Unexpectedly, the cognitive profile in the small expansion group was not milder, despite significantly lower CAP scores in CAG_{36-38} ($P = 2.36e{-}07$*). The cognitive and psychiatric profile was very similar with no significant differences in the domains of global cognitive efficiency, executive functioning, processing speed, emotional recognition, and frequency of psychiatric symptoms (90.9% in both groups). Despite the absence of significant differences in episodic memory, three CAG_{36-38} patients presented severe impairment of episodic memory characterized by amnestic syndrome with impairment in storage and intrusions in the Free Recall Cued Test (FRCT). Two other patients had visual memory deficits on the Rey's Figure despite good planning (type 1 and type 2). Another patient with visual memory deficits on the Rey's Figure also presented with storage difficulties (omission of two words after delay) in the FRCT. However, he also had moderate executive dysfunction. In CAG_{40-42} group, such severe memory impairment was not observed. Only one patient among 11 presented evident storage deficits on the FRCT with a moderate benefit from cues. Omissions after delay and imperfect recognition were found for four patients. Retrieval deficit because of executive dysfunction only was found for three patients, and no memory impairment was found for two patients. Visual memory was preserved for all patients tested in the CAG_{40-42} group.

As expected, motor scores at the time of the cognitive assessment were significantly lower in CAG_{36-38} (16.4 ± 11.8, $n = 7$) than in CAG_{40-42} (34.2 ± 14.1, $n = 10$; $P = 0.01$). Interestingly, chorea as the first presenting symptom was significantly less frequent in CAG_{36-38} (6/11) compared to CAG_{40-42} (11/11) ($P = 0.04$).

ENROLL Cohort

CAG_{36-38} French Cohort Compared to ENROLL CAG_{36-38} Individuals

The comparison of patients in the French CAG_{36-38} cohort to the CAG_{36-38} ENROLL cohort showed no significant difference for age at onset ($P = 0.97$), age at conversion for the initially premanifest individuals ($P = 0.53$), age at first visit ($P = 0.63$), or age at neuropsychological evaluation ($P = 0.97$).

The different motor and similar cognitive profile of CAG_{36-38} and CAG_{40-42} observed in the French cohort was confirmed in the ENROLL database (Table 2). Significant differences in terms of severity were found when comparing CAG_{36-38} to a higher CAG group (CAG_{43-46}).

As in the French cohort, manifest CAG_{36-38} individuals presented initially significantly more often without chorea as compared to CAG_{40-42} and CAG_{43-46} ($P = 1.4e{-}11$), despite the absence of a significant difference in the mean UHDRS score and disease duration at baseline ($P = 0.11$). Furthermore, in CAG_{36-38}, the clinician was significantly less confident in diagnosing motor-manifest HD by attributing a DCL score of 4, compared to CAG_{40-42} and CAG_{43-46} ($P = 2.4e{-}8$) Fig. 3.

Interestingly, time from estimated symptom onset to clinical diagnosis was significantly longer for CAG_{36-38} (5 ± 5.2 years, $n = 81$, 0–23 years) as compared to CAG_{40-42} (3.9 ± 4.5 years, $n = 2871$, 0–34 years; $P = 0.04$), corresponding to a greater diagnostic delay of manifest HD in CAG_{36-38}, despite the same estimated age of symptom onset (CAG_{36-38}: 54.3 ± 11.7 years, $n = 81$, 31–84 years vs. CAG_{40-42}: 53.9 ± 9.4 years, $n = 2871$, 12–83 years; $P = 0.29$) (Table 3).

There was no significant difference in the distribution of the type of symptom onset between groups according to the clinician ($P = 0.45$) or the patient himself ($P = 0.20$), but there was a significant difference regarding type of symptom onset according to the caregiver ($P = 0.03$). The type of symptom onset according to the caregiver was significantly more often cognitive in CAG_{36-38} (17.2%) than in all other groups (6.5% in CAG_{39}, 8.8% in CAG_{40-42}, and 9.3% in CAG_{43-46}; $P = 0.04$). In CAG_{36-38}, we observed a significant disagreement between clinician and caregiver regarding motor onset. For patients who were considered by the clinician to have motor signs as first symptoms, the caregiver considered symptoms to be cognitive at onset at a significantly higher proportion (4/36, 11.8%), compared to CAG_{39} (0/64, 0%), CAG_{40-42} (29/1465, 2.0%) and CAG_{43-46} (32/1549, 2.1%) ($P = 0.001$).

The cognitive profile of symptomatic CAG_{36-38} and CAG_{40-42} was similar. Global cognitive efficiency in CAG_{36-38} was evaluated at 25.1 ± 5.6 (1–30, $n = 45$, maximum score of 30) on the MMSE, corresponding to mild cognitive impairment. TFC scores in CAG_{36-38} (8.5 ± 3.3, $n = 81$) were not different from TFC scores in CAG_{40-42} (8.4 ± 3.6, $n = 3016$, 0–13, maximum score of 13), corresponding to stage 2 HD. Independence scales were also similar between CAG_{36-38} (78.8 ± 16, $n = 81$) and CAG_{40-42} (78.5 ± 17.3, $n = 3010$, maximum score

TABLE 1 *Motor and cognitive assessment in patients with Huntington's disease, carrying either $CAG_{36\text{-}38}$ or $CAG_{40\text{-}42}$ repeats in the* HTT *gene*

	$CAG_{36\text{-}38}$	$CAG_{40\text{-}42}$	*P*-value
Age at onset (years)	55.4 ± 7.6 (n = 11)	54.1 ± 9 (n = 11)	0.72
Age at neuropsychological evaluation (years)	60.7 ± 8.3 (n = 11)	59.5 ± 7.7 (n = 11)	0.73
CAP-score at age of cognitive assessment	218.2 ± 56.7 (n = 11)	461.4 ± 63.2 (n = 11)	2.36e−07*
Motor assessment			
Total motor score at age of cognitive assessment (max most severe 124)	16.4 ± 11.8 (n = 7)	34.2 ± 14.1 (n = 10)	0.01*
Psychiatric assessment			
Presence/absence of psychiatric symptoms (% presence)	10/1 (90.9)	10/1 (90.9)	1
Cognitive assessment			
Global cognitive efficiency			
Mini Mental State Examination (max best 30)	26.00 ± 3.5 (n = 9)	25.56 ± 2.2 (n = 9)	0.78
Dementia Rating Scale (max best 144)	133.6 ± 9.5 (n = 7)	132.5 ± 7.4 (n = 10)	0.79
Memory			
Free Recall cued test-free recall (max best 48)	25.3 ± 10.3 (n = 11)	26.1 ± 5.5 (n = 11)	0.82
Free Recall cued test-total recall (max best 48)	41.5 ± 8.8 (n = 11)	44.4 ± 3.4 (n = 11)	0.32
Free Recall cued test-delayed recall (max best 16)	13.1 ± 4.8 (n = 11)	15.5 ± 0.8 (n = 11)	0.12
Rey's Figure recall (max best 36)	15.0 ± 4.1 (n = 11)	16.5 ± 5.9 (n = 7)	0.54
Executive functions			
Frontal assessment battery (max best 18)	14.5 ± 3.6 (n = 10)	14.6 ± 1.6 (n = 11)	0.93
Trail making test B-A	82.1 ± 60.5 (n = 11)	91.5 ± 43.6 (n = 10)	0.69
Semantic fluency	24.9 ± 8.3 (n = 8)	22.7 ± 7.8 (n = 9)	0.58
Phonemic fluency	14.9 ± 9.3 (n = 8)	11.0 ± 2.2 (n = 4)	0.44
Wisconsin number of categories (max best 6)	5.1 ± 1.5 (n = 8)	5.7 ± 0.5 (n = 7)	0.33
Wisconsin perseverative errors	5.4 ± 7.2 (n = 8)	2.6 ± 2.8 (n = 7)	0.35
Wisconsin total errors	7.4 ± 9.3 (n = 7)	5.6 ± 3.4 (n = 7)	0.64
Social cognition			
Emotional recognition (max best 35)	22.2 ± 6.5 (n = 5)	22.8 ± 3.8 (n = 5)	0.86
Attention skills			
Digit forward (max best 9)	6.1 ± 1.1 (n = 11)	5.7 ± 1.0 (n = 11)	0.38
Digit backward (max best 8)	4 ± 1.4 (n = 11)	3.5 ± 1.4 (n = 11)	0.41
Visuoconstructive functions			
Rey's Figure copy (max best 36)	33.5 ± 2.5 (n = 11)	32.7 ± 3.4 (n = 9)	0.55

Note: Continuous variables are presented as mean ± standard deviation (n: number of subjects).
Abbreviation: Max, maximum.
*$P < 0.05$. Results were not corrected for multiple comparisons.

of 100). The clinician judged cognitive impairment as impacting work or activities of daily living frequently in $CAG_{36\text{-}38}$ (58%), which is not different from the other CAG groups ($P = 1.1e{-}5$).

Regarding the different subdomains of cognition, tests evaluating processing speed and executive functioning did not reveal any significant differences between $CAG_{36\text{-}38}$ and $CAG_{40\text{-}42}$ at baseline or last

TABLE 2 *Motor, functional, and cognitive assessment of ENROLL symptomatic participants at baseline and at last follow-up visit according to the size of CAG repeats in the* HTT *gene*

	CAG_{0-26}	CAG_{36-38}	CAG_{39}	CAG_{40-42}	CAG_{43-46}	*Global P-value*[b]	Post hoc group comparisons[c]
Baseline visit (n = 13 306)	n = 3468	n = 243	n = 355	n = 4675	n = 4565		
Symptomatic participants/ asymptomatic participants (% symptomatic)	NA	81/162 (33.3)	132/223 (37.2)	3020/1655 (64.6)	3364/1201 (73.7)	<2.2e−16	43–46 > 40–42 > 36–38
Age of all participants (years)	47.1 ± 14.7 [17–89] n = 3468	54.5 ± 14.4 [23–90] n = 243	56.4 ± 15.4 [19–91] n = 355	55.5 ± 13.5 [17–91] n = 4675	46.4 ± 10.8 [17–78] n = 4565	<2.2e−16	36–38 > 0–26 > 43–46
Age of symptomatic participants (years)	NA	62.7 ± 11.3 [33–90] n = 81	67.5 ± 11.5 [32–91] n = 132	62.2 ± 9.2 [17–91] n = 3020	50.6 ± 8.2 [17–78] n = 3364	<2.2e−16	39 > 36–38 > 43–46
Motor assessment							
Diagnostic confidence level of 4: yes/no (% yes)	4/3464 (0.1)	67/14 (82.7)	117/15 (88.6)	2823/197 (93.5)	3207/157 (95.3)	2.4e−8	43–46 > 40–42 > 36–38[a]
Total motor score (max most severe value 124)	1.6 ± 3.2 [0–48] n = 3454	30.2 ± 18.5 [0–79] n = 80	30.9 ± 21.8 [0–100] n = 129	34.7 ± 19.5 [0–107] n = 2990	40.2 ± 22.7 [0–120] n = 3346	<2.2e−16	43–46 > 36–38[a]
No chorea/chorea (% no chorea)	3294/173 (95)	14/67 (17.3)	15/117 (11.4)	116/2902 (3.8)	130/3231 (3.9)	1.4e−11	36–38 > 43–46 > 40–42[a]
Functional assessment							
Total functional score (max best 13)	12.9 ± 0.6 [0–13] n = 3465	8.5 ± 3.3 [0–13] n = 81	8.4 ± 3.8 [0–13] n = 132	8.4 ± 3.6 [0–13] n = 3016	7.8 ± 3.8 [0–13] n = 3358	8.0e−9	No significant pairwise differences[a]
Independence Scale (max best 100)	99.6 ± 2.4 [55–100] n = 3466	78.8 ± 16 [20–100] n = 81	79.1 ± 18.8 [20–100] n = 132	78.5 ± 17.3 [5–100] n = 3010	75 ± 19.6 [5–100] n = 3357	<2.2e−16	40–42 > 43–46
Cognitive assessment[d]							
Mini Mental State Examination (max best 30)	29 ± 1.5 [18–30] n = 2526	25.1 ± 5.6 [1–30] n = 45	25 ± 6 [0–30] n = 80	25.3 ± 4.5 [0–30] n = 1912	24.6 ± 4.6 [0–30] n = 2027	<0.0001	0–26 > 36–38
Processing speed[d]							
Symbol Digit (max best 110)	50 ± 12.3 [0–101] n = 3431	26.6 ± 13.6 [0–58] n = 74	24.6 ± 14.8 [0–56] n = 122	24.3 ± 13.6 [0–92] n = 2797	21.8 ± 12.8 [0–89] n = 3061	<0.0001	0–26 > 36–38 > 43–46

(Continues)

TABLE 2 *Continued*

	CAG_{0-26}	CAG_{36-38}	CAG_{39}	CAG_{40-42}	CAG_{43-46}	*Global P-value*[b]	Post hoc group comparisons[c]
Stroop Word Reading test	95.5 ± 17.7 [0–168] n = 3428	61 ± 21.8 [0–119] n = 75	60 ± 26.4 [0–118] n = 123	57.9 ± 23.7 [0–132] n = 2885	52.8 ± 23.5 [0–125] n = 3143	<0.0001	0–26 > 36–38 > 43–46
Executive functions[d]							
Trail Making test B-A	32.4 ± 30.4 [−214–220] n = 2900	77.4 ± 56.3 [0–197] n = 51	67 ± 58.1 [−132–196] n = 83	78 ± 56.5 [−120–259] n = 1979	83.8 ± 54.9 [−172–216] n = 2134	<0.0001	43–46 > 36–38 > 0–26
Semantic Fluency (Animals, 1 min)	21.9 ± 5.6 [3–48] n = 3431	14.5 ± 6.1 [1–31] n = 78	13.2 ± 6.5 [0–31] n = 125	12.6 ± 6 [0–37] n = 2939	11.5 ± 5.9 [0–42] n = 3203	<0.0001	0–26 > 36–38 > 40–42 > 43–46
Phonemic Fluency (3 letters PRV; total 3 min)	40.9 ± 12.6 [6–94] n = 2882	25.8 ± 16.1 [0–75] n = 62	25.2 ± 16.2 [0–70] n = 94	23.5 ± 13.8 [0–72] n = 2212	20.1 ± 12.6 [0–77] n = 2378	<0.0001	0–26 > 36–38 > 43–46
Last follow-up visit (n = 13 306)	n = 3468	n = 243	n = 355	n = 4675	n = 4565		
Symptomatic participants/asymptomatic participants (% symptomatic)	NA	89/154 (36.6)	145/210 (40.8)	3162/1513 (67.6)	3496/1069 (76.6)	<2.2e−16	43–46 > 40–42 > 36–38
Age of symptomatic participants (years)	48.7 ± 15 [17–91] n = 3468	63.7 ± 11.2 [37–90] n = 89	68.7 ± 11.2 [32–91] n = 144	63.5 ± 9.3 [17–91] n = 3162	51.9 ± 8.4 [17–79] n = 3496	<2.2e−16	39 > 36–38 > 43–46 > 0–26
Motor assessment							
Diagnostic confidence level of 4 yes/no (% yes)	7/3461 (0.2)	73/16 (82.0)	129/16 (89.0)	2978/184 (94.2)	3364/132 (96.2)	8.6e−13	43–46 > 40–42 > 36–38[a]
Total motor score (max most severe value 124)	1.6 ± 3.2 [0–48] n = 3448	31.5 ± 21.4 [1–98] n = 87	32.8 ± 22 [0–100] n = 139	38.1 ± 21.3 [0–117] n = 3127	45.0 ± 24.3 [0–122] n = 3458	<2.2e−16	43–46 > 40–42 > 36–38[a]
No chorea/chorea (% no chorea)	3325/138 (96.0)	16/73 (18.0)	17/126 (11.9)	160/2996 (5.1)	136/3355 (3.9)	3.3e−12	36–38 > 40–42 > 43–46[a]
Functional assessment							
Total functional score (max best 13)	12.8 ± 0.7 [0–13] n = 3461	8.0 ± 3.7 [0–13] n = 89	8.1 ± 4.0 [0–13] n = 143	7.7 ± 3.8 [0–13] n = 3158	7.0 ± 3.9 [0–13] n = 3490	1.8e−13	No significant pairwise differences[a]
Independence Scale (max best 100)	99.5 ± 2.7 [55–100] n = 3464	76.9 ± 17.4 [20–100] n = 89	76.9 ± 20.9 [10–100] n = 144	74.8 ± 18.9 [5–100] n = 3153	70.3 ± 21.4 [5–100] n = 3487	<2.2e−16	39 and 40–42 > 43–46

(Continues)

TABLE 2 *Continued*

	CAG_{0-26}	CAG_{36-38}	CAG_{39}	CAG_{40-42}	CAG_{43-46}	*Global P-value*[b]	Post hoc group comparisons[c]
Cognitive assessment[d]							
Mini Mental State Examination (max best 30)	29 ± 1.5 [18–30] n = 2526	25.1 ± 5.6 [1–30] n = 45	25 ± 6 [0–30] n = 80	25.3 ± 4.5 [0–30] n = 1912	24.6 ± 4.6 [0–30] n = 2027	<0.0001	0–26 > 36–38
Processing speed[d]							
Symbol Digit (max best 110)	50 ± 12.3 [0–101] n = 3431	26.6 ± 13.6 [0–58] n = 74	24.6 ± 14.8 [0–56] n = 122	24.3 ± 13.6 [0–92] n = 2797	21.8 ± 12.8 [0–89] n = 3061	<0.0001	0–26 > 36–38 > 43–46
Stroop Word Reading test	95.5 ± 17.7 [0–168] n = 3428	61 ± 21.8 [0–119] n = 75	60 ± 26.4 [0–118] n = 123	57.9 ± 23.7 [0–132] n = 2885	52.8 ± 23.5 [0–125] n = 3143	<0.0001	0–26 > 36–38 > 43–46
Executive functions[d]							
Trail Making test B-A	32.4 ± 30.4 [−214–220] n = 2900	77.4 ± 56.3 [0–197] n = 51	67 ± 58.1 [−132–196] n = 83	78 ± 56.5 [−120–259] n = 1979	83.8 ± 54.9 [−172–216] n = 2134	<0.0001	43–46 > 36–38 > 0–26
Semantic Fluency (animals; 1 min)	21.9 ± 5.6 [3–48] n = 3431	14.5 ± 6.1 [1–31] n = 78	13.2 ± 6.5 [0–31] n = 125	12.6 ± 6 [0–37] n = 2939	11.5 ± 5.9 [0–42] n = 3203	<0.0001	0–26 > 36–38 > 40–42 > 43–46
Phonemic Fluency (3 letters PRV; total 3 min)	40.9 ± 12.6 [6–94] n = 2882	25.8 ± 16.1 [0–75] n = 62	25.2 ± 16.2 [0–70] n = 94	23.5 ± 13.8 [0–72] n = 2212	20.1 ± 12.6 [0–77] n = 2378	<0.0001	0–26 > 36–38 > 43–46

Note: Values are presented as mean ± standard deviation [min-max], number of subjects (n) for continuous variables, and counts of yes/no (% yes) for categorical variables.
Abbreviations: maximum, max, minimum, min; NA, not applicable.
[a]Pairwise comparisons without control group.
[b]Kruskal Wallis test (numerical variables) or χ^2 test for proportion comparisons (categorical variables) indicating association between the variable and the CAG groups.
[c]Post hoc analysis: Dunnett's pairwise comparisons with Bonferroni correction (numerical variables) or pairwise χ^2 tests with Holm correction (categorical variables) between all CAG groups. Except for post hoc tests, no other correction was applied for multiple comparisons.
[d]All cognitive variables were tested using type II analysis of variance (ANOVA) F-test followed by Dunnett's post hoc pairwise comparisons based on multivariate linear regression controlling for age, sex and education.

TABLE 3 *Demographic and clinical characteristics of individuals in the ENROLL cohort according to the size of CAG repeats in the* HTT *gene*

	CAG_{36-38}	CAG_{39}	CAG_{40-42}	CAG_{43-46}	CAG_{0-26}	Global *P*-value[a]	Post hoc group comparisons[b]
No.	243	355	4675	4565	3468		
Gender, women/men (% women)	127/116 (52.3)	204/151 (57.5)	2521/2154 (53.9)	2437/2128 (53.4)	2123/1345 (61.2)	<2.2e−16	40–42 and 43–46 < 0–26
Absence/presence of family history (% absence)	48/195 (19.8)	64/291 (18.0)	714/3961 (15.3)	701/3864 (15.4)	500/2968 (14.4)	0.15	
Absence/presence of family history in symptomatic patients (% absence)	19/70 (21.3)	33/112 (22.8)	496/2666 (15.7)	557/2939 (15.9)	NA	0.02	No significant pairwise differences
Transmission maternal/paternal (% maternal) when family history present	88/65 (57.5)	124/112 (52.5)	1899/1573 (54.7)	1884/1730 (52.1)	NA	0.123	
Age at onset (years)	54.2 ± 11.7 [31–84] n = 82	60.3 ± 11.5 [36–85] n = 133	53.9 ± 9.4 [12–83] n = 2953	42.7 ± 7,9 [8–71] n = 3263	NA	<2.2e−16	39 > 36–38 > 43–46
Age at motor onset (years)	55.9 ± 11.1 [34–84] n = 78	61.1 ± 11.1 [37–85] n = 130	54.9 ± 8.6 [21–82] n = 2915	43.6 ± 7.5 [13–71] n = 3209	NA	<2.2e−16	36–38 > 43–46
Delay to diagnosis (years)	5 ± 5.2 [0–23] n = 81	4.1 ± 5.7 [0–34] n = 128	3.9 ± 4.5 [0–34] n = 2871	3.4 ± 4.1 [0–36] n = 3150	NA	2.2e−6	36–38 > 39 > 40–42 > 43–46
Disease duration at baseline (years)	8.3 ± 5.5 [0–24] n = 75	8.1 ± 6.8 [−2–38] n = 122	8.2 ± 6.0 [−1–41] n = 2825	7.8 ± 5.6 [−2–42] n = 3135	NA	0.11	
Mean duration of follow up (years)	1.62 ± 1.44 [0–5.4] n = 243	1.70 ± 1.49 [0–5.3] n = 355	1.65 ± 1.40 [0–6] n = 4675	1.56 ± 1.41 [0–6] n = 4565	1.54 ± 1.47 [0–6] n = 3468	0.0002	40–42 > 43–46 and 0–26
Psychiatric comorbidities yes/no (% yes)	82/7 (92.1)	127/18 (87.6)	2926/236 (92.5)	3253/243 (93.0)	1203/2265 (34.7)	<2.2e−16	All groups >0–26

Note: Continuous variables are presented as mean ± standard deviation [min-max], n: number of subjects.
Abbreviations: max, maximum; min, minimum; NA, not applicable.
[a]Kruskal Wallis test (numerical variables) or χ^2 test for proportion comparisons (categorical variables) indicating association between the variable and the CAG groups.
[b]Post hoc analysis: Dunnett's pairwise comparisons with Bonferroni correction (numerical variables) or pairwise χ^2 tests with Holm correction (categorical variables) between all CAG groups. Except for post hoc tests, no other correction was applied for multiple comparisons.

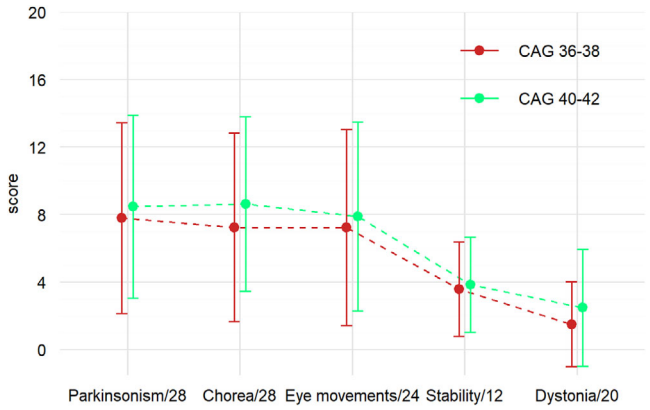

FIG. 3. Distribution of points in the different domains of the UHDRS TMS according to the CAG repeat size at baseline. Parkinsonism was rated using the seven items that assess left/right finger taps, left/right pronation/supination of the hands, left/right rigidity and bradykinesia, with a total score ranging from 0 to 28 points. Chorea was rated using the seven items that assess choreatic movements (face, buccal-oral-lingual region, trunk and left/right upper and lower extremities), with a total score ranging from 0 to 28 points. Eye movements were rated using the six items that assess eye movements (horizontal/vertical ocular pursuit, saccade initiation, saccade velocity), with a total score ranging from 0 to 24 points. Stability was rated using the three items that assess gait, tandem walking and retropulsion pull test, with a total score ranging from 0 to 12 point. Dystonia was rated using the five items that assess dystonia (trunk, left/right upper and lower extremities). [Color figure can be viewed at wileyonlinelibrary.com]

follow-up. The only significant difference between CAG_{36-38} and CAG_{40-42} could be observed in a subtest of verbal fluency (semantic fluency) with better performance for CAG_{36-38}.

Discussion

Our study is based on a large series of individuals carrying small, but pathological expansions CAG_{36-38} in the *HTT* gene. We show that these patients are as severely affected by disease as patients with larger, but still moderate expansions CAG_{40-42}. They present with less chorea resulting in a greater delay and less confidence in the diagnosis of manifest HD. Additionally, caregivers observed the type of symptoms at onset to be predominantly cognitive and behavioral, a perception not shared by the clinician or the patient themselves.

In HD with CAG_{36-38}, we found some patients to have a deficit in episodic memory. Surprisingly, this was because of a storage deficit possibly reflecting cortical impairment. Memory dysfunction in HD is usually reported to be because of retrieval difficulties reflecting executive dysfunction.[4,13] ENROLL did not allow for the evaluation of episodic memory impairment as the cognitive tests included in the battery do not contain any tests evaluating this function.

Prevalence of CAG_{36-38} in the ENROLL cohort is 1.59% (243/15 292). Prior research analyzing the prevalence of *HTT* expansions in the general population showed that 1 in 400 (0.25%) carries a CAG_{36-38} expansion.[9] As a consequence, authors hypothesized that the penetrance of small expansions might be considerably lower than previously reported and that CAG_{36-38} may have no or a late onset phenotype confounded with comorbid diseases of aging. Conversely, we attribute the under ascertainment of CAG_{36-38} patients partially to their nonspecific phenotype rather than exclusively to low penetrance, This could explain the discrepancy in prevalence data in the general population and HD cohorts, but these questions were not addressed in the present study. Penetrance rates should always be interpreted with caution because of the selection bias inherent in clinical HD cohorts for symptomatic patients and the lack of community controls. Additionally, current age at onset predictions and penetrance rates based on CAG size use only the CAG length without taking into account modifiers and repeat motif. The widely used Langbehn formula extrapolates age at onset curves for small expansion carriers from a model designed for individuals with CAG repeats in the range of 41 to 56. Small expansion carriers were excluded in this model because of potential ascertainment bias in this range.[7] To reduce this bias, a more recent analysis prospectively collected data from premanifest individuals. Nevertheless, bias may still be present because the study population represents only those seeking medical advice.[14]

Why some individuals phenoconvert and others do not is still difficult to predict. It is known that the variance in age at onset is larger in small expansion carriers indicating a greater contribution of modifiers in this group. Variance not explained by the CAG repeat is driven primarily by genetic modifiers in DNA repair genes.[6] In addition, loss of the glutamine encoding CAA interruption in the CAG tract, which lowers age at onset, is particularly frequent in patients with reduced penetrance alleles.[15] The CAG structure data were not yet available in this study, but it is possible that loss of the CAA interruption drove symptom onset in our cohort.

In our study, family history was not absent more frequently in CAG_{36-38} individuals, as would have been expected based on the proximity to the disease threshold and de novo expansion of intermediate normal alleles. This could be explained by recruitment bias in this cohort where patients are either tested because of known HD family history or because they have typical symptoms for HD.[16] This is an unavoidable bias in natural history studies.

CAG_{36-38} patients may be seen in a variety of medical services, such as geriatric, psychiatry departments, and memory clinics and therefore, elude genetic diagnosis. If they manifest late in life, as is more likely in patients with small expansions,[17] subtle cognitive changes, psychiatric symptoms, and even a decline in motor skills without unequivocal motor signs of HD may be

attributed to aging or other causes. In elderly patients, the independent co-occurrence of different neurodegenerative mechanisms and associated comorbidities such as cerebrovascular lesions can complicate diagnosis, especially when based on clinical presentation and not supported by biomarkers.

An important question that remains to be answered is whether and to what extent *HTT* expansions are present in patients with nonspecific cognitive decline that do not fulfill criteria for distinct neurodegenerative diseases. Prevalence data of *HTT* expansions in this population are scarce. First, genetic research has focused on well-defined neurodegenerative diseases like Alzheimer's disease and frontotemporal dementia where the frequency of small pathological expansions is rare.[18,19] Second, cohorts have mainly been assessed by genome-wide association study, whole exome and genome sequencing or analysis of specific genes, but these technologies are unsuitable to accurately detect pathological CAG repeats today.

The atypical profile, particularly when family history is not present and the low estimated likelihood of HD in elderly patients makes diagnosis particularly challenging in this setting. In addition, patients and caregivers are not likely to recognize subtle chorea, whereas caregivers may recognize behavioral changes and cognitive symptoms more easily, especially in the absence of chorea.

Knowledge about the clinical profile and severity of manifestations in small expansion carriers could modify diagnostic work-up in patients with nonspecific cognitive decline and improve genetic counseling for these patients and their offspring who will also be impacted by a newly diagnosed genetic disease in the family. However, pretest genetic counseling must be performed with particular care in sporadic cases where an underlying genetic cause is not expected by the patient. Current progress in research on disease modifying therapies will make it particularly important to detect at risk individuals in the population as early as possible. Longevity continues to increase and more individuals with small expansions will inevitably come to medical attention, therefore, increasing the need for information about this phenotype.

The findings of this study are in line with one of the most striking features of repeat expansion diseases that present with diverse phenotypes according to their repeat sizes resulting in a continuum of cognitive performance and clinical manifestations. Recent data suggest that even intermediate alleles $CAG_{27\text{-}35}$, not associated with disease, may influence behavior.[20] Additionally, *HTT* is now recognized to play a role in intelligence and cognitive performance. Large normal alleles or those just above disease threshold seem to confer an advantage in cognitive function and brain structure such as cortical thickness compared to smaller normal alleles.[21,22] They seem to be associated with better performance in attentional-executive function and processing speed.[23] These functions are mediated by frontostriatal circuits, which may be less affected in smaller expansions, an idea compatible with the frequent absence of chorea in these individuals.

The episodic memory storage impairment could suggest cortical involvement. Indeed, it has been shown that the cortex is involved early in the disease process even in premanifest HD carriers.[24]

Consistent with this, a study about cognitive performance in premanifest carriers showed that differences in estimated time to diagnosis based on age and CAG repeat length led to different patterns of cognitive impairment. Executive impairment was least common. Carriers far from diagnosis mainly had worse performance in visuospatial perception and episodic memory tests, reflecting cortical involvement, whereas those near diagnosis more often had worse performance in processing speed and episodic memory.[25] These findings could be interpreted as indirect evidence that HD begins with cortical damage, which is subsequently overwhelmed in later disease stages by a subcortical syndrome including dysexecutive impairment and motor dysfunction.[25]

Another interesting interpretation may take into account neurodevelopmental abnormalities in HD. Indeed, both neurodegeneration and abnormal neurodevelopment contribute to HD physiopathology.[26-29] Early cortical involvement could be interpreted as manifestations of subtle abnormal development, rather than neurodegeneration.

Previous published work suggests that cortical damage in HD, in contrast to striatal damage, is not correlated to CAG repeat size. Cortical neuron loss is often more severe than expected based on CAG length.[30-32] Consistent with this finding, it has been shown that cognitive changes occur independently of motor symptoms that are correlated to CAG size.[33] However, clinical features are correlated to atrophy patterns in the corresponding cortical brain region.[34]

This may contribute to the high clinical heterogeneity particularly in small expansion carriers. Furthermore, small expansion carriers, close to the threshold for disease are particularly impacted by the dual interplay of possible advantageous or disadvantageous effects on cognition. The coexistence of physiological and pathological neurodevelopmental mechanisms and neurodegeneration may lead to atypical and unpredictable phenotypes that mislead clinicians away from considering HD. Would an elderly patient with nonspecific motor and cognitive impairment, no family history, and showing only cortical but no striatal atrophy be referred for genetic testing?

In conclusion, HD should be considered in patients with unexplained cognitive decline including impaired episodic memory, even in the absence of typical motor symptoms or family history.

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Data Availability Statement

The corresponding author (AD) and the study biostatistician had full access to all the data, and all authors had access to the data if they wished.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.