The timing and impact of psychiatric, cognitive and motor abnormalities in Huntington's disease

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Abstract

Objective

To assess the prevalence, timing and functional impact of psychiatric, cognitive and motor abnormalities in Huntington's disease (HD), we analysed retrospective clinical data from individuals with manifest HD.

Methods

Clinical features of HD patients were analysed for 6316 individuals in the European REGISTRY study from 161 sites across 17 countries. Data came from clinical history and the Clinical Characteristics Questionnaire that assessed eight symptoms: motor, cognitive, apathy, depression, perseverative/obsessive behavior, irritability, violent/aggressive behavior, and psychosis. Multiple logistic regression was used to analyse relationships between symptoms and functional outcomes.

Results

The initial manifestation of HD is increasingly likely to be motor, and less likely to be psychiatric, as age at presentation increases. The nature of the first manifestation is not associated with pathogenic CAG repeat length. Symptom prevalence data from the patient-completed Clinical Characteristics Questionnaire correlate specifically with validated clinical measures. Using these data, we show that psychiatric and cognitive symptoms are common in HD, with earlier onsets associated with longer CAG repeats. 42.4% of HD patients reported at least one psychiatric or cognitive symptom before motor symptoms, with depression most common. Apathy and cognitive impairment tend to come later in the disease course. Each psychiatric or

cognitive symptom was associated with significantly reduced total functional capacity scores.

Conclusions

Psychiatric and cognitive symptoms occur before motor symptoms in many more HD patients than previously reported. They have a greater negative impact on daily life than involuntary movements and should be specifically targeted with clinical outcome measures and treatments.

Introduction

Huntington's disease (HD) is a central neurodegenerative disorder caused by an expanded CAG repeat (>35 CAGs) in the *Huntingtin* gene (*HTT*)[1]. Longer repeats are associated with earlier disease onset[2,3]. Neuronal loss is most prominent in the striatum but occurs widely in the brain, leading to a progressive movement disorder, cognitive decline and ultimately death. The motor disorder usually includes chorea, and may also involve dystonia, ataxia, oculomotor abnormalities and parkinsonism. In addition, individuals with HD develop a variable constellation of debilitating behavioural and psychiatric symptoms[4,5]: these 'non-motor' symptoms remain under-recognised and under-treated. Prospective studies of individuals carrying a pathogenic *HTT* CAG repeat but many years from predicted clinical onset have shown they have only subtle motor, cognitive or psychiatric deficits when compared with age and sex-matched controls[6–8]. This implies there is a window for therapeutic intervention to preserve normal brain functions. It is therefore crucial to understand in detail the timing and impact of different symptoms and signs in HD in order to target and assess potential disease-modifying therapies.

The HD Clinical Characteristics Questionnaire (HD-CCQ)[9] gathers retrospective data from individuals with HD about the prevalence and timing of eight motor, cognitive and psychiatric symptoms[10]. Here we validate the use of HD-CCQ data by showing strong and specific associations with established scores of depression, irritability and cognition. We then use HD-CCQ data to show the high prevalence of psychiatric and cognitive symptoms in HD, often in advance of motor symptoms, and their negative impact on the daily lives of patients.

Methods

Standard protocol approvals, registrations and patient consents

Participants were in the multicentre, multinational, observational REGISTRY study of European HD (http://www.ehdn.org/wp-content/uploads/2018/06/registry-protocol-3.0.pdf; NCT01590589). Data were accessed as part of European Huntington's Disease Network (EHDN) data mining project 0791. Ethical approval for REGISTRY was obtained in each participating country. All participants gave written informed consent.

Participant data

HD participant data, collected June 2004 - February 2016 across 161 sites in 17 European countries, was obtained for 6316 individuals (accessed October 2016) who had clinical HD onset, determined by the rating clinician in REGISTRY, and a confirmed pathogenic CAG length of 36-93 CAGs. Of these CAG sizes, 5027 were centrally determined by BioRep Inc. (Milan, Italy; REGISTRY protocols) and 1289 were derived by local diagnostic laboratories. Two estimates of the age at onset of symptoms and/or signs in HD were used in this study. First, the clinician-estimated age at first HD manifestation based upon all available clinical evidence at the first REGISTRY visit (coded as 'sxrater'). Having a 'sxrater' age at onset was required for inclusion in this study. Onset type was classified as motor, cognitive, psychiatric, oculomotor, other or mixed. As the clinician's estimate was given as a date, age estimates were calculated using the participant's anonymised birthday; where only a year was given, July 15th was used for estimation (15/07/xxxx). Second, the ages at onset of different symptoms in HD patients were estimated by the HD Clinical Characteristics Questionnaire (HD-CCQ) which was completed by a healthcare

professional, usually a HD-specialist nurse or similarly-qualified person, using responses from the individual with HD and their care partners (present in clinic in 93.1% of cases), and patient medical notes. The HD-CCQ comprises questions about eight symptoms commonly observed in HD, asking whether the participant has ever had the symptom (yes or no), and, if yes, the age at which the symptom was first experienced (Appendix 3). Information was available, at least in part, for 5609 individuals. The symptoms recorded (number of individuals with data) were: motor (chorea or other, consistent with HD; 5603), cognitive impairment sufficient to impact on work or daily living (5591), apathy (5584), depression (5595), perseverative/obsessive behaviour (5588), irritability (5586), violent or aggressive behaviour (5586) and psychosis (5589). For subsequent analyses, missing data were handled using pairwise deletion to maximise the number of individuals. Typically, the rater estimate of clinical onset and initial HD-CCQ would be recorded at the first REGISTRY visit, sometimes by one clinician, and sometimes by a clinician and another qualified staff member such as HD-specialist nurse, depending on local clinic set-up. Subsequent visits updated the HD-CCQ: we used data from the most recent clinic visit. We had data on Shoulson-Fahn disease stage at last clinic visit for 4554 individuals (72.1% of our study population): stage 1 (Total Functional Capacity (TFC) 11-13; N=890; 19.5%), stage 2 (TFC 7-10; N=1278; 28.1%), stage 3 (TFC 4-6; N=969; 21.3%), stage 4 (TFC 1-3; N=1133; 24.9%), stage 5 (TFC 0; N=284; 6.2%).

The Hospital Anxiety/Depression Scale (HADS) and Snaith Irritability Scale (SIS) were completed by the participant at each clinic visit and provide measures of anxiety, depression and irritability at that specific time. We used lifetime highest total

depression and total irritability scores from both the HADS and the SIS in analyses. Similarly, the symbol-digit modalities test (SDMT) and Stroop tests of cognitive ability were administered as part of the Unified Huntington's Disease Rating Scale (UHDRS)[11] at each visit. The UHDRS consists of validated questionnaires, tools and examinations related to motor, cognitive, behavioural and functional impairments seen in HD. For the SDMT and Stroop, we used the total correct scores from the most recent clinic visit. Disease duration was estimated by taking the most recent visit and subtracting the clinician's estimate of disease onset. The product of Problem Behaviours Assessment (PBA-s) severity and frequency scores from the most recent clinic was used for modelling purposes.

Statistical analyses of clinical data

Total depression scores from HADS, total irritability scores from SIS, the number of correct answers in the SDMT, the number of correct answers in Stroop tests or composite PBA-s scores were regressed on HD clinical characteristics data, age, CAG length, sex and disease duration (table 1). To calculate coefficients of determination (R^2 values, table 2), HD-CCQ age at onset data were natural log transformed. Only individuals with a known sex and a symptom onset ≥3 years were considered, and a residual vs leverage plot identified one influential data point passing Cook's distance that was removed from all R^2 calculations. *P* values were calculated comparing male and female R^2 values using Fisher's transformation[12]. A chi-square test was used to test for differences in symptom frequency, derived from the yes/no component of the HD-CCQ, between males and females.

Associations between binary responses in the HD-CCQ (1; experienced the symptom and 0; symptom not experienced) and clinical covariates were tested using logistic regression. The covariates used were sex, CAG length, alcohol consumption (units per week), tobacco use (cigarettes per day), education (years of education), TFC score and total motor score (TMS). An additional analysis regressed the type of HD onset defined by the clinician, coded as a binary variable, on the clinician's onset or CAG length (table e-2, doi:10.5061/dryad.pk0p2ngkz). This analysis was restricted to HD participants with CAGs 36-59, to be consistent with figure 1 subgroups, and also to adult-onset HD individuals (≥20 years). We also tested whether symptom presence was associated with the length of the wild-type (6-35 CAGs) and expanded CAGs (36-93 CAGs) alleles in individuals of known sex, and for whom both CAG lengths were known (table e-3, doi:10.5061/dryad.pk0p2ngkz). 19 individuals with a coincident formal diagnosis of schizophrenia, schizotypal disorder or schizoaffective disorder (ICD-10 F20, F21 or F25) were excluded from all models, although it was not possible to formally exclude these symptoms being part of the HD phenotype. Statistical analysis used *R* (version 3.6.0; R core team, 2019, https://www.r-project.org/).

Data availability

Further information and data requests should be directed to Thomas H. Massey (MasseyT1@cardiff.ac.uk). Anonymised summary data is available to qualified investigators. Furthermore, anonymised patient data is available from the European Huntington's Disease Network (EHDN) upon request given institutional assurance patient confidentiality will be upheld, and no attempt will be made to discover the identity of patients.

Results

The initial manifestation of HD varies with age and CAG length

The age at onset of the first unequivocal motor features of HD ('motor onset') has been used as a specific milestone in the natural history of HD in individuals, although it is only a crude measure of a progressive neuropathological process. It has proven particularly useful in recent genetic modifier studies of HD[13,14]. The first psychiatric and cognitive manifestations of HD are more difficult to define with certainty as they are less specific for HD and can occur many years before motor onset. The timing of the first feature of HD is typically retrospectively recorded by a rating physician in observational studies such as REGISTRY, based on clinical information and symptom history from patients and care partners[9,15,16]. The rater also records the initial major presenting feature out of a choice of six: motor, cognitive, psychiatric, oculomotor, other or mixed. We analysed the initial manifestation of HD for 6316 participants in REGISTRY[9], including 3083 males (48.8%) and 3233 females (51.2%). All participants had a confirmed genetic diagnosis of HD with a pathogenic CAG repeat length of 36-93 (figure e-1, doi:10.5061/dryad.pk0p2ngkz). The first manifestation of HD, determined by the rating physician, varied with patient age (figure 1A and table e-1, doi:10.5061/dryad.pk0p2ngkz). Individuals with onset before the age of 20, defined as juvenile HD, were equally likely to present with motor (24.5%), cognitive (21.8%) or psychiatric features (28.2%). In contrast, the initial manifestation of HD was more likely to be motor than psychiatric in adult-onset HD. As age at first manifestation increased (figure 1A and table e-2A, doi:10.5061/dryad.pk0p2ngkz) motor presentations became more likely (odds ratio (OR) = 1.06 per ten year increase in onset age, 95% confidence interval (CI) 1.04-

1.07; $P = 7.4 \times 10^{-22}$) but psychiatric presentations became less likely (OR = 0.96 per ten year increase in onset age, 95% CI 0.95-0.97; $P = 9.4 \times 10^{-16}$). For people presenting over the age of 60, over two-thirds (68.6%) had motor abnormalities at clinical onset with far fewer having psychiatric (11.5%) or cognitive (6.7%) presentations. Next, we tested whether there was any relationship between pathogenic CAG repeat length, known to be inversely correlated with age at clinical onset, and the presenting phenotype. Interestingly, there was no significant relationship between CAG length (36-59 inclusive) and the relative proportions of motor, cognitive and psychiatric onset cases (figure 1B and table e-2B, doi:10.5061/dryad.pk0p2ngkz). For the few cases with data and repeat lengths of more than 59 CAG we observed a more balanced distribution of motor, cognitive and psychiatric onsets, mirroring the trends seen for the juvenile HD cases.

Psychiatric and cognitive symptoms captured by the Clinical Characteristics Questionnaire correlate with scores from validated clinical tools

The HD Clinical Characteristics Questionnaire (HD-CCQ) was introduced to later versions of REGISTRY as the best retrospective way of capturing symptom data in existing HD populations. It is completed by a healthcare professional using information from individuals with HD and their care partners, present in clinic for over 93%, about lifetime history and age at onset of eight symptoms typical of HD. These symptoms are motor (compatible with HD), depression, irritability, violent or aggressive behavior, apathy, perseverative/obsessive behavior, psychosis and cognitive impairment sufficient to impact on work or daily living. In REGISTRY, this information was updated at each annual clinic visit.

Since prevalence data from HD-CCQ have not been used in large analyses before we first tested how well they correlated with validated clinical scores of depression (HADS), irritability (SIS) and cognition (SDMT and Stroop). To mitigate against potential effects of medication at certain times, we used the lifetime highest total depression and total irritability scores for each individual. For cognitive tests we used scores at the last recorded clinic visit as these would be expected to worsen progressively and be little affected by medication. Total depression score from HADS was significantly increased in individuals with depression recorded in HD-CCQ (table 1; increase of 1.49 units, 95% CI 1.09-1.89; $P = 5.7 \times 10^{-13}$). An increase in HADS score was also observed in individuals with HD-CCQ apathy, probably because apathy, common in HD, may be mistaken for depression by individuals and their care partners when completing the HD-CCQ. Total irritability score from SIS was significantly increased in individuals with HD-CCQ irritability (increase of 1.82 units, 95% CI 1.37-2.27; $P = 2.0 \times 10^{-15}$), and also with violent/aggressive behaviour (increase of 1.57 units, 95% CI 1.08-2.06; $P = 3.3 \times 10^{-10}$), as expected. Both SDMT and Stroop scores of cognitive ability were significantly decreased in individuals with cognitive impairment as recorded in HD-CCQ (reductions of 3.52 units, 95% CI 2.71-4.33; $P = 2.3 \times 10^{-17}$ and 3.41 units, 95% CI 2-65-4.17; $P = 1.4 \times 10^{-22}$, respectively). Significant associations between cognitive scores and motor and apathy symptoms were also observed. In addition, we found robust and specific associations between neuropsychiatric symptoms recorded in HD-CCQ and their related symptoms scored using the validated short-form Problem Behaviors Assessment (PBA-s; supplemental table e-4, doi:10.5061/dryad.pk0p2ngkz). The specificity of the associations between HD-CCQ data and recognised clinical scales validated the use of HD-CCQ data in subsequent analyses.

Psychiatric symptoms are common in HD and are associated with CAG repeat length

We next analysed the lifetime prevalence of the eight symptoms recorded in HD-CCQ in 5609 individuals with HD at their most recent clinic visit (table 2). The mean age at last recorded clinic visit was 53.3 years; 53.5 years for males with data (range 10.4 – 92.6 years; N = 2569) and 53.2 years for females (range 7.9 – 90.2 years; N = 2698). Almost all (>99%) had experienced motor symptoms compatible with HD. Although these symptoms are not defined explicitly in HD-CCQ, contemporaneous data from UHDRS showed that 96.8% of our study population had chorea, alongside variable amounts of incoordination, dystonia and rigidity. In HD gene carriers these motor symptoms are likely to be specific manifestations of HD. The next most prevalent symptom was depression, occurring in 64.5% of HD individuals with significantly more females affected than males (70.4% vs 58.2%; OR 1.70, 95% CI 1.52-1.90; $P = 2.6 \times 10^{-21}$). Cognitive impairment sufficient to impact upon work or activities of daily living, apathy and irritability were also each observed in over half of our HD population. Cognitive impairment and apathy were equally likely in males and females, but there was significantly more irritability observed in males (62.9% vs 56.9%; OR 0.78, 95% CI 0.70-0.87; $P = 4.0 \times 10^{-6}$). An excess of violent or aggressive behaviour was also observed in the male group (34.9% vs 27.0%; OR 0.69, 95% CI 0.62-0.77; $P = 2.0 \times 10^{-10}$). Psychosis was the least prevalent of the eight recorded symptoms, although this was still observed in over 11% of individuals with HD with no significant difference in prevalence between males and females.

There was a strong inverse correlation between pathogenic CAG repeat length (40-55 CAG inclusive) and mean age at symptom onset for all symptoms analysed

(figure 2). We found no effect of wild-type CAG allele length on any symptom onset, nor any significant statistical interaction between expanded and wild-type repeat lengths (table e-3, doi:10.5061/dryad.pk0p2ngkz). Pathogenic CAG length explained 66.3% of the variance in age at onset of motor symptoms, in line with previous estimates[2,3,17–23], but also between 37.5% and 61.9% of the variance in onset of each of the psychiatric symptoms analysed (table 2). Depression had the weakest association with CAG repeat length (R^2= 37.5%), likely reflecting the high prevalence of the symptom in the general population independent of HD and the lack of use of universal diagnostic criteria. CAG length accounted for significantly more of the variance in age at onset of perseverative/obsessive behaviour in males (table 2; $P = 3.7 \times 10^{-3}$) and irritability in females ($P = 1.3 \times 10^{-3}$).

The timing of motor and psychiatric symptoms in HD varies with symptom type and CAG length

Given that motor onset is often used as a specific milestone in the natural history of HD, we investigated the timing of each of the seven psychiatric/cognitive symptoms relative to the age at first motor symptoms recorded in HD-CCQ (figure 2). The differences in ages between first motor symptoms and each of the psychiatric symptoms were approximately normally distributed, with a wide range of at least +/- 20 years in each case (figures 2 and e-2, doi:10.5061/dryad.pk0p2ngkz). In those patients reporting depression, onset occurred before motor symptoms in 39.2% (N= 1369/3495). For patients with irritability, onset occurred before motor symptoms in 30.8% (N= 996/3235). Perseverative/obsessive behaviour tended to occur later in the disease course, after motor symptoms, as did psychosis although numbers were smaller. Cognitive impairment and apathy had the most positively skewed

distributions with onset occurring after motor onset in 2179/3225 (67.6%) and 1981/2852 (69.5%) of individuals, respectively. Overall, 42.4% of HD patients (N= 2140/5042) reported at least one psychiatric or cognitive symptom in advance of motor symptoms, with a further 22.3% (N= 1126/5042) reporting at least one of these symptoms at the same time as motor abnormalities.

We next assessed whether there were any patterns in the mean ages of onset of the different symptoms when plotted by CAG repeat length (figure 3). Some consistent relationships between symptoms were observed. Depression usually had the youngest mean age at onset, followed by motor impairment and then apathy and cognitive impairment as the latest symptoms. Mean age at onset of irritability preceded that of motor onset at shorter repeat lengths (40-43 CAGs, inclusive) but tended to follow it at longer repeat lengths (44-53 CAGs, inclusive). The mean difference in years from onset of first symptom to last decreased with CAG repeat length from approximately 8 years for 40 repeats to 4 years for 55 repeats (figure 3).

Cognitive and psychiatric symptoms are significantly associated with reduced functional capacity

To assess whether psychiatric, cognitive or motor symptoms were associated with altered functional abilities we used multiple logistic regression (table 4). This analysis incorporated sex, pathogenic CAG length, duration of disease from clinical onset to last clinic visit, alcohol consumption, tobacco use, educational attainment, total functional capacity score and total motor score as predictors of the presence/absence of each HD-CCQ symptom. The presence of any of the psychiatric or cognitive symptoms was significantly associated with lower total

functional capacity (TFC), an indication of impaired ability to work, manage personal finances and function independently. Cognitive impairment was most significantly associated with reduced TFC (OR per unit decrease in TFC = 1.28, 95% CI 1.23-1.35; $P = 1.6 \times 10^{-25}$). Depression was significantly associated with lower total motor scores (indicating fewer motor symptoms or signs), fitting with its prevalence early in the disease course. Finally, significant associations were observed between depression and female sex (OR = 1.77, 95% CI 1.44-2.17; $P = 7.0 \times 10^{-8}$) and tobacco use and irritability (OR per extra cigarette per day = 1.02, 95% CI 1.01-1.03; $P = 1.0 \times 10^{-4}$). Although not reaching strict criteria for significance after correcting for multiple tests, associations were also found between male sex and irritability (OR = 0.75, 95% CI 0.61-0.92; $P = 5.4 \times 10^{-3}$) and lower educational attainment and psychosis (OR per extra year of education = 0.92, 95% CI 0.88-0.97; $P = 2.2 \times 10^{-3}$).

Discussion

In this large study of over 6000 patients we have shown that the initial manifestation of HD varies significantly with age: late onset (>60 years) is usually associated with motor abnormalities, whereas early onset (<20 years; juvenile HD) is associated with a wider range of motor, cognitive and psychiatric presentations (figure 1A). These results extend prior studies which have shown that motor presentation of HD is common in late-onset disease (65.5% of an earlier REGISTRY cohort[24]), with more variable presentations in juvenile HD[25,26]. Approximately 20% of HD patients present with rater-determined psychiatric features, in line with previous findings (table e-1, doi:10.5061/dryad.pk0p2ngkz)[9]. Cognitive onset of HD might be under-reported in older age-groups due to it being regarded as coincident 'age-related' change. Importantly, our results show there is little relationship between pathogenic CAG repeat length and onset type in adult-onset HD (figure 1B), despite both being associated with age at clinical onset. These data fit a model in which age at clinical onset is driven primarily by CAG repeat length, but modified by environmental factors and variants at other genomic loci[14,23,27,28]. The age and physiology of the brain at clinical onset subsequently determines the types of symptoms that become manifest.

Previous analysis of a smaller cohort showed that the expanded CAG repeat is fully dominant for motor onset of HD, with no effect of the normal *HTT* CAG allele[17]. We confirmed this result and showed that the same is true for all psychiatric and cognitive symptoms (table e-3, doi:10.5061/dryad.pk0p2ngkz). The age at onset of each symptom recorded by HD-CCQ was inversely correlated with CAG length (figure 3), with motor symptoms best correlated and depression least correlated (table 3). These data are consistent with previous reports showing that CAG length accounts for 47-72% of the variance in age at motor onset of HD[29], but do not fit with

previous studies that reported no correlation between CAG repeat length and psychiatric symptoms[30–33]. However, these studies were small and often examined incident psychiatric symptoms, which can fluctuate over time, rather than lifetime history as here. Increasingly accurate CAG tract sizing will improve the accuracy of correlations between repeat length and symptoms[14,34,35].

Most modifier studies of HD have used age at motor onset as a quantitative trait. Motor signs (predominantly chorea at onset) in the context of an expanded CAG repeat in *HTT* have high specificity for HD and most individuals with manifest HD report motor symptoms. However, psychiatric and cognitive symptoms are often more debilitating for patients and can occur early in the disease course[36]. These symptoms are common in HD (table 2), and much more prevalent than in the non-HD population[5,10,37]. Neuropsychiatric symptoms are also likely underestimated in HD due to pathological unawareness of these traits by patients[38]. Recent genetic evidence has shown that polygenic risk scores for psychiatric disorders, particularly depression and schizophrenia, are associated with increased risk of corresponding psychiatric symptoms in HD[39]. This suggests that the expanded *HTT* CAG repeat might lower the genetic threshold for manifestation of typical psychiatric symptoms[39]. In agreement, we found the expected relationships between female sex and depression and male sex and irritability in our cohort (table 4). The nominally significant negative association of psychosis in HD with educational level (table 4) also corroborates work showing that higher levels of education are associated with decreased schizophrenia risk[40].

The HD-CCQ captures quantitative information not available elsewhere on symptom prevalence and timing in the HD population. Prior to its introduction in REGISTRY, age at first motor symptoms was not routinely recorded for all HD patients. HD-CCQ

provides particular insight into neuropsychiatric symptoms but is not designed to capture the subtle early motor or cognitive signs found in prospective studies[7,8]. As it relies on retrospective reporting by patients and care partners the HD-CCQ is necessarily coarse, although the data it generates correlate well with more precise measures of depression, irritability and cognition (table 1). Cognitive impairment measured by SDMT or Stroop correlated most strongly with lifetime history of cognitive impairment in HD-CCQ, as expected, but also showed significant correlations with motor symptoms and apathy. These results fit with other studies showing that these symptoms track together in the disease trajectory[39,41]. There was also a significant association between cognitive impairment and psychosis, which fits the cognitive deficits observed in schizophrenia[42]. Conversely, validated depression and irritability scores correlated well with their respective prevalence data from HD-CCQ but were not associated with motor or cognitive impairment (table 1).

Despite considerable variation in the timing of psychiatric and motor symptoms, there are some conserved patterns (figures 2 & 3). Depression, and less often irritability, can precede motor symptoms by many years. Conversely, apathy and cognitive impairment tend to occur after motor symptoms, although patients do recognise and report these symptoms less readily than depression or irritability. Overall, the HD-CCQ data show that 64.8% of our HD population (N = 3266/5042) reported at least one psychiatric or cognitive symptom by the time of first motor symptoms. This is a much higher figure than previously reported based on clinician estimates of first HD manifestation (figure 1)[9], most likely because it is difficult to confidently attribute early psychiatric symptoms to HD. Clinically, it is currently impossible to distinguish between symptoms arising as a result of the HD mutation and those from primary psychiatric disorders, particularly in younger pre-manifest

patients in whom diseases such as depression are common[43]. Furthermore, environmental effects on mental health, such as living in a family with HD, should not be overlooked. Future studies of psychiatric and cognitive symptoms and signs in HD gene carriers against gene-negative community controls might help define a HD-specific neuropsychiatric phenotype that would enable more confident attribution of early abnormalities to HD.

We acknowledge several potential limitations of these data: they are retrospective, subject to recall bias, and cross-sectional. Symptom onset data based on patient and care partner memory cannot be used to define unequivocal clinical onset of HD. Furthermore, HD-CCQ data depend on the interpretation of questions: for example, 'motor symptoms' are not explicitly defined and so although 96.8% of our population had chorea this was not documented in HD-CCQ. Future iterations might usefully subdivide 'motor symptoms' into 'chorea' and 'other HD-related motor abnormalities'. Our analyses are based on data from the most recent clinic visit which is at different points of the disease course in different individuals. We controlled for this by using disease duration, the time between first onset and last clinic visit, as a covariate in analyses. The use of psychoactive medications is found in up to 60% of HD patients and might confound motor and neuropsychiatric phenotypes[9,44]. Of drugs prescribed for chorea, tetrabenazine can induce depression and antipsychotics can reduce irritability. They also suppress motor manifestations which might affect the total motor scores used here as a co-variate (table 4). It is hard to control for these effects. Drugs prescribed to treat symptoms once they are present will not influence symptom onset data. We used worst-ever depression and irritability scores when validating the use of HD-CCQ to mitigate against the effects of medication prescribed at certain times.

Previous prospective studies of phenotype in HD such as PREDICT-HD and TRACK-HD have shown subtle early reductions in psychiatric and cognitive function years in advance of clinical onset[7,8]. The HD-CCQ accesses retrospective data from large existing populations of manifest HD patients and shows similar trends. Since the HD-CCQ is part of ongoing longitudinal observational studies such as ENROLL-HD, future analyses of larger populations will be possible and of benefit. The presence of psychiatric and cognitive symptoms in HD patients is associated with significantly reduced functional capacity, emphasizing the importance of early management of these symptoms[45,46]. Although recent models of HD staging and progression do not directly include psychiatric and cognitive symptoms[47–49], work is underway to include them in ongoing observational studies and clinical trials to improve the accuracy of clinical outcome measures. Given the prevalence, timing and impact of psychiatric and cognitive abnormalities in HD demonstrated here, their treatment should form a central part of assessing the efficacy of novel treatments that are potentially disease-modifying, such as Huntingtin-lowering[50].

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B.Mc., J-M.L., M.E.M., M.O., N.M.W., P.H.: nothing to disclose

Appendix 1 – Authors

Name	Location	Contribution/Role
Branduff McAllister, BSc, PhD	Cardiff University, Cardiff, UK	Organized data; Designed and executed statistical analyses; Wrote first paper draft; Reviewed and critiqued paper manuscript
James F. Gusella, PhD	Massachusetts General Hospital, Boston, USA	Reviewed and critiqued paper manuscript
Bernhard Landwehrmeyer, MD, PhD	University of Ulm, Ulm, Germany	Reviewed and critiqued paper manuscript
Jong-Min Lee, PhD	Massachusetts General Hospital, Boston, USA	Reviewed and critiqued paper manuscript
Marcy E. MacDonald, PhD	Massachusetts General Hospital, Boston, USA	Reviewed and critiqued paper manuscript
Michael Orth, MD, PhD	Swiss Huntington's disease Centre, Bern, Switzerland	Reviewed and critiqued paper manuscript
Anne E. Rosser, MB BChir, FRCP, PhD	Cardiff University, Cardiff, UK	Reviewed and critiqued paper manuscript
Nigel M. Williams, BSc, PhD	Cardiff University, Cardiff, UK	Reviewed and critiqued paper manuscript
Peter Holmans, BA, PhD	Cardiff University, Cardiff, UK	Designed and conceptualized study; Designed and critiqued statistical analyses; Reviewed and critiqued paper manuscript
Lesley Jones, BSc, PhD (*)	Cardiff University, Cardiff, UK	Designed and conceptualized study; Wrote first paper draft; Reviewed and critiqued paper manuscript
Thomas H. Massey, MA, BM Bch, DPhil (*), (†)	Cardiff University, Cardiff, UK	Designed and conceptualized study; Wrote first paper draft; Reviewed and critiqued paper manuscript

(*) indicates corresponding authors

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Appendix 2 – Co-investigators of the European Huntington's Disease Network REGISTRY Study

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Brigitte Herranhof	1	Site Investigator
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Monika Scheibl	1	Site Investigator
Helmut Schöggl	1	Site Investigator
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Florian Brugger	2	Site Investigator
Lisa Buratti	2	Site Investigator
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Caroline Hepperger	2	Site Investigator
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Anna Hotter	2	Site Investigator
Anna Hussl	2	Site Investigator
Barbara Larcher	2	Site Investigator
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Fabienne Sprenger	2	Site Investigator
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Caterina Mariotti	58	Site Investigator
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Martina Petrollini	60	Site Investigator
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Anna Wasielewska	76	Site Investigator
Jacek Anioła Anna Bryl	77	Site Investigator
Anna Ciesielska	77	Site Investigator
Aneta Klimberg	77	Site Investigator
Jerzy Marcinkowski	77	Site Investigator
Husam Samara	77	Site Investigator
Justyna Sempołowicz	77	Site Investigator
Bartłomiej Wiśniewski	77	Site Investigator
Daniel Zielonka	77	Site Investigator
Anna Gogol (formerly Kalbarczyk)	78	Site Investigator
Piotr Janik	78	Site Investigator
Zygmunt Jamrozik	78	Site Investigator

Name	Location	Contribution/Role
Anna Kaminska	78	Site Investigator
Hubert Kwiecinski+	78	Site Investigator
Jakub Antczak	79	Site Investigator
Katarzyna Jachinska	79	Site Investigator
Wioletta Krysa	79	Site Investigator
Maryla Rakowicz	79	Site Investigator
Rafal Rola	79	Site Investigator
Danuta Ryglewicz	79	Site Investigator
Halina Sienkiewicz-Jarosz	79	Site Investigator
Iwona Stępniak	79	Site Investigator
Anna Sułek	79	Site Investigator
Grzegorz Witkowski	79,163	Site Investigator, Language Coordinator
Jacek Zaremba	79	Site Investigator, REGISTRY Steering Committee
Elzbieta Zdzienicka	79	Site Investigator
Karolina Ziora-Jakutowicz	79	Site Investigator
Cristina Januário	80	Site Investigator
Filipa Júlio	80	Site Investigator
Manuel Almeida	81	Site Investigator
Ana Calado	81	Site Investigator
Margarida Dias	81	Site Investigator
Joana Morgado	81	Site Investigator
Cristina Semedo	81	Site Investigator
Leonor Correia Guedes	82,163	Site Investigator, Language Coordinator
Miguel Coelho	82	Site Investigator
Joaquim J Ferreira	82	Site Investigator, REGISTRY Steering Committee
Andreia Magalhães	82	Site Investigator
Tiago Mestre	82,163	Site Investigator, Language Coordinator
Tiago Mendes	82,83	Site Investigator
Dulce Neutel	82	Site Investigator
Filipe Rodrigues	82	Site Investigator
Anabela Valadas	82	Site Investigator
Cristina Costa	83	Site Investigator
Helena Cardoso	83	Site Investigator
Mariana Santos	83	Site Investigator
Gonçalo Cação	84	Site Investigator
Sara Cavaco	84	Site Investigator
Joana Damásio	84	Site Investigator

Name	Location	Contribution/Role
Joana Fernandes	84	Site Investigator
Alexandra Gonçalves	84	Site Investigator
Rui Loureiro	84	Site Investigator
Inês Moreira	84	Site Investigator
Marina Magalhães	84	Site Investigator
Paula Salgado	84	Site Investigator
Carlos Andrade	85	Site Investigator
Andreia Costa	85	Site Investigator
Carolina Garrett	85	Site Investigator
Miguel Gago	85	Site Investigator
Joana Guimarães	85	Site Investigator
João Massano	85	Site Investigator
Joana Meireles	85	Site Investigator
Ana Monteiro	85	Site Investigator
Diana Khasanova	86	Site Investigator
Zuleykha Zalyalova	86	Site Investigator
Sergey Illarioshkin	87	Site Investigator, REGISTRY Steering Committee
Sergey Klyushnikov	87	Site Investigator
Olga Sidorova	87	Site Investigator
Oleg Smirnov	87	Site Investigator
Elizaveta Yudina	87,163	Site Investigator, Language Coordinator
Yury Seliverstov	87,163	Site Investigator, Language Coordinator
Victoria Antonova	88	Site Investigator
Svetlana Kopishinskaya	88	Site Investigator
Maria Korotysh	88	Site Investigator
Rim Magzhanov	89	Site Investigator
Elena Saifullina	89	Site Investigator
Sergey Kurbatov	90	Site Investigator
Pilar Solis	91	Site Investigator
Carmen Durán Herrera	92	Site Investigator
Patrocinio Garcia Moreno	92	Site Investigator
Jordi Bas	93	Site Investigator
Núria Busquets	93	Site Investigator
Matilde Calopa	93	Site Investigator
Serge Jaumà Classen	93	Site Investigator
Nadia Rodríguez Dedichá	93	Site Investigator
María Teresa Buongiorno	94	Site Investigator
Andrés de la Cerda Santa María	94	Site Investigator
Esteban Muñoz	94	Site Investigator
Pilar Santacruz	94	Site Investigator
Miquel Aguilar Barbera	95	Site Investigator
Ana Rojo Sebastián	95	Site Investigator, REGISTRY Steering Committee
Sonia Arribas Pardo	95	Site Investigator
Dolors Badenes Guia	95	Site Investigator
Noemi Calzado	95	Site Investigator
Laura Casas Hernanz	95	Site Investigator
Juan Pablo Tartari Díaz-Zorita	95	Site Investigator
Judit López Catena	95	Site Investigator
Pilar Quiléz Ferrer	95	Site Investigator
Gemma Tome Carruesco	95	Site Investigator
Misericordia Floriach Robert	96	Site Investigator
Cèlia Mareca Viladrich	96	Site Investigator
Elvira Roca	96	Site Investigator
Jesús Miguel Ruiz Idiago	96	Site Investigator
Antonio Villa Riballo	96	Site Investigator
Antonia Campolongo	97	Site Investigator
Ramon Fernandez de Bobadilla	97	Site Investigator
Andrea Horta	97,163	Site Investigator, Language Coordinator
Jaime Kulisevsky Bojarsky	97	Site Investigator
Saul Martinez-Horta	97,163	Site Investigator, Language Coordinator
Javier Pagonabarraga	97	Site Investigator
Jesus Perez Perez	97	Site Investigator
Roser Ribosa	97	Site Investigator
Carolina Villa	97	Site Investigator
Maria Angeles Acera Gil	98	Site Investigator
Koldo Berganzo Corrales	98	Site Investigator
Juan Carlos Gomez Esteban	98	Site Investigator
Amaia González	98	Site Investigator
Beatriz Tijero Merino	98	Site Investigator
Esther Cubo	99	Site Investigator
Cecilia Gil Polo	99	Site Investigator
Natividad Mariscal	99	Site Investigator
Jesús Sánchez	99	Site Investigator
Sandra Gutierrez Romero	100	Site Investigator

Name	Location	Contribution/Role
José Matías Arbelo	100	Site Investigator
Rocío Malo de Molina	100	Site Investigator
Idaira Martín	100	Site Investigator
Juan Manuel Periañez	100	Site Investigator
Beatriz Udaeta	100	Site Investigator
Fernando Alonso-Frech	101	Site Investigator
María del Valle Loarte	101	Site Investigator
Francisco Barrero	102	Site Investigator
Blas Morales	102	Site Investigator
Belén Frades	103	Site Investigator
Marina Ávila Villanueva	103	Site Investigator
Maria Ascension Zea Sevilla	103	Site Investigator
María del Mar Fenollar	104	Site Investigator
Rocío García-Ramos García	104	Site Investigator
Clara Villanueva	104	Site Investigator
Mónica Bascuñana	105	Site Investigator
Marta Fatás Ventura	105	Site Investigator
Juan García Caldentey	105,106,109	Site Investigator
Guillermo García Ribas	105	Site Investigator
Justo García de Yébenes	105	Site Investigator
José Luis López–Sendón Moreno	105	Site Investigator
Verónica Mañanes Barral	105	Site Investigator
Patricia Trigo Cubillo	105,163	Site Investigator, Language Coordinator
Cici Feliz	106	Site Investigator
Pedro José García Ruíz	106	Site Investigator
Ana García	106	Site Investigator
Rosa Guerrero López	106	Site Investigator
Antonio Herranz Bárcenas	106	Site Investigator
Asunción Martínez-Descals	106,163	Site Investigator, Language Coordinator
Angel Martínez Pueyo	106	Site Investigator
Veronica Puertas Martin	106	Site Investigator
Noelia Rodríguez Martínez	106	Site Investigator
Teresa Montojo	106	Site Investigator
María José Sainz Artiga	106	Site Investigator
Vicenta Sánchez	106	Site Investigator
María Dolores Alarcón	107	Site Investigator
Carmen Antúnez Almagro	107	Site Investigator
Esther Diéguez	107	Site Investigator
Lorenza Fortuna	107	Site Investigator
Agustina Legaz	107	Site Investigator
Salvadora Manzanares	107	Site Investigator
Juan Marín Muñoz	107	Site Investigator
María Martirio Antequera Torres	107	Site Investigator
Fuensanta Noguera Perea	107	Site Investigator
Laura Vivancos	107	Site Investigator
Sonia González	108	Site Investigator
Luis Menéndez Guisasola	108	Site Investigator
Marta Para Prieto	108	Site Investigator
René Ribacoba	108	Site Investigator
Carlos Salvador	108	Site Investigator
Pablo Sánchez Lozano	108	Site Investigator
Inés Legarda Ramirez	109	Site Investigator
Dolors Moragues Benito	109	Site Investigator
Penelope Navas Arques	109	Site Investigator
Monica Rodriguez Lopera	109	Site Investigator
Barbara Vives Pastor	109	Site Investigator
Itziar Gaston	110	Site Investigator
Fermin Garcia-Amigot	110	Site Investigator
Maria Dolores Martinez-Jaurrieta	110	Site Investigator
Maria Antonia Ramos-Arroyo	110	Site Investigator, REGISTRY Steering Committee
Astrid Adarmes	111	Site Investigator
Maravilla Bernal-Escudero	111	Site Investigator
Fátima Carrillo	111	Site Investigator
Silvia Jesús	111	Site Investigator
Pablo Mir	111	Site Investigator
Laura Vargas-González	111	Site Investigator
Fátima Damas Hermoso	112	Site Investigator
José Manuel García Moreno	112	Site Investigator
Javier Abril Jaramillo	112	Site Investigator
Carolina Mendez Lucena	112	Site Investigator
Eva María Pacheco Cortegana	112	Site Investigator
José Chacón Peña	112	Site Investigator
Luis Redondo	112	Site Investigator
Violeta Sánchez Sánchez	112	Site Investigator

Name	Location	Contribution/Role
Cristina Melgar Fernandez	113	Site Investigator
María Dolores Romero Lemos	113	Site Investigator
Maite Paredes Mata	113	Site Investigator
Rocío Villagrán Casado	113	Site Investigator
Maria Bosca	114	Site Investigator
Juan Andres Burguera	114	Site Investigator
Francisco Castera Brugada	114	Site Investigator
Jose Maria Millán Salvador	114	Site Investigator
Carmen Peiró Vilaplana	114	Site Investigator
Pilar Solís	114	Site Investigator
Begoña Jeweinat Figuerola	114	Site Investigator
Paloma Millan Palanca	115	Site Investigator
Elena Bellosta Diago	115	Site Investigator
Javier López del Val	115	Site Investigator
Laura Martinez Martinez	115	Site Investigator
Elena López	115	Site Investigator
Jan Wahlström+	116	Site Investigator, REGISTRY Steering Committee
Ulrika Høsterey-Ugander	116	Site Investigator
Gunnel Fredlund	116	Site Investigator
Radu Constantinescu	116	Site Investigator
Kajsa Lewin	116	Site Investigator
Liselotte Neleborn-Lingefjärd	116	Site Investigator
Maria Berglund	116	Site Investigator
Peter Berglund	116	Site Investigator
Petra Linnsand	116	Site Investigator
Åsa Petersén	117	Site Investigator
Jan Reimer	117	Site Investigator
Håkan Widner	117	Site Investigator
Mouna Esmaeilzadeh	118	Site Investigator
Joakim Tedroff	118	Site Investigator
Elisabeth Winnberg	118	Site Investigator
Stanislav Benaminov	119	Site Investigator
Elisabeth Björnsson	119	Site Investigator
Daniel Merrick	119	Site Investigator
Martin Paucar	119	Site Investigator
Sven Pålhagen	119	Site Investigator, REGISTRY Steering Committee
Per Svenningsson	119	Site Investigator
Tina Wallden	119	Site Investigator
Måns Berglund	120	Site Investigator
Ghada Loutfi	120	Site Investigator
Carina Olofsson	120	Site Investigator
Eva-Lena Stattin	120	Site Investigator
Laila Westman	120	Site Investigator
Birgitta Wikström	120	Site Investigator
Camilla Ekwall	121	Site Investigator
Marie-Lousie Göller	121	Site Investigator
Anders Johansson	121	Site Investigator
Valter Niemelä	121	Site Investigator
Dag Nyholm	121	Site Investigator
Leif Wiklund	121	Site Investigator
Jean-Marc Burgunder	122,161	Site Investigator, REGISTRY Steering Committee
Jessica Koehli	122	Site Investigator
Yanik Stebler	122	Site Investigator
Alain Kaelin	123	Site Investigator
Irene Romero	123	Site Investigator
Michael Schüpbach	123	Site Investigator
Sabine Weber Zaugg	123	Site Investigator
Federica Esposito	124	Site Investigator
Jean-Marc Good	124	Site Investigator
Karin Paus	124	Site Investigator
Francois Vingerhoets	124	Site Investigator
Christian Wider+	124	Site Investigator
Hans H. Jung	125	Site Investigator
Jens A. Petersen	125	Site Investigator
Maria Ligon-Auer	125	Site Investigator
Violeta Mihaylova	125	Site Investigator
Lorna Downie	126	Site Investigator
Roisin Jack	126	Site Investigator
Kirsty Matheson	126	Site Investigator
Zosia Miedzybrodzka	126	Site Investigator
Daniela Rae	126	Site Investigator
Sheila A Simpson	126	Site Investigator
Fiona Summers	126	Site Investigator
Alexandra Ure	126	Site Investigator

Name	Location	Contribution/Role
Vivien Vaughan	126	Site Investigator
Timothy Harrower	127,135	Site Investigator
Nathan Vernon	127	Site Investigator
Shahbana Akhtar	128	Site Investigator
Jenny Crooks	128	Site Investigator
Adrienne Curtis	128	Site Investigator
Jenny de Souza (Keylock)	128	Site Investigator
John Piedad	128	Site Investigator
Hugh Rickards	128	Site Investigator
Jan Wright	128	Site Investigator
Diane Haig-Brown	129,154	Site Investigator
Janet Craven	129,154	Site Investigator
Andrew Pallett	129	Site Investigator
Steve Simpson	129,154	Site Investigator
Rebecca Weekes	129,154	Site Investigator
Elizabeth Coulthard	130	Site Investigator
Louise Gethin	130	Site Investigator
Beverley Hayward	130	Site Investigator
Kasia Sieradzan	130	Site Investigator
Abigail Wright	130,163	Site Investigator, Language Coordinator
Roger A. Barker	131	Site Investigator
Deidre O'Keefe	131	Site Investigator
Anna Gerrtiz (nee Di Pietro)	131	Site Investigator
Kate Fisher	131	Site Investigator
Anna Goodman	131	Site Investigator
Susan Hill	131	Site Investigator
Sarah Mason	131	Site Investigator
Rachel Swain	131	Site Investigator
Natalie Valle Guzman	131	Site Investigator
Jonathan Bisson	132	Site Investigator
Monica Busse	132	Site Investigator
Cynthia Butcher	132	Site Investigator
Jenny Callaghan	132,149	Site Investigator, Language Coordinator
Rebecca Cousins	132	Site Investigator
Stephen Dunnett	132	Site Investigator, REGISTRY Steering Committee
Catherine Clenaghan	132	Site Investigator
Ruth Fullam	132,149	Site Investigator, Language Coordinator
Sarah Hunt	132	Site Investigator
Lesley Jones	132	Site Investigator
Una Jones	132	Site Investigator
Hanan Khalil	132	Site Investigator
Sara Minster	132,163	Site Investigator, Language Coordinator
Michael Owen	132	Site Investigator
Kathleen Price	132	Site Investigator
Jenny Townhill	132,163	Site Investigator, Language Coordinator
Anne Rosser	132	Site Investigator
David Goudie	133	Site Investigator
Lindsay Buchanan	133	Site Investigator
Paula McFadyen	133	Site Investigator
Alison Tonner	133	Site Investigator
Anne-Marie Taylor	133	Site Investigator
Maureen Edwards	134	Site Investigator
Carrie Ho (Scottish Huntington´s Association)	134	Site Investigator
Marie McGill	134	Site Investigator
Mary Porteous	134	Site Investigator
Pauline Pearson	134	Site Investigator
Sarah Irvine	135	Site Investigator
Peter Brockie	136	Site Investigator
Jillian Foster	136	Site Investigator
Nicola Johns	136	Site Investigator
Sue McKenzie	136	Site Investigator
Jean Rothery	136	Site Investigator
Gareth Thomas	136	Site Investigator
Shona Yates	136	Site Investigator
Christian Neumann	137	Site Investigator
Kirsten Patterson	137	Site Investigator
David Thomson	137	Site Investigator
Catherine Deith	138	Site Investigator
Jane Ireland	138	Site Investigator
Stuart Ritchie	138	Site Investigator
Pauline Brown	139	Site Investigator
Liz Burrows	139	Site Investigator
Amy Fletcher	139	Site Investigator
Alison Harding	139	Site Investigator

Name	Location	Contribution/Role
Kaye Harrison	139	Site Investigator
Fiona Laver	139	Site Investigator
Mark Silva	139	Site Investigator
Aileen Thomson	139	Site Investigator
Carol Chu	140	Site Investigator
Carole Evans	140	Site Investigator
Deena Gallentree	140	Site Investigator
Stephanie Hamer	140,142	Site Investigator
Alison Kraus	140,142	Site Investigator
Ivana Markova	140,142	Site Investigator
Ashok Raman	140,142	Site Investigator
Liz Rowett	140,142	Site Investigator
Alyson Andrew	141	Site Investigator
Julie Frost	141	Site Investigator
Rupert Noad	141	Site Investigator
Jeremy Cosgrove	142	Site Investigator
Deena Gallantree	142	Site Investigator
Emma Hobson	142	Site Investigator
Stuart Jamieson	142	Site Investigator
Mandy Longthorpe	142	Site Investigator
Hannah Musgrave	142	Site Investigator
Caroline Peacy	142	Site Investigator
Jean Toscano	142	Site Investigator
Sue Wild	142	Site Investigator
Pam Yardumian	142	Site Investigator
Carole Clayton	143	Site Investigator
Heather Dipple	143	Site Investigator
Dawn Freire-Patino	143	Site Investigator
Caroline Hallam	143	Site Investigator
Julia Middleton	143	Site Investigator
Sundus Alusi	144	Site Investigator
Rhys Davies	144	Site Investigator
Kevin Foy	144	Site Investigator
Emily Gerrans	144	Site Investigator
Louise Pate	144	Site Investigator
Uruj Anjum	145	Site Investigator
Jan Coebergh	145	Site Investigator
Charlotte Eddy	145	Site Investigator
Nayana Lahiri	145,147	Site Investigator
Meriel McEntagart	145	Site Investigator
Michael Patton	145	Site Investigator
Maria Peterson	145	Site Investigator
Sarah Rose	145	Site Investigator
Thomasin Andrews	146,147	Site Investigator
Andrew Dougherty	146	Site Investigator
Charlotte Golding	146,147	Site Investigator
Fred Kavalier	146	Site Investigator
Hana Laing	146	Site Investigator
Alison Lashwood	146	Site Investigator
Dene Robertson	146	Site Investigator
Deborah Ruddy	146	Site Investigator
Alastair Santhouse	146	Site Investigator
Anna Whaite	146	Site Investigator
Stefanie Gosling (nee Brown)	147	Site Investigator
Stefania Bruno	147	Site Investigator
Elvina Chu	147,151	Site Investigator
Karen Doherty	147	Site Investigator
Salman Haider	147	Site Investigator
Davina Hensman	147	Site Investigator
Monica Lewis	147	Site Investigator
Marianne Novak	147	Site Investigator
Aakta Patel	147	Site Investigator
Nicola Robertson	147	Site Investigator
Elisabeth Rosser	147	Site Investigator
Sarah Tabrizi	147	Site Investigator, REGISTRY Steering Committee
Rachel Taylor	147	Site Investigator
Thomas Warner	147	Site Investigator
Edward Wild	147	Site Investigator
Oda Ackermann	148	Site Investigator
Sophie Duport	148	Site Investigator
Adrienne Scott	148	Site Investigator
Nicholas Stoy	148	Site Investigator
Jenny Vaughn	148	Site Investigator
Natalie Arran	149	Site Investigator

Name	Location	Contribution/Role
Judith Bek	149	Site Investigator
David Craufurd	149	Site Investigator
Marianne Hare	149,155	Site Investigator
Liz Howard	149	Site Investigator
Susan Huson	149	Site Investigator
Liz Johnson	149	Site Investigator
Mary Jones	149	Site Investigator
Ashok Krishnamoorthy	149	Site Investigator
Helen Murphy	149	Site Investigator
Emma Oughton	149	Site Investigator
Lucy Partington-Jones	149	Site Investigator
Dawn Rogers	149,163	Site Investigator, Language Coordinator
Andrea Sollom	149	Site Investigator
Julie Snowden	149	Site Investigator
Cheryl Stopford	149	Site Investigator
Jennifer Thompson	149	Site Investigator
Iris Trender-Gerhard	149	Site Investigator
Nichola Verstraelen (formerly Ritchie)	149	Site Investigator
Leann Westmoreland	149	Site Investigator
Ginette Cass	150	Site Investigator
Lynn Davidson	150	Site Investigator
Jill Davison	150	Site Investigator
Neil Fullerton	150	Site Investigator
Katrina Holmes	150	Site Investigator
Suresh Komati	150	Site Investigator
Sharon McDonnell	150	Site Investigator
Zeid Mohammed	150	Site Investigator
Karen Morgan	150	Site Investigator
Lois Savage	150	Site Investigator
Baldev Singh	150	Site Investigator
Josh Wood	150	Site Investigator
Caroline Knight	151	Site Investigator
Mari O'Neill	151	Site Investigator
Debasish Das Purkayastha	151	Site Investigator
Andrea H Nemeth	152	Site Investigator
Gill Siuda	152	Site Investigator
Ruth Valentine	152	Site Investigator
Kathryn Dixon	152,156	Site Investigator
Richard Armstrong	152,156	Site Investigator
David Harrison	153	Site Investigator
Max Hughes	153	Site Investigator
Sandra Large	153	Site Investigator
John O Donovan	153	Site Investigator
Amy Palmer	153	Site Investigator
Andrew Parkinson	153	Site Investigator
Beverley Soltysiak	153	Site Investigator
Leanne Timings	153	Site Investigator
Josh Williams	153	Site Investigator
John Burn	154	Site Investigator
Wendy Bailey	154	Site Investigator
Caroline Coleman	154	Site Investigator
Tahir Majeed	155	Site Investigator
Nicola Verstraelen (Ritchie)	155	Site Investigator
Wendy Barrett	156	Site Investigator
Aileen Ho	156	Site Investigator
Oliver Bandmann	157	Site Investigator
Alyson Bradbury	157	Site Investigator
Helen Fairtlough	157	Site Investigator
Kay Fillingham	157	Site Investigator
Isabella Foustanos	157	Site Investigator
Paul Gill	157	Site Investigator
Mbombe Kazoka	157	Site Investigator
Kirsty O'Donovan	157	Site Investigator
Louise Nevitt	157	Site Investigator
Nadia Peppa	157,163	Site Investigator, Language Coordinator
Oliver Quarrell	157	Site Investigator, REGISTRY Steering Committee
Cat Taylor	157	Site Investigator
Katherine Tidswell	157	Site Investigator
Christopher Kipps	158	Site Investigator
Lesley MacKinnon	158	Site Investigator
Veena Agarwal	158	Site Investigator
Elaine Hayward	158	Site Investigator
Kerry Gunner	158	Site Investigator
Kayla Harris	158	Site Investigator

Name	Location	Contribution/Role
Mary Anderson	158	Site Investigator
Melanie Heywood	158	Site Investigator
Liane Keys	158	Site Investigator
Sarah Smalley	158	Site Investigator
George El-Nimr	159	Site Investigator
Allison Duffell	159	Site Investigator
Sue Wood	159	Site Investigator
Karen Kennedy (nee Smith)	159	Site Investigator
Lesley Gowers	160	Site Investigator
Kingsley Powell	160	Site Investigator
Pamela Bethwaite	160	Site Investigator
Rachel Edwards	160	Site Investigator
Kathleen Fuller	160	Site Investigator
Michelle Phillips	160	Site Investigator
Louis Tan	161	Site Investigator
Puay Ngoh Lau	161	Site Investigator
Emmanuel Pica	161	Site Investigator
Ida Biunno	162	Site Investigator, REGISTRY Steering Committee
Juliana Bronzova	163	Site Investigator, REGISTRY Steering Committee
Joe Giuliano	164	Site Investigator, REGISTRY Steering Committee
Olivia J. Handley	163	Site Investigator, REGISTRY Steering Committee
Torsten Illmann	165	Site Investigator, REGISTRY Steering Committee
Jamie Levey	163	Site Investigator, REGISTRY Steering Committee
Tim McLean	163	Site Investigator, REGISTRY Steering Committee
Susana Pro Koivisto	163,167	Site Investigator, REGISTRY Steering Committee, Language Coordinator
Markku Päivärinta	168	Site Investigator, REGISTRY Steering Committee
Tereza Uhrova	169	Site Investigator, REGISTRY Steering Committee
Verena Baake (formerly Rödig)	163	Site Investigator, Language Coordinator
Katrin Barth	163	Site Investigator, Language Coordinator
Monica Bascuñana Garde	163	Site Investigator, Language Coordinator
Kristina Becanovic	163	Site Investigator, Language Coordinator
Tomáš Bernard	163	Site Investigator, Language Coordinator
Sabrina Betz	163	Site Investigator, Language Coordinator
Adrien Come	163	Site Investigator, Language Coordinator
Selene Capodarca	163	Site Investigator, Language Coordinator
Sébastien Charpentier	163	Site Investigator, Language Coordinator
Wildson Vieira da Silva	163	Site Investigator, Language Coordinator
Martina Di Renzo	163	Site Investigator, Language Coordinator
Ana Maria Finisterra	163	Site Investigator, Language Coordinator
Camille Genoves	163	Site Investigator, Language Coordinator
Mette Gilling	163	Site Investigator, Language Coordinator
Olivia J Handley	163	Site Investigator, Language Coordinator
Carina Hvalstedt	163	Site Investigator, Language Coordinator
Hasina Hussain	163	Site Investigator, Language Coordinator
Kerstin Koppers	163	Site Investigator, Language Coordinator
Claudia Lamanna	163	Site Investigator, Language Coordinator

Name	Location	Contribution/Role
Matilde Laurà	163	Site Investigator, Language Coordinator
Kristina Münkel	163	Site Investigator, Language Coordinator
Lisanne Mütze	163	Site Investigator, Language Coordinator
Martin Oehmen	163	Site Investigator, Language Coordinator
Helene Padieu	163	Site Investigator, Language Coordinator
Laurent Paterski	163	Site Investigator, Language Coordinator
Beate Rindal	163	Site Investigator, Language Coordinator
Niini Røren (formerly Heinonen)	163	Site Investigator, Language Coordinator
Ana Salgueiro	163	Site Investigator, Language Coordinator
Pavla Šašinková	163	Site Investigator, Language Coordinator
Catherine Taylor	163	Site Investigator, Language Coordinator
Erika Timewell	163	Site Investigator, Language Coordinator
Marleen R van Walsem	163	Site Investigator, Language Coordinator
Marie-Noelle Witjes-Ané	163	Site Investigator, Language Coordinator
Daniel Zielonka	163	Site Investigator, Language Coordinator
Eugeniusz Zielonka	163	Site Investigator, Language Coordinator

Affiliations:

1: Graz (Medizinische Universitäts Graz, Psychiatrie), Austria
2: Innsbruck (Universitätsklinik Innsbruck, Neurologie), Austria
3: Salzburg (Christian-Doppler-Klinik Salzburg, Universitätsklinikum der PMU, Universitätsklinik für Neurologie), Austria
4: Vienna-UNI , Austria
5: Bierbeek, Belgium
6: Bruxelles (Vrije Universiteit Brussel), Belgium
7: Bruxelles (Erasmes) , Belgium
8: Bruxelles (St-Luc), Belgium
9: Charleroi (Institut de Pathologie et de Génétique (IPG)), Belgium
10: Leuven (Universitair Ziekenhuis Gasthuisberg), Belgium
11: Olomouc (Neurologická klinika, Fakultní nemocnice Olomouc), Czech Republic
12: Prague (Extrapyramidové centrum, Neurologická klinika, 1. LF UK a VFN), Czech Republic
13: Aarhus (Aarhus University Hospital), Denmark
14: Copenhagen University Hospital (Rigshospitalet, Memory clinic), Denmark
15: Odense (Odense University Hospital), Denmark
16: Aland, Finland
17: Helsinki - Vaestoliitto (Department of Medical Genetics), Finland
18: Kuopio: Anu Bruun, Finland
19: Oulu (Dep. of Neurology), Finland

20: Oulu (Dep. of Medical Genetics), Finland
21: Tampere (Terveystalo Healthcare Service Centre), Finland
22: Turku-Suvituuli (Rehabilitation Centre Suvituuli), Finland
23: Angers (Centre de référence des maladies neurogénétique- CHU d'Angers), France
24: Bordeaux (Hôpital Pellegrin), France
25: Clermont-Ferrand (Hôpital Gabriel Montpied), France
26: Creteil (Hôpital Henri Mondor), France
27: Lille-Amiens (Lille (CHRU Roger Salengro)) , France
28: Lille-Amiens (Amiens (CHU Sud)) , France
29: Marseille (Hôpital La Timone), France
30: Paris (Hôpital de la Pitié Salpêtrière), France
31: Rouen (Hôpital Charles Nicolle), France
32: Strasbourg (Hôpital Civil), France
33: Toulouse (Hôpital Purpan), France
34: Aachen (Universitätsklinikum Aachen, Neurologische Klinik), Germany
35: Berlin (Universitätsmedizin Berlin, Klinik und Poliklinik für Neurologie), Germany
36: Bochum (Huntington-Zentrum (NRW) Bochum im St. Josef-Hospital), Germany
37: Bremen, Germany
38: Dinslaken (Reha Zentrum in Dinslaken im Gesundheitszentrums Lang), Germany
39: Dresden (Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Klinik und Poliklinik für Neurologie), Germany
40: Erlangen (Universitätsklinikum Erlangen, Molekulare Neurologie und Klinik für Neurologie), Germany
41: Freiburg (Universitätsklinik Freiburg, Neurologie), Germany
42: Hamburg (Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Neurologie), Germany
43: Hannover (Neurologische Klinik mit Klinischer Neurophysiologie, Medizinische Hochschule Hannover), Germany
44: Itzehoe (Schwerpunktpraxis Huntington Neurologie und Psychiatrie), Germany
45: Marburg KPP (Klinik für Psychiatrie und Psychotherapie Marburg-Süd), Germany
46: Marburg UNI (Universitätsklinik Marburg, Sprechstunde für choreatiforme Bewegungsstörungen), Germany
47: München (Huntington-Ambulanz im Neuro-Kopfzentrum - Klinikum rechts der Isar der Neurologischen Klinik und Poliklinik der Technischen Universität München), Germany
48: Münster (Universitätsklinikum Münster, Klinik und Poliklinik für Neurologie), Germany
49: Taufkirchen (Isar-Amper-Klinikum - Klinik Taufkirchen (Vils)), Germany
50: Ulm (Universitätsklinikum Ulm, Neurologie), Germany
51: Würzburg (Universitätsklinikum Würzburg, Neurologie), Germany
52: Bari (Neurophysiopathology of Pain Unit, Basic Medical, Neuroscience and Sensory System Department, University of Bari), Italy

53: Bologna (DIBINEM - Alma Mater Studiorum - Università di Bologna, IRCCS Istituto delle Scienze Neurologiche di Bologna), Italy
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56: Florence (Department of NEUROFARBA, University of Florence & Careggi University Hospital, IRCSS " Don Gnocchi "), Italy
57: Genoa (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova), Italy
58: Milan (SODS Genetica delle Malattie Neurodegenerative e Metaboliche & U.O. Neurologia, Fondazione IRCCS Istituto Neurologico Carlo Besta), Italy
59: Naples (Department of Neurosciences and Reproductive and Odontostomatological Sciences Federico II University of Naples), Italy
60: Pozzilli (IS) (IRCCS Neuromed), Italy
61: IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy
62: Rome (LIRH Foundation), Italy
63: Rome (Department of Neurology, Università Cattolica del Sacro Cuore; Institute of Translational Pharmacology & Institute of Cognitive Sciences and Technologies, National Research Council of Italy), Italy
64: Rome (Azienda Ospedaliera Sant'Andrea; Department of Neuroscience, Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University of Rome; Institute of Translational Pharmacology & Institute of Cognitive Sciences and Technologies, National Research Council of Italy), Italy
65: Enschede (Medisch Spectrum Twente), Netherlands
66: Groningen (Polikliniek Neurologie), Netherlands
67: Leiden (Leiden University Medical Centre (LUMC)), Netherlands
68: Maastricht, Netherlands
69: Nijmegen (Universitair Medisch Centrum St. Radboud, Neurology), Netherlands
70: Bergen (Haukeland University Hospital, Dept of Medical Genetics and Olaviken Psychiatric Hospital), Norway
71: Bergen (NKS Olaviken`s HD clinic), Norway
72: Oslo University Hospital (Dept. of Medical Genetics, Dept. of Neurology, Dept.of Neurorehabilitation), Norway
73: Trondheim (St. Olavs Hospital), Norway
74: Gdansk (St. Adalbert Hospital, Gdansk, Medical University of Gdansk, Neurological and Psychiatric Nursing Dpt.), Poland
75: Katowice (Medical University of Silesia, Katowice), Poland
76: Krakow (Krakowska Akademia Neurologii), Poland
77: Poznan (Poznan University of Medical Sciences), Poland

78: Warsaw-MU (Medical University of Warsaw, Neurology), Poland
79: Warsaw-IPiN (Institute of Psychiatry and Neurology Dep. of Genetics, First Dep. of Neurology), Poland
80: Coimbra – (Hospital Universitário de Coimbra), Portugal
81: Lisbon-Central (Hospital dos Capuchos, Centro Hositalar Lisboa Central), Portugal
82: Lisbon-HSM (Hospital de Santa Maria, Clinical Pharmacology Unit, Instituto de Medicina Molecular), Portugal
83: Lisbon-HFF (Hospital Fernando da Fonseca), Portugal
84: Porto-HGSA (Hospital Santo António- Centro Hospitalar do Porto), Portugal
85: Porto- HSJ (Hospital de São João), Portugal
86: Kazan, Russian Federation
87: Moscow – (Research Center of Neurology) , Russian Federation
88: Nizhny Novgorod – (Nizhny Novgorod Medical Academy, Neurology Department), Russian Federation
89: Ufa – (Bashkir State Medical University, Department of Neurology, Neurosurgery, and Medical Genetics), Russian Federation
90: Voronezh, Russian Federation
91: Alicante-Alcoy (Hospital Virgen de los Lirios), Spain
92: Badajoz (Hospital Infanta Cristina), Spain
93: Barcelona-Bellvitge (Hospital Universitari de Bellvitge), Spain
94: Barcelona- Clínic i Provincial (Hospital Clínic i Provincial), Spain
95: Barcelona-Hospital Mútua de Terrassa, Spain
96: Barcelona-Merced (Hospital Mare de Deu de La Merced), Spain
97: Barcelona-Santa Cruz y San Pablo (Hospital de la Santa Creu i Sant Pau), Spain
98: Bilbao (Hospital de Cruces), Spain
99: Burgos (Servicio de Neurología Hospital General Yagüe), Spain
100: Canarias (Hospital Insular de Gran Canaria), Spain
101: Fuenlabrada (Hospital Universitario), Spain
102: Granada (Hospital Universitario San Cecilio, Neurología), Spain
103: Madrid-BTCIEN (Fundación CIEN), Spain
104: Madrid-Clínico (Hospital Clínico Universitario San Carlos), Spain
105: Madrid RYC (Hospital Ramón y Cajal, Neurología), Spain
106: Madrid FJD (Madrid-Fundación Jiménez Díaz), Spain
107: Murcia (Hospital Universitario Virgen de la Arrixaca), Spain
108: Oviedo (Hospital Central de Asturias), Spain
109: Palma de Mallorca (Hospital Universitario Son Espases), Spain
110: Pamplona (Complejo Hospitalario de Navarra), Spain
111: Sevilla (Hospital Universitario Virgen del Rocío), Spain
112: Sevilla (Hospital Virgen Macarena), Spain
113: Sevilla (Residencia Santa Ana), Spain

114: Valencia (Hospital la Fe), Spain
115: Zaragoza (Hospital Clínico), Spain
116: Göteborg (Sahlgrenska University Hospital), Sweden
117: Lund (Dept Neurology, Skånes Universityhospital), Sweden
118: Stockholm-Ersta, Sweden
119: Stockholm Karolinska University Hospital, Sweden
120: Umeå (Umeå University Hospital), Sweden
121: Uppsala University Hospital, Sweden
122: Bern (Swiss HD Zentrum), Switzerland
123: Bern (Zentrum für Bewegungsstörungen, Neurologische Klinik und Poliklinik, Universität Bern), Switzerland
124: Lausanne, Switzerland
125: Zürich (University Hospital and University of Zurich), Switzerland
126: Aberdeen (NHS Grampian Clinical Genetics Centre & University of Aberdeen), UK
127: Barnstaple, UK
128: Birmingham (The Barberry Centre, Dept of Psychiatry), UK
129: Blanford Forum, UK
130: Bristol (North Bristol NHs Trust, Southmead hospital), UK
131: Cambridge (Cambridge Centre for Brain Repair, Forvie Site), UK
132: Cardiff (Schools of Medicine and Biosciences, Cardiff University), UK
133: Dundee (Scottish Huntington's Association, Ninewells Hospital), UK
134: Edinburgh (SE Scotland Genetic Service, Western General Hospital), UK
135: Exeter (Department of Neurology Royal Devon and Exeter Foundation Trust Hospital), UK
136: Fife (Scottish Huntington's Association Whyteman's Brae Hospital), UK
137: Forth Valley (Neurology Department, Forth Valley Royal Hospital), UK
138: Glasgow (Glasgow HD Management Clinic, Southern General Hospital), UK
139: Gloucester (Department of Neurology Gloucestershire Royal Hospital), UK
140: Hull (Castle Hill Hospital), UK
141: Launceston (Millaton Court), UK
142: Leeds (Chapel Allerton Hospital, Department of Clinical Genetics), UK
143: Leicester (Leicestershire Partnership Trust, Mill Lodge), UK
144: Liverpool (Walton Centre for Neurology and Neurosurgery), UK
145: London (St. Georges-Hospital), UK
146: London (Guy's Hospital), UK
147: London (The National Hospital for Neurology and Neurosurgery), UK
148: London (Royal Hospital for Neuro-disability), UK
149: Manchester (Genetic Medicine, University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust), UK
150: Newcastle-upon-Tyne (Centre for Life, Institute of Medical Genetics), UK
151: Northampton (St Andrew’s Healthcare), UK

152: Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford), UK
153: Plymouth (Plymouth Huntington Disease Service, Mount Gould Hospital), UK
154: Poole (Brain Injury Service, Poole Hospital), UK
155: Preston (Neurology Department, Preston Royal Hospital), UK
156: Reading (Royal Berkshire Hospital), UK
157: Sheffield (The Royal Hallamshire Hospital– Sheffield Children's Hospital), UK
158: Southampton (Southampton General Hospital), UK
159: Stoke on Trent (Bucknall Hospital), UK
160: Swindon (Victoria Centre, Great Western Hospital), UK
161: EHDN's associate site in Singapore: National Neuroscience Institute Singapore,
162: Institute for Genetic and Biomedical Research, University of Milan, Italy
163: European Huntington's Disease Network (EHDN), Ulm, Germany,
164: CHDI Foundation, Inc., New York, USA
165: 2mt Software GmbH, Ulm, Germany
166: Clinic of Neurology, Charles University and General Teaching Hospital, Prague, Czech Republic, Czech Republic
167: Center for Rare Disorders, Oslo University Hospital HF, Rikshospitalet, Norway
168: Department of Neurology, Turku University Hospital, Turku, Finland
169: Clinic of Psychiatry, Charles University and General Teaching Hospital, Prague, Czech Republic

Appendix 3 – Huntington's disease clinical characteristics questionnaire (HD-CCQ) questions

Symptom	Question
Motor	Have motor symptoms compatible with HD ever been a part of the subject's medical history? At what age did the subject's motor symptoms begin?
Cognitive	Has significant cognitive impairment (severe enough to impact on work or activities of daily living) or dementia ever been a part of the subject's medical history? At what age did cognitive impairment first start to have an impact on daily life?
Apathy	Has apathy ever been a part of the subject's medical history? At what age did apathy begin?
Depression	Has depression (includes treatment with antidepressants with or without a formally-stated diagnosis of depression) ever been a part of the subject's medical history? At what age did the depression begin?
Perseverative/ obsessive behaviours (POB)	Has perseverative/obsessive behaviours ever been a part of the subject's medical history? At what age did perseverative/obsessive behaviour begin?
Irritability	Has irritability ever been a part of the subject's medical history? At what age did the irritability begin?
Violent or aggressive behaviour (VAB)	Has violent or aggressive behaviour ever been a part of the subject's medical history? At what age did violent or aggressive behaviour begin?
Psychosis	Has psychosis (hallucinations or delusions) ever been a part of the subject's medical history? At what age did psychosis (hallucinations or delusions) begin?

Questionnaire taken from the European Huntington's Disease Network's (EHDN) data dictionary for Registry (Version 3).

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Tables

	TDS (N=2403)		TIS (N=2403)		SDMT (N=3137)		Stroop Interference (N=3273)	
	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*
Motor	0.15 (±1.85)	8.71×10^{-1}	0.67 (±1.93)	4.93×10^{-1}	-12.37 (±3.90)	**5.62×10^{-10}**	-9.34 (±3.76)	**1.19×10^{-6}**
Cognitive	0.38 (±0.39)	5.28×10^{-2}	-0.41 (±0.40)	*4.53×10^{-2}*	-3.52 (±0.81)	**2.28×10^{-17}**	-3.41 (±0.76)	**3.29×10^{-18}**
Apathy	1.73 (±0.40)	**4.05×10^{-17}**	0.48 (±0.42)	*2.36×10^{-2}*	-2.70 (±0.83)	**2.37×10^{-10}**	-2.15 (±0.79)	**1.00×10^{-7}**
Depression	1.49 (±0.40)	**5.67×10^{-13}**	1.13 (±0.42)	**1.37×10^{-7}**	-0.09 (±0.84)	8.41×10^{-1}	-0.53 (±0.79)	1.88×10^{-1}
POB	-0.15 (±0.42)	4.96×10^{-1}	0.04 (±0.44)	8.70×10^{-1}	-1.28 (±0.85)	*3.26×10^{-3}*	-1.10 (±0.80)	*7.45×10^{-3}*
Irritability	0.15 (±0.43)	4.97×10^{-1}	1.82 (±0.45)	**1.99×10^{-15}**	1.28 (±0.89)	*4.52×10^{-3}*	1.01 (±0.84)	*1.76×10^{-2}*
VAB	0.72 (±0.47)	*2.65×10^{-3}*	1.57 (±0.49)	**3.29×10^{-10}**	-1.24 (±0.97)	*1.26×10^{-2}*	-1.20 (±0.92)	*1.06×10^{-2}*
Psychosis	-0.45 (±0.68)	1.98×10^{-1}	-0.50 (±0.71)	1.67×10^{-1}	-2.53 (±1.38)	**3.38×10^{-4}**	-3.18 (±1.28)	**1.07×10^{-6}**
Age	0.01 (±0.02)	2.18×10^{-1}	-0.09 (±0.02)	**8.17×10^{-13}**	-0.53 (±0.05)	**1.02×10^{-99}**	-0.52 (±0.05)	**2.89×10^{-104}**
CAG	-0.03 (±0.06)	3.54×10^{-1}	-0.21 (±0.07)	**1.17×10^{-9}**	-1.56 (±0.14)	**3.97×10^{-102}**	-1.25 (±0.13)	**2.38×10^{-71}**
Sex (F)	-0.12 (±0.37)	5.17×10^{-1}	0.35 (±0.38)	7.14×10^{-2}	-1.28 (±0.76)	**9.73×10^{-4}**	-1.22 (±0.72)	**9.13×10^{-4}**
Duration	0.05 (±0.04)	*5.62×10^{-3}*	0.02 (±0.04)	3.08×10^{-1}	-0.41 (±0.08)	**4.78×10^{-25}**	-0.32 (±0.07)	**4.82×10^{-18}**

Table 1. Association of validated clinical scores with the HD Clinical Characteristics Questionnaire symptoms (shown in italics), and other covariates. For binary covariates (CCQ symptoms and sex) "effect" is the increase/decrease in the clinical score associated with presence of that covariate. For quantitative covariates (age, CAG, duration), "effect" is the change in clinical score associated with an increase of one unit in the covariate. In addition to having a confirmed onset and pathogenic CAG length (36-93), individuals must have no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. Significant associations after Bonferroni correction for 4 phenotypes and 12 covariates are shown in bold ($P < 1.04 \times 10^{-3}$) and nominally significant P values are italicised ($P < 0.05$). CI: confidence interval; TDS: Total depression score from the Hospital Anxiety and Depression Scale; TIS: Total irritability score from Snaith's irritability scale; SDMT: Symbol digits modalities test; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour; Sex (F): female.

	Males			Females			OR (95% CI)	*P* value (c^2)
	Yes	No	Frequency	Yes	No	Frequency		
Motor	2691	28	98.97%	2859	25	99.13%	1.19 (0.69 - 2.05)	5.29×10^{-1}
Cognitive	1584	1132	58.32%	1688	1187	58.71%	1.02 (0.91 - 1.13)	7.66×10^{-1}
Apathy	1456	1259	53.63%	1495	1374	52.11%	0.94 (0.85 - 1.05)	2.56×10^{-1}
Depression	1582	1135	58.23%	2025	853	70.36%	1.70 (1.52 - 1.90)	**2.57×10^{-21}**
POB	1005	1711	37.00%	1038	1834	36.14%	0.96 (0.86 - 1.07)	5.04×10^{-1}
Irritability	1706	1006	62.91%	1634	1240	56.85%	0.78 (0.70 - 0.87)	**4.03×10^{-6}**
VAB	947	1769	34.87%	777	2100	27.01%	0.69 (0.62 - 0.77)	**1.99×10^{-10}**
Psychosis	319	2396	11.75%	325	2549	11.31%	0.96 (0.81 - 1.13)	6.06×10^{-1}

Table 2. Lifetime prevalence of motor and psychiatric symptoms in males and females with HD. Data from HD Clinical Characteristics Questionnaire at last recorded clinic visit in Registry. Chi-square (c^2) tests the difference between prevalence in males and females. Odds ratios (OR) >1 indicates the symptom is more common in females; odds ratios <1 indicates the symptom is more common in males. To be included, individuals must have a pathogenic CAG length (36-93) and confirmed clinical HD onset. Significant *P* values in bold ($P < 6.25 \times 10^{-3}$, multiple testing correction). CI: confidence interval; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

	Male		Female		*P*	Both	
	R^2 (95% CI)	N	R^2 (95% CI)	N		R^2 (95% CI)	N
Motor	0.678 (0.657 - 0.697)	2684	0.649 (0.628 - 0.670)	2844	5.42×10^{-2}	0.663 (0.648 - 0.677)	5528
Cognitive	0.610 (0.579 - 0.639)	1570	0.629 (0.600 - 0.656)	1681	3.80×10^{-1}	0.619 (0.598 - 0.639)	3251
Apathy	0.595 (0.562 - 0.627)	1423	0.562 (0.528 - 0.595)	1462	1.83×10^{-1}	0.578 (0.554 - 0.601)	2885
Depression	0.412 (0.374 - 0.449)	1551	0.351 (0.318 - 0.385)	1994	*3.50×10^{-2}*	0.375 (0.350 - 0.400)	3545
POB	0.539 (0.496 - 0.581)	973	0.440 (0.394 - 0.485)	1016	**3.67×10^{-3}**	0.489 (0.457 - 0.52)	1989
Irritability	0.463 (0.428 - 0.498)	1670	0.547 (0.513 - 0.579)	1601	**1.25×10^{-3}**	0.503 (0.478 - 0.527)	3271
VAB	0.479 (0.431 - 0.524)	927	0.478 (0.426 - 0.528)	761	9.79×10^{-1}	0.477 (0.442 - 0.511)	1688
Psychosis	0.401 (0.316 - 0.484)	312	0.424 (0.340 - 0.504)	318	7.29×10^{-1}	0.411 (0.351 - 0.469)	630

Table 3. Variance in age at onset (R^2) explained by pathogenic CAG repeat length for eight symptoms in males and females with HD. Ages at onset were logarithmically transformed and plotted against CAG length. *P* values test difference between male and female R^2. Significant *P* values ($P < 6.25 \times 10^{-3}$; multiple testing correction) are in bold and nominally significant *P* values ($P < 0.05$) italicised. Individuals had to have a clinical onset of HD, a known sex and a pathogenic CAG length (36-93) to be included. CI: confidence interval; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

	Motor (N=1644)		Cognitive (N=1644)		Apathy (N=1643)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex (F)	0.49 (0.14 - 1.66)	2.51×10^{-1}	1.20 (0.97 - 1.49)	9.75×10^{-2}	1.07 (0.87 - 1.31)	5.13×10^{-1}
CAG	0.95 (0.83 - 1.10)	5.10×10^{-1}	1.01 (0.98 - 1.03)	6.64×10^{-1}	0.99 (0.96 - 1.01)	2.32×10^{-1}
Duration	0.91 (0.82 - 1.01)	8.32×10^{-2}	1.00 (0.98 - 1.03)	6.99×10^{-1}	1.00 (0.98 - 1.02)	8.96×10^{-1}
Alcohol	1.00 (0.93 - 1.08)	9.61×10^{-1}	1.02 (1.01 - 1.04)	*8.78×10^{-3}*	1.00 (0.99 - 1.02)	5.56×10^{-1}
Tobacco	1.10 (0.96 - 1.26)	1.54×10^{-1}	1.01 (0.99 - 1.02)	3.00×10^{-1}	1.02 (1.00 - 1.03)	*4.94×10^{-3}*
Education	0.89 (0.75 - 1.06)	1.97×10^{-1}	1.01 (0.98 - 1.05)	4.03×10^{-1}	0.98 (0.95 - 1.01)	2.02×10^{-1}
TFC	1.05 (0.75 - 1.46)	7.85×10^{-1}	0.78 (0.74 - 0.81)	**1.58×10^{-25}**	0.87 (0.84 - 0.91)	**1.14×10^{-9}**
TMS	1.17 (1.08 - 1.27)	**7.81×10^{-5}**	1.00 (0.99 - 1.00)	2.67×10^{-1}	1.00 (0.99 - 1.00)	2.59×10^{-1}

	Depression (N=1645)		POB (N=1641)		Irritability (N=1645)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex (F)	1.77 (1.44 - 2.17)	**6.98×10^{-8}**	1.07 (0.86 - 1.32)	5.68×10^{-1}	0.75 (0.61 - 0.92)	*5.36×10^{-3}*
CAG	0.96 (0.93 - 0.98)	**1.32×10^{-4}**	1.00 (0.97 - 1.02)	6.93×10^{-1}	0.99 (0.97 - 1.01)	4.74×10^{-1}
Duration	1.03 (1.01 - 1.05)	*1.10×10^{-2}*	1.03 (1.00 - 1.05)	*1.68×10^{-2}*	1.03 (1.01 - 1.05)	*6.84×10^{-3}*
Alcohol	0.99 (0.98 - 1.01)	2.66×10^{-1}	1.00 (0.99 - 1.02)	5.14×10^{-1}	1.01 (0.99 - 1.02)	4.79×10^{-1}
Tobacco	1.02 (1.01 - 1.03)	*8.14×10^{-4}*	1.01 (1.00 - 1.02)	2.04×10^{-1}	1.02 (1.01 - 1.03)	**1.02×10^{-4}**
Education	0.99 (0.96 - 1.02)	5.83×10^{-1}	1.00 (0.97 - 1.03)	8.21×10^{-1}	1.00 (0.97 - 1.03)	8.44×10^{-1}
TFC	0.90 (0.86 - 0.94)	**7.30×10^{-6}**	0.89 (0.85 - 0.93)	**1.10×10^{-6}**	0.93 (0.89 - 0.97)	*8.83×10^{-4}*
TMS	0.98 (0.98 - 0.99)	**2.59×10^{-5}**	0.99 (0.99 - 1.00)	6.09×10^{-2}	0.99 (0.98 - 1.00)	*7.46×10^{-3}*

	VAB (N=1645)		Psychosis (N=1642)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex (F)	0.75 (0.60 - 0.94)	*1.27×10^{-2}*	0.81 (0.57 - 1.14)	2.23×10^{-1}
CAG	1.00 (0.98 - 1.02)	9.42×10^{-1}	0.99 (0.95 - 1.02)	4.84×10^{-1}
Duration	1.04 (1.02 - 1.06)	*9.10×10^{-4}*	1.02 (0.98 - 1.05)	3.47×10^{-1}
Alcohol	1.00 (0.99 - 1.01)	9.29×10^{-1}	1.02 (1.00 - 1.04)	*3.35×10^{-2}*
Tobacco	1.02 (1.01 - 1.03)	*2.08×10^{-3}*	1.00 (0.98 - 1.02)	8.38×10^{-1}
Education	0.99 (0.95 - 1.02)	3.69×10^{-1}	0.92 (0.88 - 0.97)	*2.24×10^{-3}*
TFC	0.88 (0.84 - 0.93)	**2.07×10^{-7}**	0.83 (0.77 - 0.89)	**3.33×10^{-7}**
TMS	0.99 (0.99 - 1.00)	7.49×10^{-2}	0.99 (0.98 - 1.00)	1.47×10^{-1}

Table 4. Psychiatric and cognitive symptoms are associated with reduced functional capacity. Multiple logistic regression using binary HD-CCQ data for 8 symptoms (0 = no symptom; 1 = reported symptom) and clinical covariates. Significant associations after Bonferroni correction for 8 symptoms and 8 covariates are shown in bold ($P < 7.81 \times 10^{-4}$) and nominally significant associations in italics ($P < 0.05$). With the exception of sex, the odds ratio (OR) indicates the effect on the outcome probability associated with an increase of one unit in the covariate. In addition to having a confirmed onset and pathogenic CAG length (36-93), individuals must have no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. CI: confidence interval; Sex (F): female; POB: perseverative/obsessive behaviour; TFC: total functional capacity; TMS: total motor score; VAB: violent or aggressive behaviour.

Figure Legends

Figure 1. The initial manifestation of HD varies with age and CAG length.

All included individuals had a pathogenic CAG length (36-93) and confirmed HD onset age determined by a rating clinician. **(A)** Frequency of different onset types in four age groups, chosen to show juvenile HD and then 20 year bins for clarity. Total N=6289; <20 years, N=188; 20-40 years, N=2216; 40-60 years, N=3276; >60 years, N=609. **(B)** Frequency of different onset types in six CAG length groups, chosen for clarity across the pathogenic range. Total N=6289; 36-39 CAG, N=156; 40-44 CAG, N=3813; 45-49 CAG, N=1735; 50-54 CAG, N=387; 55-59 CAG, N=97; >60 CAG, N=101.

Figure 2. The onsets of cognitive and psychiatric symptoms relative to motor onset in HD.

The age at onset of motor symptoms was subtracted from the age at onset of each cognitive/psychiatric symptom when present. Timings of up to +/- 40 years relative to motor onset shown. Only individuals with a rater-confirmed age at onset and CAG length (36-93) were included. Data from HD-CCQ. (**A**) Cognitive impairment N=3225; (**B**) Apathy N=2852; (**C**) Depression N=3495; (**D**) Irritability N=3235.

Figure 3. Mean ages at onset for motor and psychiatric symptoms at different CAG repeat lengths.

Shown are the mean ages at symptom onset as recorded by the HD Clinical Characteristics Questionnaire for apathy (N = 2739), cognitive impairment (N = 3069), depression (N = 3399), irritability (N = 3117) and motor symptoms (N = 4889).