

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/132820/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

McAllister, Branduff, Gusella, James F., Landwehrmeyer, G. Bernhard, Lee, Jong-Min, MacDonald, Marcy E., Orth, Michael, Rosser, Anne E., Williams, Nigel M., Holmans, Peter, Jones, Lesley and Massey, Thomas H. 2020. The onset and prevalence of motor and psychiatric symptoms in Huntington's disease. BioRxiv 10.1101/2020.05.26.116798 file

Publishers page:

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



The onset and prevalence of motor and psychiatric symptoms in Huntington's disease

Branduff McAllister, BSc, PhD¹, James F. Gusella, PhD², G. Bernhard Landwehrmeyer, MD PhD³, Jong-Min Lee, PhD², Marcy E. MacDonald, PhD², Michael Orth, MD PhD⁴, Anne E. Rosser, MB BChir, FRCP, PhD^{5,6}, Nigel M. Williams, BSc, PhD¹, REGISTRY Investigators of the European Huntington's disease network⁷, Peter Holmans, BA, PhD¹, Lesley Jones, BSc, PhD^{1*} & Thomas H. Massey, MA, BM BCh, DPhil^{1*}

1 Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom

2 Molecular Neurogenetic Unit, Center for Genomic Medicine, Massachusetts General Hospital and Department of Genetics, Harvard Medical School, Boston MA 02114 USA

3 University of Ulm, Department of Neurology, Ulm, Germany

4 Swiss Huntington's disease Centre, Siloah, Bern, Switzerland

5 Brain Repair Group, Schools of Medicine and Biosciences, Cardiff University, Cardiff, United Kingdom

6 Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, United Kingdom

7 <http://www.ehdn.org/wp-content/uploads/REGISTRY-contributors-full-list.pdf>. See Appendix

* Corresponding authors

Lesley Jones, Hadyn Ellis Building, Cardiff University, Cardiff CF24 4HQ, United Kingdom.

Phone: 00442920688469. Email: JonesL1@cardiff.ac.uk

Thomas Massey, Hadyn Ellis Building, Cardiff University, Cardiff CF24 4HQ, United Kingdom.

Phone: 00442920688353. Email: MasseyT1@cardiff.ac.uk

Word count: 3634

Running title: Onset and type of symptoms in Huntington's disease

Key words: Huntington, onset, symptom, psychiatric

Financial disclosures related to this manuscript: none

Funding sources: BMc was supported by a PhD studentship from Cardiff University School of Medicine. TM was supported by a Welsh Clinical Academic Track Fellowship, an MRC Clinical Training Fellowship (MR/P001629/1) and a Patrick Berthoud Charitable Trust Fellowship through the Association of British Neurologists. LJ, NW and PH were supported by an MRC Centre grant (MR/L010305/1).

Abstract

Background

Huntington's disease is characterised by a range of motor, psychiatric and cognitive symptoms. These present in different combinations through the disease course and impact on daily life and functioning. Huntington's disease is caused by a dominant CAG repeat expansion in the *HTT* gene, and longer repeats are associated with earlier onset of motor symptoms.

Objectives

To investigate the onset, prevalence and functional impact of motor and psychiatric symptoms of Huntington's disease.

Methods

We analysed clinical phenotype data from the European REGISTRY study for 6316 individuals with manifest Huntington's disease. Onset and prevalence data for motor and psychiatric symptoms were extracted from the clinical history part of REGISTRY and the detailed Clinical Characteristics Questionnaire. Generalised linear models were constructed to assess relationships between symptoms and functional outcomes.

Results

As age at first presentation of Huntington's disease increases, the likelihood that the initial presenting symptom is motor also increases. This is not associated with pathogenic CAG repeat length. At a population level there were conserved relationships between symptoms across different repeat lengths, with depression often occurring early followed by motor and then cognitive symptoms. There were significant relationships between all individual psychiatric and cognitive symptoms and reduced functional capacity.

Conclusions

There are conserved patterns of symptoms in HD that can be quantified. Psychiatric and behavioural symptoms significantly impair daily functioning and should be considered part of the disease trajectory at any age.

Introduction

Huntington's disease (HD) is an autosomal dominant central neurodegeneration caused by an expanded CAG tract in exon 1 of the *Huntingtin* gene (*HTT*)¹. Degeneration is most prominent in the medium spiny neurons of the striatum but occurs widely in the brain, leading to a progressive movement disorder, usually involving chorea, cognitive decline and ultimately death. In addition, individuals with HD develop a variable constellation of debilitating behavioural and psychiatric symptoms alongside their motor problems^{2,3}. The length of the CAG expansion is inversely correlated with the age at onset of disease symptoms and accounts for up to 70% of the variance observed in motor onset, as determined by a clinical rater⁴⁻⁹.

Clinical onset of the first symptom of HD has been used as a specific identifiable milestone in the natural history of the disease in an individual. It has proven particularly useful in recent studies of genes that modify the onset of HD^{10,11}, although it is only a crude measure of the lifelong pathological process. Onset information is typically recorded by a rating physician in observational studies such as the European REGISTRY¹²⁻¹⁴. The rater also records the initial major presenting symptom out of a choice of six: motor, cognitive, psychiatric, oculomotor, other or mixed. Later versions of REGISTRY incorporated the HD Clinical Characteristics Questionnaire (HD-CCQ)¹² to ask individuals with HD whether they had experienced a range of motor and psychiatric symptoms, and at what age those symptoms started¹⁵. The symptom groupings recorded were motor, depression, irritability, violent or aggressive behaviour, apathy, perseverative/obsessive behaviour, psychosis and cognitive impairment sufficient to impact on work or daily living. Importantly, individuals with HD were asked to report the presence or absence of these symptoms independent of whether they considered them directly related to HD or not. These symptom onset data were collected alongside multiple other assessments of HD phenotype, including the Unified Huntington's Disease Rating Scale (UHDRS)¹⁶. The UHDRS consists of a series of validated questionnaires, tools and examinations related to motor, cognitive, behavioural and functional impairments seen in HD.

To address the onset and relationships of multiple symptoms in individuals with HD, we analysed detailed phenotypic data from over 6000 participants in the REGISTRY study. We highlight how the presenting symptoms of HD vary with age at onset and CAG repeat length. We find that on average there is a consistent disease trajectory for HD with depression often occurring earliest, followed by motor symptoms and then later apathy and cognitive decline. We show that the presence of psychiatric symptoms is significantly associated with reduced functional capacity, highlighting the importance of recognising and managing these common features of HD.

Methods

HD participants

Participants were in the multicentre, multinational, observational REGISTRY study of European HD (<http://www.euro-hd.net/html/REGISTRY>) and 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, and all participants gave written informed consent.

Participant data

HD participant data, collected between June 2004 and February 2016 across 161 sites in 17 European countries, was obtained for 6316 individuals who had a recorded HD age at onset, determined by the rating clinician in REGISTRY, and a confirmed pathogenic CAG length between 36-93 CAGs. Of these CAG sizes, 5027 had been centrally determined by BioRep Inc. (Milan, Italy) in line with REGISTRY protocols (https://www.enroll-hd.org/enrollhd_documents/2016-10-R1/REGISTRY-protocol-3.0.pdf), and 1289 had been derived from local diagnostic laboratories. Two onset estimates were used in this study. Firstly, the clinician's estimate of age at clinical HD onset (sxrater) was determined using all available clinical evidence at the first REGISTRY visit. This was a requirement for incorporation into this study. It additionally classified onset type 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, symptom onsets were determined from the HD Clinical Characteristics Questionnaire (HD-CCQ) which was completed by a healthcare professional using responses from the individual with HD and their carer/partner. HD-CCQ comprises questions about eight symptoms seen in HD and in our study information was available, at least in part, for 5609 individuals: motor (data from 5603 individuals), cognitive (5591), apathy (5584), depression (5595), perseveration/obsessive behaviour (5588), irritability (5586), violent or aggressive behaviour (5586) and psychotic symptoms (5589). For each symptom, the participant was asked if they had ever had the symptom (yes or no), and, if yes, the age the symptom was first experienced. For subsequent analyses, missing data were handled using pairwise deletion to maximise the number of individuals. Typically, the rater estimate of onset and initial HD-CCQ would be recorded at the first REGISTRY visit, sometimes by the same clinician or sometimes by separate staff members depending on local clinic set-up. Subsequent visits would update the HD-CCQ: we used data from the most recent clinic visit.

Statistical analyses of clinical data

To calculate coefficients of determination (R^2 values), 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 transformation¹⁷. 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. Analysis was restricted to HD participants with 40-55 CAGs, a total functional capacity (TFC) score >0 , and a clinical onset ≥ 20 years. The

covariates used were sex, CAG length, alcohol consumption (units per week), tobacco use (cigarettes per day), education (years of education), total functional capacity 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 S2). Finally, we 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 S3). 19 individuals with a recorded co-morbidity of schizophrenia, schizotypal disorder or schizoaffective disorder (ICD-10 F20, F21 or F25) were excluded from all models. It was not possible to formally exclude these symptoms being part of the HD phenotype in these few individuals. Statistical analysis used *R* (version 3.6.0; R core team, 2019, <https://www.r-project.org/>).

Results

The initial symptom of HD varies with age and CAG length

We analysed the initial major symptom at HD clinical onset for 6316 participants with manifest disease in REGISTRY¹². All participants had a confirmed genetic diagnosis of HD with a pathogenic CAG repeat length of 36-93 (Fig. S1). The initial major symptom at onset, determined by the rating physician, varied with the age at which HD became clinically manifest (Fig. 1A and Table S1). Individuals with onset before the age of 20, usually categorised as Juvenile Huntington's disease (JHD), were equally likely to present with motor symptoms (24.5%), cognitive symptoms (21.8%) or psychiatric symptoms (28.2%). In contrast, for adult-onset HD motor presentations became significantly more likely ($P = 7.4 \times 10^{-22}$) and psychiatric presentations significantly less likely ($P = 9.4 \times 10^{-16}$) as age at first symptom increased (Fig. 1A and Table S2A). For people presenting over the age of 60, 68.6% had motor symptoms at clinical onset with just 11.5% having psychiatric and 6.7% cognitive presentations. Next, we tested whether there was any relationship between pathogenic CAG repeat length, known to be inversely correlated with age at symptom 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 (Fig. 1B and Table S2B). 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 JHD cases.

Psychiatric symptoms are common in HD with onsets captured by the Clinical Characteristics Questionnaire

The HD Clinical Characteristics Questionnaire (HD-CCQ) gathers information directly from individuals with HD and their carers/companions about whether they have ever had a range of motor, psychiatric and behavioural symptoms, and at what age these symptoms were first experienced. Importantly, symptoms are recorded whether or not they are considered part of HD in that individual. We analysed the lifetime prevalence of these eight symptoms in 5609 individuals with HD at their most recent recorded clinic visit and compared males and females (Table 1). The mean age (\pm standard deviation) at last recorded clinic visit was 53.3 ± 13.0 years. Almost all (>99%) individuals with HD had experienced motor symptoms and there was no difference in prevalence between males and females. 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%; $P = 2.6 \times 10^{-21}$). 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%; $P = 4.0 \times 10^{-6}$). An excess of violent or aggressive behaviour was also observed in the male group (34.9% vs 27.0%; $P = 2.0 \times 10^{-10}$). 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.

To assess the reliability of HD-CCQ symptom data we compared the age at first clinical onset of HD, as determined by the rating physician in REGISTRY, to the age at relevant symptom onset recorded from patients/carers in HD-CCQ for three different onset groups: motor, cognitive and psychiatric (Fig. S2). There was very strong correlation between ages at first motor symptom onset, whether rater-determined or from HD-CCQ (Fig. S2A). 92.1% (N=2604) had the two recorded motor onsets within 2 years of each other. Similarly, there was strong correlation between ages at cognitive symptom onset, whether rater-determined or from HD-CCQ (Fig. S2B). 76.7% (N=277) had clinician and HD-CCQ onsets within 2 years of each other. Most of the discrepancies occurred where the clinician's estimate at onset was earlier than the HD-CCQ (20.2%; N=77), probably reflecting the more stringent requirement in HD-CCQ for cognitive impairment to impact on work and/or daily life. Finally, there was also good correlation between ages at first psychiatric symptom onset whether rater-determined or as part of HD-CCQ, although the data were more dispersed (72.7%; N=905 within 2 years of each other; Fig. S2C). 19.5% (N=243) had HD-CCQ psychiatric onset over 2 years before their rater-determined HD (psychiatric) onset, probably reflecting coincident mental health issues such as depression that are prevalent in the general population but not necessarily attributable to HD. Overall, these data provide some support for using HD-CCQ data in quantitative analyses of HD phenotypes.

Presence of psychiatric symptoms is associated with CAG repeat length

To assess the temporal relationships of different symptoms in HD we plotted mean age at symptom onset from HD-CCQ against CAG repeat length for different symptoms (Fig. 2). 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. 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 S3). Pathogenic CAG length explained 66.3% of the variance in age at onset of motor symptoms, in line with previous estimates^{4-6,9,18-22}, 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. 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 onsets of motor and psychiatric symptoms in HD are temporally related

Consistent relationships were observed between many of the symptoms across different repeat lengths (Fig. 2 and Table S4). Depression usually had the earliest mean age at onset,

followed by motor impairment and then apathy and cognitive impairment as the latest symptoms. Onset of irritability preceded motor onset at shorter repeat lengths (40-43 CAGs, inclusive) but tended to follow it at longer repeat lengths (44-53 CAGs, inclusive). Perseverative/obsessive behaviour tended to occur later in the disease course, similar to cognitive impairment, whereas violent or aggressive behaviour tended to follow irritability. The mean age at onset of psychosis was variably placed, in part due to the smaller number of HD individuals who reported the symptom, although it usually occurred later in the disease course. 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 (Fig. 2). Plotting the difference in age between motor onset and the onset of a specific psychiatric symptom for all the individuals in our study underscored the variable presentation of symptoms at an individual level (Fig. S3).

Psychiatric symptoms are significantly associated with reduced functional capacity

To assess whether motor and psychiatric symptoms were associated with altered functional abilities we used multiple logistic regression (Table 3). This analysis incorporated sex, pathogenic CAG length, 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 symptoms was significantly associated with a lower total functional capacity score, an indication of impaired ability to work, manage personal finances and function independently. In addition, depression was significantly more prevalent in females ($P = 2.5 \times 10^{-6}$), and irritability significantly more prevalent in males ($P = 3.7 \times 10^{-3}$). Violent or aggressive behaviour was also nominally associated with male sex ($P = 2.2 \times 10^{-2}$). Total motor score was significantly and positively associated with the presence of motor symptoms ($P = 1.5 \times 10^{-4}$), as expected. Depression was significantly associated with a lower total motor score ($P = 3.4 \times 10^{-5}$), indicating its onset at an early stage of HD. Finally, significant associations were observed between tobacco use and irritability ($P = 3.1 \times 10^{-3}$), and between lower educational attainment and psychosis ($P = 4.7 \times 10^{-4}$).

Discussion

In this study of over 6000 patients we have shown that the initial clinical presentation of HD varies with age: late onset (>60 years) is usually associated with motor symptoms, whereas early onset (<20 years; JHD) is associated with variable motor, cognitive or psychiatric presentations (Fig. 1A). A previous smaller study using REGISTRY found that 65.5% of the late onset cohort (defined as >59 years) had motor symptoms recorded first, with chorea and gait/balance problems most common²³. We note that cognitive onset of HD might be under-reported in older age-groups due to it being regarded as coincident 'age-related' change. JHD is known to present more variably²⁴⁻²⁶ and motor phenotypes in younger patients are not always captured effectively by the UHDRS motor scores which are weighted towards chorea and dystonia rather than the rigidity often seen in JHD^{27,28}. Importantly, our results show little relationship between pathogenic repeat length and onset type (Fig. 1B), despite CAG repeat length being highly correlated with age at first symptom onset. Overall, these data suggest that the age at onset of symptoms in an individual is determined by CAG repeat length in combination with other genetic and environmental factors. The resultant age at which onset occurs then influences the types of symptoms that becomes manifest, particularly in the youngest and oldest age ranges. Consistent with this idea, recent genetic studies have shown that variants at modifier loci across the genome contribute to differences in the age at onset of motor symptoms and disease progression in HD^{11,29,30}.

Most modifier studies of HD have used age at motor onset as a quantitative trait, as diagnosis of motor signs in the context of an expanded CAG repeat in *HTT* has high specificity for HD and most individuals with manifest HD will have motor symptoms. This is reinforced by the high concordance between the onset of motor symptoms captured by the rating physician in REGISTRY and those recorded from patients/carers in HD-CCQ (92.1%; Fig. S2). Therefore, although motor onset is mostly captured retrospectively and can be difficult to pinpoint, it is the most reliable of the onset characteristics in this study. In situations where the initial presentation of HD is psychiatric it is reasonable to use HD-CCQ motor onset in analyses.

Psychiatric, cognitive and behavioural symptoms (Table 1) are significantly more prevalent in HD than in the non-HD population^{3,15,31,32}. The HD-CCQ captures unique quantitative information regarding symptom prevalence and onset, and does not judge whether symptoms are HD-related or not. The concordance between symptom onset recorded by the rating physician in REGISTRY and that recorded in HD-CCQ for cognitive and psychiatric symptoms, although not as strong as for motor symptoms, provides some validation for using HD-CCQ data in genetic and other analyses (Fig. S2).

We saw a significant influence of the expanded CAG but no influence of the wild-type CAG length on onset age for any symptom in the HD-CCQ. While an influence of the normal *HTT* CAG allele on onset was previously reported in small HD cohorts³³⁻³⁶, a recent much larger study determined there was no influence of the normal *HTT* allele¹⁸. All symptom onsets were inversely correlated with CAG length (Fig. 2) with motor symptoms best correlated and depression least correlated (Table 2). These data are consistent with previous reports showing that CAG length accounts for 47-72% of the variance in age at clinical onset of HD³⁷. As exact CAG length, not polyglutamine length, is now known to be important in determining age at onset^{11,38,39}, improved CAG sizing measures are likely to increase the accuracy of correlations between repeat length and symptoms³⁹. Previous studies detected

no correlation of CAG repeat length and the presence of psychiatric symptoms measured using a variety of psychiatric instruments⁴⁰⁻⁴³. However, these studies were small and often examined incident psychiatric symptoms, which can fluctuate over time, rather than lifetime history as here.

The average pattern of onset of different symptoms in HD was strikingly conserved across CAG repeat lengths of 40-50 (Fig. 2). The mean age at onset of depression is earliest at each repeat length followed by irritability and motor symptoms and then apathy and cognitive impairment some years later. There are potential biases in these data: they are retrospective, based on the most recent clinic visit, and the tools for identifying apathy and cognitive impairment are insensitive. Furthermore, the use of medications such as antidyskinetics and antidepressants is found in up to 60% of HD patients and might influence phenotypes^{12,44} - although probably not symptom onsets given that medications are usually prescribed reactively. These data contrast with the physician estimates of initial HD symptom from REGISTRY where motor is by far the most common presenting symptom over the age of 20 (Fig. 1A). This apparent discrepancy arises as the HD-CCQ records the lifetime prevalence of symptoms in individuals with HD irrespective of whether they are considered directly due to HD. Psychiatric symptoms in 'pre-manifest' individuals carrying the HD mutation have often been attributed to co-incident diagnoses rather than HD itself. This is particularly true of depression which is common in non-HD populations of young adults⁴⁵⁻⁴⁷. However, rates of depression given by the HD-CCQ are at the higher end of the previously reported 33-70% prevalence rate in HD, depending on whether studies were reporting depressive symptoms (higher estimates), or a formal diagnosis of depressive disorder (lower estimates)³.

Our finding that psychosis in HD was negatively associated with educational level (Table 3) agrees with previous work showing that higher levels of education are associated with decreased schizophrenia risk⁴⁸. 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 HD⁴⁹. This suggests that the increased frequency of psychiatric symptoms in HD compared with the general population may be partly due to the presence of an expanded CAG repeat in *HTT* lowering the genetic threshold for manifestation of such symptoms⁴⁹, and so the associations observed with these symptoms in the general population should also be observed in HD cases. In agreement, we found the expected relationships between female sex and depression and male sex and irritability in our cohort (Table 3). Overall, these data argue that psychiatric symptoms manifesting at any age in an individual carrying the HD mutation should be considered part of the disease phenotype.

In conclusion, detailed information on the onset of different symptoms in HD enables quantitative analyses of symptom relationships at both the individual and population level. These data show that multiple symptoms occur in the majority of individuals with HD and that, unsurprisingly, their presence is related to CAG length. The presence of psychiatric and behavioural symptoms in HD patients is associated with significantly reduced functional capacity, emphasising the importance of managing these symptoms that have deleterious effects on quality of life^{50,51}. It is notable that recent models of HD staging and progression do not directly include these psychiatric and behavioural symptoms that the patients and their carers find most difficult and distressing⁵²⁻⁵⁴. Work is underway to include detailed ratings of psychiatric symptoms in ongoing observational studies, as well as in clinical trials,

in order to capture the full breadth of the HD phenotype and improve the accuracy of clinical outcome measures.

Acknowledgments

We thank all the patients who contributed data to this research. B.Mc. was supported by a PhD studentship from Cardiff University School of Medicine. J.F.G. and M.E.M. received support from NIH grant NS091161 and from the CHDI Foundation, Inc. J-M.L. received support from grant R01NS105709. A.E.R. received support from MRC, Wellcome Trust, Campaign for Alzheimer's Research in Europe, Horizon 2020, JPND and Health and Care Research Wales. L.J., N.M.W. and P.H. were supported by an MRC Centre grant (MR/L010305/1). T.H.M. was supported by a Welsh Clinical Academic Track Fellowship, an MRC Clinical Training Fellowship (MR/P001629/1) and a Patrick Berthoud Charitable Trust Fellowship through the Association of British Neurologists.

Authors' Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

B.Mc.: 1C, 2A, 2B, 3A, 3B

J.F.G.: 3B

G.B.L.: 3B

J-M.L.: 3B

M.E.M.: 3B

M.O.: 3B

A.E.R.: 3B

N.M.W.: 3B

P.H.: 1A, 1B, 2A, 2C, 3B

L.J.: 1A, 1B, 3A, 3B

T.H.M.: 1A, 1B, 3A, 3B

Financial Disclosures of all authors (for the preceding 12 months)

J.F.G.: Scientific Advisory Board member and has a financial interest in Triplet Therapeutics, Inc. His NIH-funded project is using genetic and genomic approaches to uncover other genes that significantly influence when diagnosable symptoms emerge and how rapidly they worsen in Huntington Disease. The company is developing new therapeutic approaches to address triplet repeat disorders such Huntington's Disease, Myotonic Dystrophy and

spinocerebellar ataxias. His interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

G.B.L.: Consulting services, advisory board functions, clinical trial services and/or lectures for Allergan, Alnylam, Amarin, AOP Orphan Pharmaceuticals AG, Bayer Pharma AG, CHDI Foundation, GlaxoSmithKline, Hoffmann-LaRoche, Ipsen, ISIS Pharma, Lundbeck, Neurosearch Inc, Medesis, Medivation, Medtronic, NeuraMetrix, Novartis, Pfizer, Prana Biotechnology, Sangamo/Shire, Siena Biotech, Temmler Pharma GmbH and Teva Pharmaceuticals. He has received research grant support from the CHDI Foundation, the Bundesministerium für Bildung und Forschung (BMBF), the Deutsche Forschungsgemeinschaft (DFG), the European Commission (EU-FP7, JPND). His study site Ulm has received compensation in the context of the observational Enroll-HD Study, TEVA, ISIS and Hoffmann-Roche and the Gossweiler Foundation. He receives royalties from the Oxford University Press and is employed by the State of Baden-Württemberg at the University of Ulm.

A.E.R.: Chair of European Huntington's Disease Network (EHDN) executive committee, Global PI for Triplet Therapeutics

L.J. is a member of the scientific advisory boards of LoQus23 Therapeutics and Triplet Therapeutics.

T.H.M. is an associate member of the scientific advisory board of LoQus23 Therapeutics.

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

References

- 1 The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* 1993; **72**: 971–83.
- 2 Bates GP, Dorsey R, Gusella JF, *et al.* Huntington disease. *Nat Rev Dis Prim* 2015; **1**: 15005.
- 3 Craufurd D, Snowden J. Neuropsychiatry and Neuropsychology. In: Bates GP, Tabrizi SJ, Jones L, eds. *Huntington's Disease*, 4th edn. New York: Oxford University Press, 2014: 36–65.
- 4 Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet* 2004; **65**: 267–77.
- 5 Wexler NS, Lorimer J, Porter J, *et al.* Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci U S A* 2004; **101**: 3498–503.
- 6 Andrew SE, Paul Goldberg Y, Kremer B, *et al.* The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* 1993; **4**: 398–403.
- 7 Andresen JM, Gayán J, Djoussé L, *et al.* The relationship between CAG repeat length and age of onset differs for Huntington's disease patients with juvenile onset or adult onset. *Ann Hum Genet* 2007; **71**: 295–301.
- 8 Andresen JM, Gayán J, Cherny SS, *et al.* Replication of twelve association studies for Huntington's disease residual age of onset in large Venezuelan kindreds. *J Med Genet* 2007; **44**: 44–50.
- 9 Duyao M, Ambrose C, Myers R, *et al.* Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nat Genet* 1993; **4**: 387–92.
- 10 GeM-HD Consortium. Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease. *Cell* 2015; **162**: 516–26.
- 11 Lee J-M, Correia K, Loupe J, *et al.* CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset. *Cell* 2019; **178**: 887–900.
- 12 Orth M, Handley OJ, Schwenke C, *et al.* Observing Huntington's Disease: the European Huntington's Disease Network's REGISTRY. *PLoS Curr* 2010; **2**: RRN1184.
- 13 Landwehrmeyer GB, Fitzer-Attas CJ, Giuliano JD, *et al.* Data Analytics from Enroll-HD, a Global Clinical Research Platform for Huntington's Disease. *Mov Disord Clin Pract* 2017; **4**: 212–24.
- 14 Dorsey ER. Characterization of a large group of individuals with huntington disease and their relatives enrolled in the COHORT study. *PLoS One* 2012; **7**: e29522.
- 15 Eddy CM, Parkinson EG, Rickards HE. Changes in mental state and behaviour in Huntington's disease. *The Lancet Psychiatry* 2016; **3**: 1079–86.

- 16 Unified Huntington's disease rating scale: Reliability and consistency. *Mov Disord* 1996; **11**: 136–42.
- 17 Fisher R. On the 'Probable Error' of a Coefficient of Correlation Deduced from a Small Sample. *Metron* 1921; **1**: 3–32.
- 18 Lee J-M, Ramos EM, Lee J-H, *et al.* CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. *Neurology* 2012; **78**: 690–5.
- 19 Rinaldi C, Salvatore E, Giordano I, *et al.* Predictors of survival in a Huntington's disease population from southern Italy. *Can J Neurol Sci* 2012; **39**: 48–51.
- 20 Snell R, MacMillan J, Cheadle J, *et al.* Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. *Nat Genet* 1993; **4**: 393–7.
- 21 Illarioshkin SN, Igarashi S, Onodera O, *et al.* Trinucleotide repeat length and rate of progression of Huntington's disease. *Ann Neurol* 1994; **36**: 630–5.
- 22 Kiebertz K, MacDonald M, Shih C, *et al.* Trinucleotide repeat length and progression of illness in Huntington's disease. *J Med Genet* 1994; **31**: 872–4.
- 23 Oosterloo M, Bijlsma EK, van Kuijk SM, *et al.* Clinical and genetic characteristics of late-onset Huntington's disease. *Park Relat Disord* 2019; **61**: 101–5.
- 24 Nance MA. Genetic testing of children at risk for Huntington's disease. *Neurology* 1997; **49**: 1048–53.
- 25 Fusilli C, Migliore S, Mazza T, *et al.* Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis. *Lancet Neurol* 2018; **17**: 986–93.
- 26 Cronin T, Rosser A, Massey T. Clinical Presentation and Features of Juvenile-Onset Huntington's Disease: A Systematic Review. *J Huntingtons Dis* 2019; **8**: 171–9.
- 27 Quarrell OWJ. Juvenile Huntington's Disease. In: Bates GP, Tabrizi SJ, Jones L, eds. *Huntington's Disease*, 4th edn. New York: Oxford University Press (OUP), 2014: 66–85.
- 28 Horton MC, Nopoulos P, Nance M, *et al.* Assessment of the Performance of a Modified Motor Scale as Applied to Juvenile Onset Huntington's Disease. *J Huntingtons Dis* 2019; **8**: 181–93.
- 29 Hensman Moss DJ, Pardiñas AF, Langbehn D, *et al.* Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study. *Lancet Neurol* 2017; **16**: 701–11.
- 30 Huntington's GM of, Disease Consortium (GeM-HD). Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease. *Cell* 2015; **162**: 516–26.
- 31 Rocha NP, Mwangi B, Gutierrez Candano CA, Sampaio C, Furr Stimming E, Teixeira AL. The Clinical Picture of Psychosis in Manifest Huntington's Disease: A Comprehensive Analysis of the Enroll-HD Database. *Front Neurol* 2018; **9**: 930.
- 32 Oosterloo M, Craufurd D, Nijsten H, van Duijn E. Obsessive-Compulsive and Perseverative Behaviors in Huntington's Disease. *J Huntingtons Dis* 2019; **8**: 1–7.
- 33 Kehoe P, Krawczak M, Harper PS, Owen MJ, Jones AL. Age of onset in Huntington

- disease: sex specific influence of apolipoprotein E genotype and normal CAG repeat length. *J Med Genet* 1999; **36**: 108–11.
- 34 Farrer LA, Cupples LA, Wiater P, Conneally PM, Gusella JF, Myers RH. The Normal Huntington Disease (HD) Allele, or a Closely Linked Gene, Influences Age at Onset of HD. *Am J Hum Genet* 1993; **53**: 125–30.
- 35 Djoussé L, Knowlton B, Hayden M, *et al.* Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease. *Am J Med Genet A* 2003; **119A**: 279–82.
- 36 Aziz NA, Jurgens CK, Landwehrmeyer GB, *et al.* Normal and mutant HTT interact to affect clinical severity and progression in Huntington disease. *Neurology* 2009; **73**: 1280–5.
- 37 Cazeneuve C, Durr A. Genetic and Molecular Studies. In: Bates GP, Tabrizi SJ, Jones L, eds. *Huntington's Disease*, 4th Editio. New York: Oxford University Press (OUP), 2014: 109–30.
- 38 Wright GEB, Collins JA, Kay C, *et al.* Length of Uninterrupted CAG, Independent of Polyglutamine Size, Results in Increased Somatic Instability, Hastening Onset of Huntington Disease. *Am J Hum Genet* 2019; **104**: 1116–26.
- 39 Ciosi M, Maxwell A, Cumming SA, *et al.* A genetic association study of glutamine-encoding DNA sequence structures, somatic CAG expansion, and DNA repair gene variants, with Huntington disease clinical outcomes. *EBioMedicine* 2019; **48**: 568–80.
- 40 Zappacosta B, Monza D, Meoni C, *et al.* Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease. *Arch Neurol* 1996; **53**: 493–7.
- 41 Weigell-Weber M, Schmid W, Spiegel R. Psychiatric symptoms and CAG expansion in Huntington's disease. *Am J Med Genet* 1996; **67**: 53–7.
- 42 Berrios GE, Wagle AC, Markova IS, *et al.* Psychiatric symptoms and CAG repeats in neurologically asymptomatic Huntington's disease gene carriers. *Psychiatry Res* 2001; **102**: 217–25.
- 43 Vassos E, Panas M, Kladi A, Vassilopoulos D. Effect of CAG repeat length on psychiatric disorders in Huntington's disease. *J Psychiatr Res* 2008; **42**: 544–9.
- 44 Orth M, Bronzova J, Tritsch C, Ray Dorsey E, Ferreira JJ, Gemperli A. Comparison of Huntington's Disease in Europe and North America. *Mov Disord Clin Pract* 2017; **4**: 358–67.
- 45 Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychol Bull* 2017; **143**: 783–822.
- 46 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 593–602.
- 47 Bromet E, Andrade LH, Hwang I, *et al.* Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med* 2011; **9**: 90.

- 48 Escott-Price V, Bracher-Smith M, Menzies G, *et al.* Genetic liability to schizophrenia is negatively associated with educational attainment in UK Biobank. *Mol Psychiatry* 2019; published online Jan. DOI:10.1038/s41380-018-0328-6.
- 49 Ellis N, Tee A, McAllister B, *et al.* Genetic Risk Underlying Psychiatric and Cognitive Symptoms in Huntington's Disease. *Biol Psychiatry* 2020; **87**: 857-865.
- 50 Tabrizi SJ, Scahill RI, Owen G, *et al.* Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013; **12**: 637-49.
- 51 Bachoud-Lévi A-C, Ferreira J, Massart R, *et al.* International Guidelines for the Treatment of Huntington's Disease. *Front Neurol* 2019; **10**: 710.
- 52 Shahn Z, Li Y, Sun Z, Mohan A, Sampaio C, Hu J. G-Computation and Hierarchical Models for Estimating Multiple Causal Effects From Observational Disease Registries With Irregular Visits. *AMIA Jt Summits Transl Sci proceedings AMIA Jt Summits Transl Sci* 2019; **2019**: 789-98.
- 53 Sun Z, Li Y, Ghosh S, *et al.* A Data-Driven Method for Generating Robust Symptom Onset Indicators in Huntington's Disease Registry Data. *AMIA . Annu Symp proceedings AMIA Symp* 2017; **2017**: 1635-44.
- 54 Long JD, Mills JA. Joint modeling of multivariate longitudinal data and survival data in several observational studies of Huntington's disease. *BMC Med Res Methodol* 2018; **18**: 138.

Appendix

European Huntington's Disease Network REGISTRY Study Investigators

REGISTRY Steering committee: Anne-Catherine Bachoud-Lévi, Anna Rita Bentivoglio, Ida Biunno, Raphael M Bonelli, Jean-Marc Burgunder, Stephen B Dunnett, Joaquim J Ferreira, Olivia J. Handley, Arvid Heiberg, Torsten Illmann, G Bernhard Landwehrmeyer, Jamie Levey, Maria A. Ramos-Arroyo, Jørgen E Nielsen, Susana Pro Koivisto, Markku Päivärinta, Raymund A.C. Roos, Ana Rojo Sebastián, Sarah J Tabrizi, Wim Vandenberghe, Christine Verellen-Dumoulin, Tereza Uhrova, Jan Wahlström, Jacek Zaremba

Language coordinators: Verena Baake, Katrin Barth, Monica Bascuñana Garde, Sabrina Betz, Reineke Bos, Jenny Callaghan, Adrien Come, Leonor Correia Guedes, Daniel Ecker, Ana Maria Finisterra, Ruth Fullam, Mette Gilling, Lena Gustafsson, Olivia J. Handley, Carina Hvalstedt, Christine Held, Kerstin Koppers, Claudia Lamanna, Matilde Laurà, Asunción Martínez Descals, Saül Martínez-Horta, Tiago Mestre, Sara Minster, Daniela Monza, Lisanne Mütze, Martin Oehmen, Michael Orth, Hélène Padieu, Laurent Paterski, Nadia Peppà, Susana Pro Koivisto, Martina Di Renzo, Amandine Rialland, Niini Røren, Pavla Šašinková, Erika Timewell, Jenny Townhill, Patricia Trigo Cubillo, Wildson Vieira da Silva, Marleen R van Walsem, Carina Whalstedt, Marie-Noelle Witjes-Ané, Grzegorz Witkowski, Abigail Wright, Daniel Zielonka, Eugeniusz Zielonka, Paola Zinzi

AUSTRIA

Graz (Medizinische Universitäts Graz, Psychiatrie): Raphael M Bonelli, Sabine Lilek, Karen Hecht, Brigitte Herranhof, Anna Holl (formerly Hödl), Hans-Peter Kapfhammer, Michael Koppitz, Markus Magnet, Nicole Müller, Daniela Otti, Annamaria Painold, Karin Reisinger, Monika Scheibl, Helmut Schögl, Jasmin Ullah

Innsbruck (Universitätsklinik Innsbruck, Neurologie): Eva-Maria Braunwarth, Florian Brugger, Lisa Buratti, Eva-Maria Hametner, Caroline Hepperger, Christiane Holas, Anna Hotter, Anna Hussl, Christoph Müller, Werner Poewe, Klaus Seppi, Fabienne Sprenger, Gregor Wenning

BELGIUM

Bierbeek: Andrea Boogaerts, Godelinde Calmeyn, Isabelle Delvaux, Dirk Liessens, Nele Somers

Charleroi (Institut de Pathologie et de Génétique (IPG)): Michel Dupuit, Cécile Minet, Dominique van Paemel, Pascale Ribaï, Christine Verellen-Dumoulin

Leuven: (Universitair Ziekenhuis Gasthuisberg,): Andrea Boogaerts, Wim Vandenberghe, Dimpna van Reijen

CZECH REPUBLIC

Prague (Extrapyramidové centrum, Neurologická klinika, 1. LF UK a VFN): Jiří Klempíř, Veronika Majerová, Jan Roth, Irena Stárková

DENMARK

Copenhagen (Neurogenetics Clinic, Danish Dementia Research Centre, Rigshospitalet, University of Copenhagen): Lena E. Hjermand, Oda Jacobsen, Jørgen E Nielsen, Ida Unmack Larsen, Tua Vinther-Jensen

FINLAND

Turku-Suvituuli (Rehabilitation Centre Suvituuli): Heli Hiivola, Hannele Hyppönen, Kirsti Martikainen, Katri Tuuha

FRANCE

Angers (Centre de référence des maladies neurogénétique- CHU d'Angers): Philippe Allain,

Dominique Bonneau, Marie Bost, Bénédicte Gohier, Marie-Anne Guérid, Audrey Olivier, Adriana Prundean, Clarisse Scherer-Gagou, Christophe Verny

Bordeaux (Hôpital CHU Pellegrin): Blandine Babiloni, Sabrina Debruxelles, Charlotte Duché, Cyril Goizet, Laetitia Jameau, Danielle Lafoucrière, Umberto Spampinato

Lille-Amiens:

Lille (CHRU Roger Salengro) : Rekha Barthélémy, Christelle De Bruycker, Maryline Cabaret, Anne-Sophie Carette, Eric Decorte Luc Defebvre, Marie Delliaux, Arnaud Delval, Alain Destee, Kathy Dujardin, Marie-Hélène Lemaire, Sylvie Manouvrier, Mireille Peter, Lucie Plomhouse, Bernard Sablonnière, Clémence Simonin, Stéphanie Thibault-Tanchou, Isabelle Vuillaume

Amiens (CHU Nord) : Marcellin Bellonet, Hassan Berrissoul, Stéphanie Blin, Françoise Courtin, Cécile Duru, Véronique Fasquel, Olivier Godefroy, Pierre Krystkowiak, Béatrice Mantoux, Martine Roussel, Sandrine Wannepain

Marseille (Hôpital La Timone) : Jean-Philippe Azulay, Marie Delfini, Alexandre Eusebio, Frédérique Fluchere, Laura Mundler

Strasbourg (Hôpital Civil) : Mathieu Anheim, Celine Julié, Ouhaïd Lagha Boukbiza, Nadine Longato, Gabrielle Rudolf, Christine Tranchant, Marie-Agathe Zimmermann

GERMANY

Aachen (Universitätsklinikum Aachen, Neurologische Klinik): Christoph Michael Kosinski, Eva Milkereit, Daniela Probst, Kathrin Reetz, Christian Sass, Johannes Schiefer, Christiane Schlangen, Cornelius J. Werner

Berlin (Klinik und Poliklinik für Neurologie - Charité - Universitätsmedizin Berlin): Harald Gelderblom, Josef Priller, Harald Prüß, Eike Jakob Spruth

Bochum (Huntington-Zentrum (NRW) Bochum im St. Josef-Hospital): Gisa Ellrichmann, Lennard Herrmann, Rainer Hoffmann, Barbara Kaminski, Peter Kotz, Christian Prehn, Carsten Saft

Dinslaken (Reha Zentrum in Dinslaken im Gesundheitszentrums Lang): Herwig Lange, Robert Maiwald

Dresden (Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Klinik und Poliklinik für Neurologie): Matthias Löhle, Antonia Maass, Simone Schmidt, Cecile Bosredon, Alexander Storch, Annett Wolz, Martin Wolz

Freiburg (Universitätsklinik Freiburg, Neurologie): Philipp Capetian, Johann Lambeck, Birgit Zucker

Hamburg (Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Neurologie): Kai Boelmans, Christos Ganos, Walburgis Heinicke, Ute Hidding, Jan Lewerenz, Alexander Münchau, Michael Orth, Jenny Schmalfeld, Lars Stubbe, Simone Zittel

Hannover (Neurologische Klinik mit Klinischer Neurophysiologie, Medizinische Hochschule Hannover): Gabriele Diercks, Dirk Dressler, Heike Gorzolla, Christoph Schrader, Pawel Tacik

Itzehoe (Schwerpunktpraxis Huntington, Neurologie und Psychiatrie): Michael Ribbat

Marburg KPP (Klinik für Psychiatrie und Psychotherapie Marburg-Süd): Bernhard Longinus

Marburg Uni (Universität Marburg, Neurologie): Katrin Bürk, Jens Carsten Möller, Ida

Risling

München (Huntington-Ambulanz im Neuro-Kopfzentrum - Klinikum rechts der Isar der Neurologischen Klinik und Poliklinik der Technischen Universität München): Mark Mühlau, Alexander Peinemann, Michael Städtler, Adolf Weindl, Juliane Winkelmann, Cornelia Ziegler

Münster (Universitätsklinikum Münster, Klinik und Poliklinik für Neurologie): Natalie Bechtel, Heike Beckmann, Stefan Bohlen, Eva Hölzner, Herwig Lange, Ralf Reilmann,

Stefanie Rohm, Silke Rumpf , Sigrun Schepers, Natalia Weber

Taufkirchen (Isar-Amper-Klinikum - Klinik Taufkirchen (Vils)): Matthias Dose, Gabriele Leythäuser, Ralf Marquard, Tina Raab, Alexandra Wiedemann

Ulm (Universitätsklinikum Ulm, Neurologie): Katrin Barth, Andrea Buck, Julia Connemann, Daniel Ecker, Carolin Geitner, Christine Held, Andrea Kesse, Bernhard Landwehrmeyer, Christina Lang, Jan Lewerenz, Franziska Lezius, Solveig Nepper, Anke Niess, Michael Orth, Ariane Schneider, Daniela Schwenk, Sigurd Süßmuth, Sonja Trautmann, Patrick Weydt

ITALY

Bari Clinica Neurologica - Neurophysiopatology of Pain Unit UNIVERSITA' DI BARI): Claudia Cormio, Vittorio Scirucchio, Claudia Serpino, Marina de Tommaso

Bologna (DIBINEM - Alma Mater Studiorum - Università di Bologna; IRCCS Istituto delle Scienze Neurologiche di Bologna): Sabina Capellari, Pietro Cortelli, Roberto Galassi, Rizzo Giovanni, Roberto Poda, Cesa Scaglione

Florence (Dipartimento di Scienze Neurologiche e Psichiatriche Università degli Studi di Firenze-Azienda Ospedaliera Universitaria Careggi): Elisabetta Bertini, Elena Ghelli, Andrea Ginestroni, Francesca Massaro, Claudia Mechi, Marco Paganini, Silvia Piacentini, Silvia Pradella, Anna Maria Romoli, Sandro Sorbi

Genoa (Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Università di Genova): Giovanni Abbruzzese, Monica Bandettini di Poggio, Giovanna Ferrandes, Paola Mandich, Roberta Marchese

Milan (Fondazione IRCCS Istituto Neurologico Carlo Besta):

Alberto Albanese, Daniela Di Bella, Anna Castaldo, Stefano Di Donato, Cinzia Gellera, Silvia Genitrini, Caterina Mariotti, Daniela Monza, Lorenzo Nanetti, Dominga Paridi, Paola Soliveri, Chiara Tomasello

Naples (Dipartimento di Neuroscienze, Scienze Riproduttive e Odontostomatologiche, Università Federico II): Giuseppe De Michele, Luigi Di Maio, Marco Massarelli, Silvio Peluso, Alessandro Roca, Cinzia Valeria Russo, Elena Salvatore, Pierpaolo Sorrentino

Pozzilli (IS) (Centro di Neurogenetica e Malattie Rare - IRCCS Neuromed): Enrico Amico, Mariagrazia Favellato, Annamaria Griguoli, Irene Mazzante, Martina Petrollini, Ferdinando Squitieri and **Rome (Lega Italiana Ricerca Huntington e malattie correlate - onlus / www.LIRH.it):** Barbara D'Alessio, Chiara Esposito

Rome (Istituto di Farmacologia Traslazionale & Istituto di Scienze e Tecnologie della Cognizione /CNR, Istituto di Neurologia Università Cattolica del Sacro Cuore): Anna Rita Bentivoglio, Marina Frontali, Arianna Guidubaldi, Tamara Ialongo, Gioia Jacopini, Carla Piano, Silvia Romano, Francesco Soletti, Maria Spadaro, Paola Zinzi

NETHERLANDS

Enschede (Medisch Spectrum Twente): Monique S.E. van Hout, Marloes E. Verhoeven, Jeroen P.P. van Vugt, A. Marit de Weert

Groningen (Polikliniek Neurologie): J.J.W. Bolwijn, M. Dekker, B. Kremer, K.L. Leenders, J.C.H. van Oostrom

Leiden (Leiden University Medical Centre (LUMC)): Simon J. A. van den Bogaard, Reineke Bos, Eve M. Dumas, Ellen P. 't Hart, Raymund A.C. Roos

Nijmegen (Universitair Medisch Centrum St. Radboud, Neurology): Berry Kremer, C.C.P. Verstappen

NORWAY

Oslo University Hospital (Rikshospitalet, Dept. of Medical Genetics and Dept. of Neurology): Olaf Aaserud, Jan Frich C., Arvid Heiberg, Marleen R. van Walsem, Ragnhild

Wehus

Oslo University Hospital (Ullevål, Dept. of Medical Genetics and Dept. of

Neurorehabilitation): Kathrine Bjørge, Madeleine Fannemel, Per F. Gørvell, Eirin Lorentzen, Susana Pro Koivisto, Lars Retterstøl, Bodil Stokke

Trondheim (St. Olavs Hospital): Inga Bjørnevoll, Sigrid Botne Sando

POLAND

Gdansk (St. Adalbert Hospital, Gdansk, Medical University of Gdansk, Neurological and Psychiatric Nursing Dpt.): Artur Dziadkiewicz, Malgorzata Nowak, Piotr Robowski, Emilia Sitek, Jaroslaw Slawek, Witold Soltan, Michal Szinwelski

Katowice (Medical University of Silesia, Katowice): Magdalena Blaszyk, Magdalena Boczarska-Jedynak, Ewelina Ciach-Wysocka, Agnieszka Gorzkowska, Barbara Jasinska-Myga, Gabriela Kłodowska-Duda, Gregorz Opala, Daniel Stempel

Krakow (Krakowska Akademia Neurologii): Krzysztof Banaszkiwicz, Dorota Boćwińska, Kamila Bojakowska-Jaremek, Małgorzata Dec, Malgorzata Krawczyk, Monika Rudzińska, Elżbieta Szczygieł, Andrzej Szczudlik, Anna Wasielewska, Magdalena Wójcik

Poznan (Poznan University of Medical Sciences, Poland): Anna Bryl, Anna Ciesielska, Aneta Klimberg, Jerzy Marcinkowski, Husam Samara, Justyna Sempołowicz, Daniel Zielonka

Warsaw-MU (Medical University of Warsaw, Neurology): Anna Gogol (formerly Kalbarczyk), Piotr Janik, Hubert Kwiecinski, Zygmunt Jamrozik

Warsaw-IPiN (Institute of Psychiatry and Neurology Dep. of Genetics, First Dep. of Neurology): Jakub Antczak, Katarzyna Jachinska, Wioletta Krysa, Maryla Rakowicz, Przemyslaw Richter, Rafal Rola, Danuta Ryglewicz, Halina Sienkiewicz-Jarosz, Iwona Stępnia, Anna Sułek, Grzegorz Witkowski, Jacek Zaremba, Elzbieta Zdzienicka, Karolina Zieora-Jakutowicz

PORTUGAL

Coimbra (Hospital Universitário de Coimbra): Cristina Januário, Filipa Júlio

Lisbon (Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon): Joaquim J Ferreira, Miguel Coelho, Leonor Correia Guedes, Tiago Mendes, Tiago Mestre, Anabela Valadas

Porto (Hospital de São João, (Faculdade de Medicina da Universidade do Porto)): Carlos Andrade, Miguel Gago, Carolina Garrett, Maria Rosália Guerra.

SPAIN

Badajoz (Hospital Infanta Cristina): Carmen Durán Herrera, Patrocinio Moreno Garcia

Barcelona-Hospital Mútua de Terrassa: Miquel Aguilar Barbera, Dolores Badenes Guia, Laura Casas Hernanz, Judit López Catena, Pilar Quiléz Ferrer, Ana Rojo Sebastián, Gemma Tome Carruesco

Barcelona-Bellvitge (Hospital Universitari de Bellvitge): Jordi Bas, Núria Busquets, Matilde Calopa

Barcelona-Merced (Hospital Mare de Deu de La Merced): Misericordia Floriach Robert, Celia Mareca Viladrich, Jesús Miguel Ruiz Idiago, Antonio Villa Riballo

Burgos (Servicio de Neurología Hospital General Yagüe): Esther Cubo, Cecilia Gil Polo, Natividad Mariscal Perez, Jessica Rivadeneyra

Granada (Hospital Universitario San Cecilio, Neurología): Francisco Barrero, Blas Morales

Madrid-Clinico (Hospital Clínico Universitario San Carlos): María Fenollar, Rocío García-Ramos García, Paloma Ortega, Clara Villanueva

Madrid RYC (Hospital Ramón y Cajal, Neurología): Javier Alegre, Mónica Bascuñana, Juan Garcia Caldentey, Marta Fatás Ventura, Guillermo García Ribas, Justo García de Yébenes,

José Luis López-Sendón Moreno, Patricia Trigo Cubillo

Madrid FJD (Madrid-Fundación Jiménez Díaz): Javier Alegre, Fernando Alonso Frech, Justo García de Yébenes, Pedro J García Ruíz, Asunción Martínez-Descals, Rosa Guerrero, María José Saiz Artiga, Vicenta Sánchez

Murcia (Hospital Universitario Virgen de la Arrixaca): María Fuensanta Noguera Perea, Lorenza Fortuna, Salvadora Manzanares, Gema Reinante, María Martirio Antequera Torres, Laura Vivancos Moreau

Oviedo (Hospital Central de Asturias): Sonia González González, Luis Menéndez Guisasola, Carlos Salvador, Esther Suárez San Martín

Palma de Mallorca (Hospital Universitario Son Espases): Inés Legarda Ramirez, Aranzazú Gorospe, Mónica Rodríguez Lopera, Penelope Navas Arques, María José Torres Rodríguez, Barbara Vives Pastor

Pamplona (Complejo Hospitalario de Navarra): Itziar Gaston, Maria Dolores Martinez-Jaurrieta, Maria A. Ramos-Arroyo

Sevilla ("Hospital Virgen Macarena"): Jose Manuel Garcia Moreno, Carolina Mendez Lucena, Fatima Damas Hermoso, Eva Pacheco Cortegana, José Chacón Peña, Luis Redondo

Sevilla (Hospital Universitario Virgen del Rocío): Fátima Carrillo, María Teresa Cáceres, Pablo Mir, María José Lama Suarez, Laura Vargas-González

Valencia (Hospital la Fe): Maria E. Bosca, Francisco Castera Brugada, Juan Andres Burguera, Anabel Campos Garcia, Carmen Peiró Vilaplana

SWEDEN

Göteborg (Sahlgrenska University Hospital): Peter Berglund, Radu Constantinescu, Gunnel Fredlund, Ulrika Høsterey-Ugander, Petra Linnsand, Liselotte Neleborn-Lingefjärd, Jan Wahlström, Magnus Wentzel

Umeå (Umeå University Hospital): Ghada Loutfi, Carina Olofsson, Eva-Lena Stattin, Laila Westman, Birgitta Wikström

SWITZERLAND

Bern: Jean-Marc Burgunder, Yanik Stebler (**Swiss HD Zentrum**), Alain Kaelin, Irene Romero, Michael Schüpbach, Sabine Weber Zaugg (**Zentrum für Bewegungsstörungen, Neurologische Klinik und Poliklinik, Universität Bern**)

Zürich (Department of Neurology, University Hospital Zürich): Maria Hauer, Roman Gonzenbach, Hans H. Jung, Violeta Mihaylova, Jens Petersen

UNITED KINGDOM

Aberdeen (NHS Grampian Clinical Genetics Centre & University of Aberdeen): Roisin Jack, Kirsty Matheson, Zosia Miedzybrodzka, Daniela Rae, Sheila A Simpson, Fiona Summers, Alexandra Ure, Vivien Vaughan

Birmingham (The Barberrry Centre, Dept of Psychiatry): Shahbana Akhtar, Jenny Crooks, Adrienne Curtis, Jenny de Souza (Keylock), John Piedad, Hugh Rickards, Jan Wright

Bristol (North Bristol NHS Trust, Southmead hospital): Elizabeth Coulthard, Louise Gethin, Beverley Hayward, Kasia Sieradzan, Abigail Wright

Cambridge (Cambridge Centre for Brain Repair, Forvie Site): Matthew Armstrong, Roger A. Barker, Deidre O'Keefe, Anna Di Pietro, Kate Fisher, Anna Goodman, Susan Hill, Ann Kershaw, Sarah Mason, Nicole Paterson, Lucy Raymond, Rachel Swain, Natalie Valle Guzman

Cardiff (Schools of Medicine and Biosciences, Cardiff University): Monica Busse, Cynthia Butcher, Jenny Callaghan, Stephen Dunnett, Catherine Clenaghan, Ruth Fullam, Olivia Handley, Sarah Hunt, Lesley Jones, Una Jones, Hanan Khalil, Sara Minster, Michael Owen,

Kathleen Price, Anne Rosser, Jenny Townhill

Edinburgh (Molecular Medicine Centre, Western General Hospital, Department of Clinical Genetics): Maureen Edwards, Carrie Ho (Scottish Huntington's Association), Teresa Hughes (Scottish Huntington's Association), Marie McGill, Pauline Pearson, Mary Porteous, Paul Smith (Scottish Huntington's Association)

Fife (Scottish Huntington's Association Whyteman's Brae Hospital): Peter Brockie, Jillian Foster, Nicola Johns, Sue McKenzie, Jean Rothery, Gareth Thomas, Shona Yates

Gloucester (Department of Neurology Gloucestershire Royal Hospital): Liz Burrows, Carol Chu, Amy Fletcher, Deena Gallantrae, Stephanie Hamer, Alison Harding, Stefan Klöppel, Alison Kraus, Fiona Laver, Monica Lewis, Mandy Longthorpe, Ivana Markova, Ashok Raman, Nicola Robertson, Mark Silva, Aileen Thomson, Sue Wild, Pam Yardumian

Hull (Castle Hill Hospital): Carol Chu, Carole Evans, Deena Gallantrae, Stephanie Hamer, Alison Kraus, Ivana Markova, Ashok Raman

Leeds (Chapel Allerton Hospital, Department of Clinical Genetics): Leeds (Chapel Allerton Hospital, Clinical Genetics): Carol Chu, Stephanie Hamer, Emma Hobson, Stuart Jamieson, Alison Kraus, Ivana Markova, Ashok Raman, Hannah Musgrave, Liz Rowett, Jean Toscano, Sue Wild, Pam Yardumian

Leicester (Leicestershire Partnership Trust, Mill Lodge): Colin Bourne, Jackie Clapton, Carole Clayton, Heather Dipple, Dawn Freire-Patino, Janet Grant, Diana Gross, Caroline Hallam, Julia Middleton, Ann Murch, Catherine Thompson

Liverpool (Walton Centre for Neurology and Neurosurgery): Sundus Alusi, Rhys Davies, Kevin Foy, Emily Gerrans, Louise Pate

London (Guy's Hospital): Thomasin Andrews, Andrew Dougherty, Charlotte Golding, Fred Kavalier, Hana Laing, Alison Lashwood, Dene Robertson, Deborah Ruddy, Alastair Santhouse, Anna Whaite

London (The National Hospital for Neurology and Neurosurgery): Thomasin Andrews, Stefania Bruno, Karen Doherty, Charlotte Golding, Salman Haider, Davina Hensman, Nayana Lahiri, Monica Lewis, Marianne Novak, Aakta Patel, Nicola Robertson, Elisabeth Rosser, Sarah Tabrizi, Rachel Taylor, Thomas Warner, Edward Wild

Manchester (Genetic Medicine, University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust): Natalie Arran, Judith Bek, Jenny Callaghan, David Craufurd, Ruth Fullam, Marianne Hare, Liz Howard, Susan Huson, Liz Johnson, Mary Jones, Helen Murphy, Emma Oughton, Lucy Partington-Jones, Dawn Rogers, Andrea Sollom, Julie Snowden, Cheryl Stopford, Jennifer Thompson, Iris Trender-Gerhard, Nichola Verstraelen (formerly Ritchie), Leann Westmoreland

Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford): Richard Armstrong, Kathryn Dixon, Andrea H Nemeth, Gill Siuda, Ruth Valentine

Plymouth (Plymouth Huntington Disease Service, Mount Gould Hospital): David Harrison, Max Hughes, Andrew Parkinson, Beverley Soltysiak

Sheffield (The Royal Hallamshire Hospital– Sheffield Children's Hospital): Oliver Bandmann, Alyson Bradbury, Paul Gill, Helen Fairtlough, Kay Fillingham, Isabella Foustanos, Mbombe Kazoka, Kirsty O'Donovan, Nadia Peppas, Cat Taylor, Katherine Tidswell, Oliver Quarrell

EHDN's associate site in Singapore: National Neuroscience Institute Singapore: Jean-Marc Burgunder, Puay Ngoh Lau, Emmanul Pica, Louis Tan

Mainline figures & tables

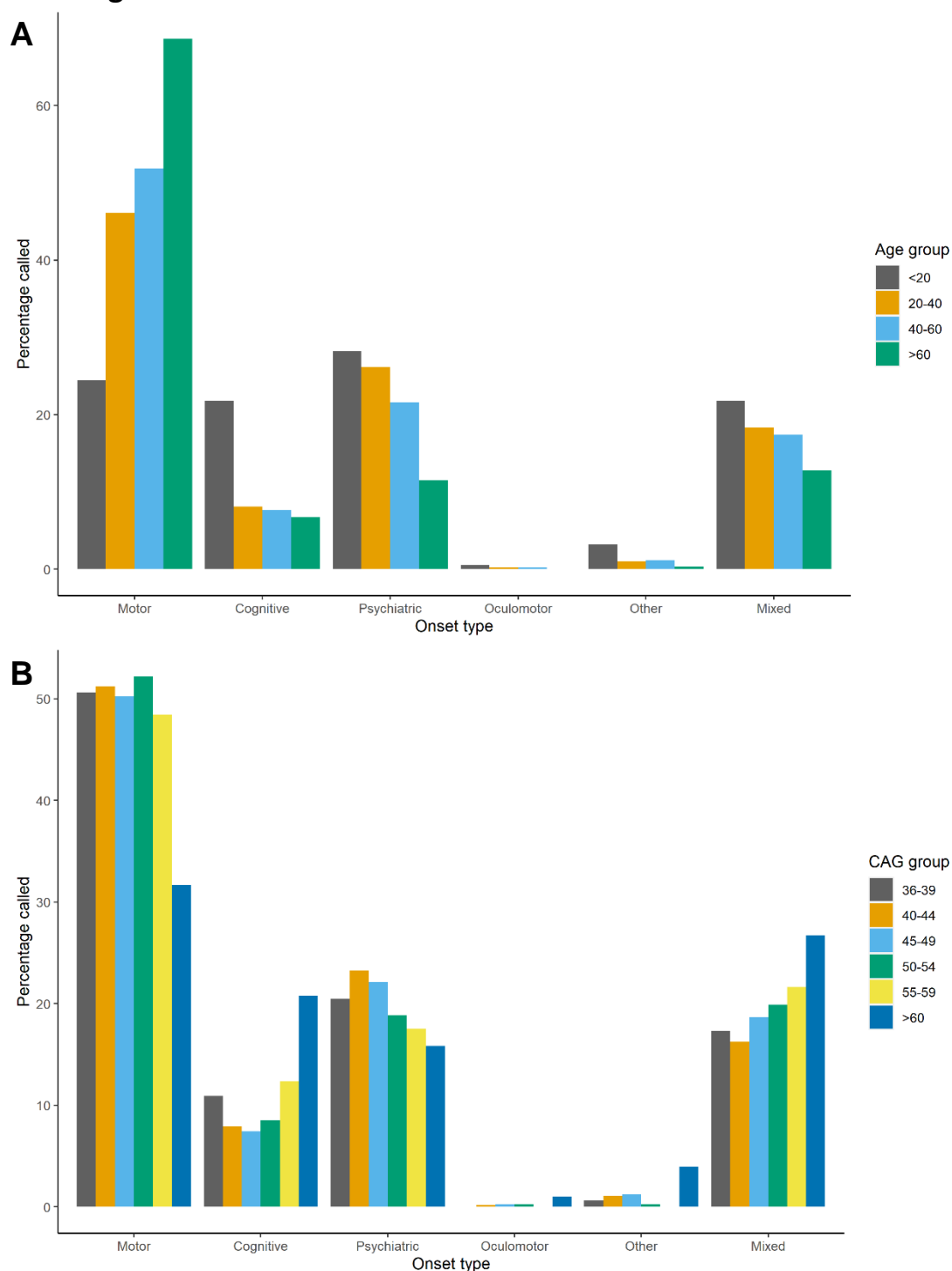


Figure 1. The initial symptom of HD varies by age and CAG length. All included individuals had a pathogenic CAG length (36-93) and confirmed HD onset age determined by a rating clinician. **(A)** Frequency of different onset types in four age groups, chosen to show juvenile HD and then 20 year bins for 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.

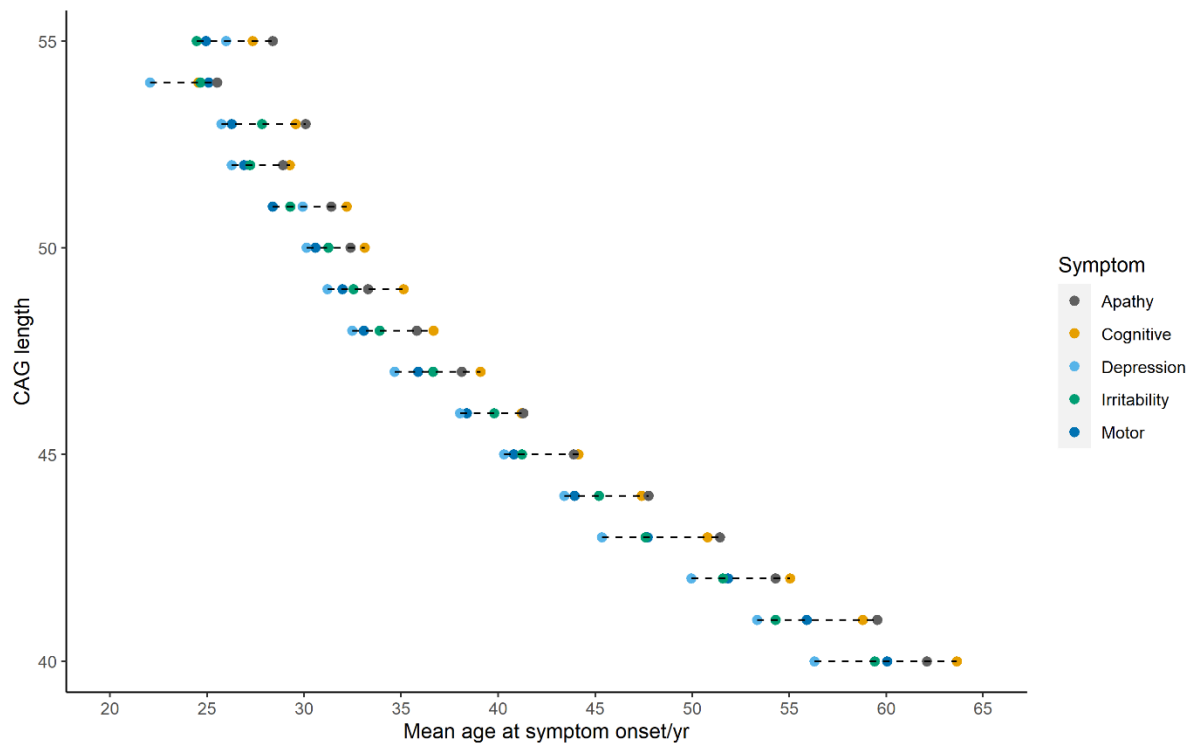


Figure 2. Mean ages at onset for motor and psychiatric symptoms at different CAG repeat lengths. Shown are the mean symptom ages as recorded by the HD Clinical Characteristics Questionnaire for apathy (N = 2739), cognitive impairment (N = 3069), depression (N = 3399), irritability (N = 3117) and motor symptoms (N = 4889). Numerical data, as well as data for perseverative/obsessive behaviour (POB), violent or aggressive behaviour (VAB) and psychosis (PSY) symptoms, are shown in Table S4.

	Males			Females			P value (χ^2)
	Yes	No	Frequency	Yes	No	Frequency	
Motor	2691	28	98.97%	2859	25	99.13%	5.29 x 10 ⁻¹
Cognitive	1584	1132	58.32%	1688	1187	58.71%	7.66 x 10 ⁻¹
Apathy	1456	1259	53.63%	1495	1374	52.11%	2.56 x 10 ⁻¹
Depression	1582	1135	58.23%	2025	853	70.36%	2.57 x 10⁻²¹
POB	1005	1711	37.00%	1038	1834	36.14%	5.04 x 10 ⁻¹
Irritability	1706	1006	62.91%	1634	1240	56.85%	4.03 x 10⁻⁶
VAB	947	1769	34.87%	777	2100	27.01%	1.99 x 10⁻¹⁰
Psychosis	319	2396	11.75%	325	2549	11.31%	6.06 x 10 ⁻¹

Table 1. 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 tests the difference between prevalence in males and females. Significant *P* values in bold ($P < 6.25 \times 10^{-3}$, multiple testing correction). POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

	Male		Female		<i>P</i>	Both	
	R ²	N	R ²	N		R ²	N
Motor	0.678	2684	0.649	2844	5.42 x 10 ⁻²	0.663	5528
Cognitive	0.610	1570	0.629	1681	3.80 x 10 ⁻¹	0.619	3251
Apathy	0.595	1423	0.562	1462	1.83 x 10 ⁻¹	0.578	2885
Depression	0.412	1551	0.351	1994	3.50 x 10 ⁻²	0.375	3545
POB	0.539	973	0.440	1016	3.67 x 10⁻³	0.489	1989
Irritability	0.463	1670	0.547	1601	1.25 x 10⁻³	0.503	3271
VAB	0.479	927	0.478	761	9.79 x 10 ⁻¹	0.477	1688
Psychosis	0.401	312	0.424	318	7.29 x 10 ⁻¹	0.411	630

Table 2. Variance in age at onset (R²) 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 R². Significant *P* values ($P < 6.25 \times 10^{-3}$) 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. POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

	Motor (N=1465)		Cognitive (N=1465)		Apathy (N=1465)		Depression (N=1467)	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
Sex	-4.898	2.20×10^{-1}	0.176	1.36×10^{-1}	0.027	8.07×10^{-1}	0.543	2.49×10^{-6}
CAG	-6.252	1.23×10^{-1}	-0.021	8.62×10^{-1}	0.101	3.60×10^{-1}	-0.206	7.64×10^{-2}
Alcohol	-1.348	7.01×10^{-1}	0.301	<i>1.79×10^{-2}</i>	0.036	7.44×10^{-1}	-0.193	9.29×10^{-2}
Tobacco	11.498	1.60×10^{-1}	0.099	4.04×10^{-1}	0.201	7.09×10^{-2}	0.316	<i>9.91×10^{-3}</i>
Education	-3.975	3.16×10^{-1}	0.109	3.62×10^{-1}	-0.176	1.11×10^{-1}	-0.087	4.58×10^{-1}
TFC	5.799	4.23×10^{-1}	-2.095	9.09×10^{-28}	-1.115	9.88×10^{-11}	-0.988	7.13×10^{-8}
TMS	43.080	1.48×10^{-4}	-0.302	1.03×10^{-1}	-0.273	1.10×10^{-1}	-0.759	3.39×10^{-5}

	POB (N=1464)		Irritability (N=1467)		VAB (N=1467)		Psychosis (N=1464)	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
Sex	0.068	5.97×10^{-1}	-0.324	3.69×10^{-3}	-0.308	2.22×10^{-2}	-0.391	2.79×10^{-1}
CAG	-0.156	2.36×10^{-1}	0.009	9.35×10^{-1}	0.183	1.69×10^{-1}	-0.395	2.95×10^{-1}
Alcohol	0.143	2.53×10^{-1}	0.151	2.15×10^{-1}	0.068	6.02×10^{-1}	0.431	1.51×10^{-1}
Tobacco	0.062	6.31×10^{-1}	0.347	3.10×10^{-3}	0.267	<i>4.01×10^{-2}</i>	0.003	9.93×10^{-1}
Education	-0.026	8.40×10^{-1}	-0.055	6.26×10^{-1}	-0.189	1.67×10^{-1}	-1.334	4.71×10^{-4}
TFC	-1.109	3.52×10^{-8}	-0.754	1.65×10^{-5}	-1.183	1.95×10^{-8}	-2.364	3.05×10^{-5}
TMS	-0.252	2.01×10^{-1}	-0.446	<i>1.06×10^{-2}</i>	-0.299	1.46×10^{-1}	-0.414	4.38×10^{-1}

Table 3. Multiple logistic regression of the lifetime presence or absence of eight HD symptoms on clinical covariates. Binary HD-CCQ data were used (0 = no symptom; 1 = reported symptom). Significant associations after Bonferroni correction for 8 symptoms are shown in bold ($P < 6.25 \times 10^{-3}$) and nominally significant associations in italics ($P < 0.05$). In addition to having a confirmed onset and pathogenic CAG length, individuals must have had onset ≥ 20 years, TFC > 0 and no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. β : standardised coefficient; POB: perseverative/obsessive behaviour; TFC: total functional capacity; TMS: total motor score; VAB: violent or aggressive behaviour.