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

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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 rater[4–9].

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 REGISTRY[12–14]. 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 started[15]. 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 transformation[17]. 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 REGISTRY[12]. 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 x 10^{-22}) and psychiatric presentations significantly less likely (P = 9.4 x 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 (± 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 x 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 x 10^{-6}). An excess of violent or aggressive behaviour was also observed in the male group (34.9% vs 27.0%; P = 2.0 x 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 x 10^{-3}) and irritability in females (P = 1.3 x 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 common[23]. 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 variably[24–26] 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 cohorts[33–36], a recent much larger study determined there was no influence of the normal *HTT* allele[18]. 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 HD[37]. 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 symptoms[39]. Previous studies detected

no correlation of CAG repeat length and the presence of psychiatric symptoms measured using a variety of psychiatric instruments[40–43]. 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 adults[45–47]. 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 risk[48]. 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[49]. 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 symptoms[49], 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 distressing[52–54]. 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.

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.

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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

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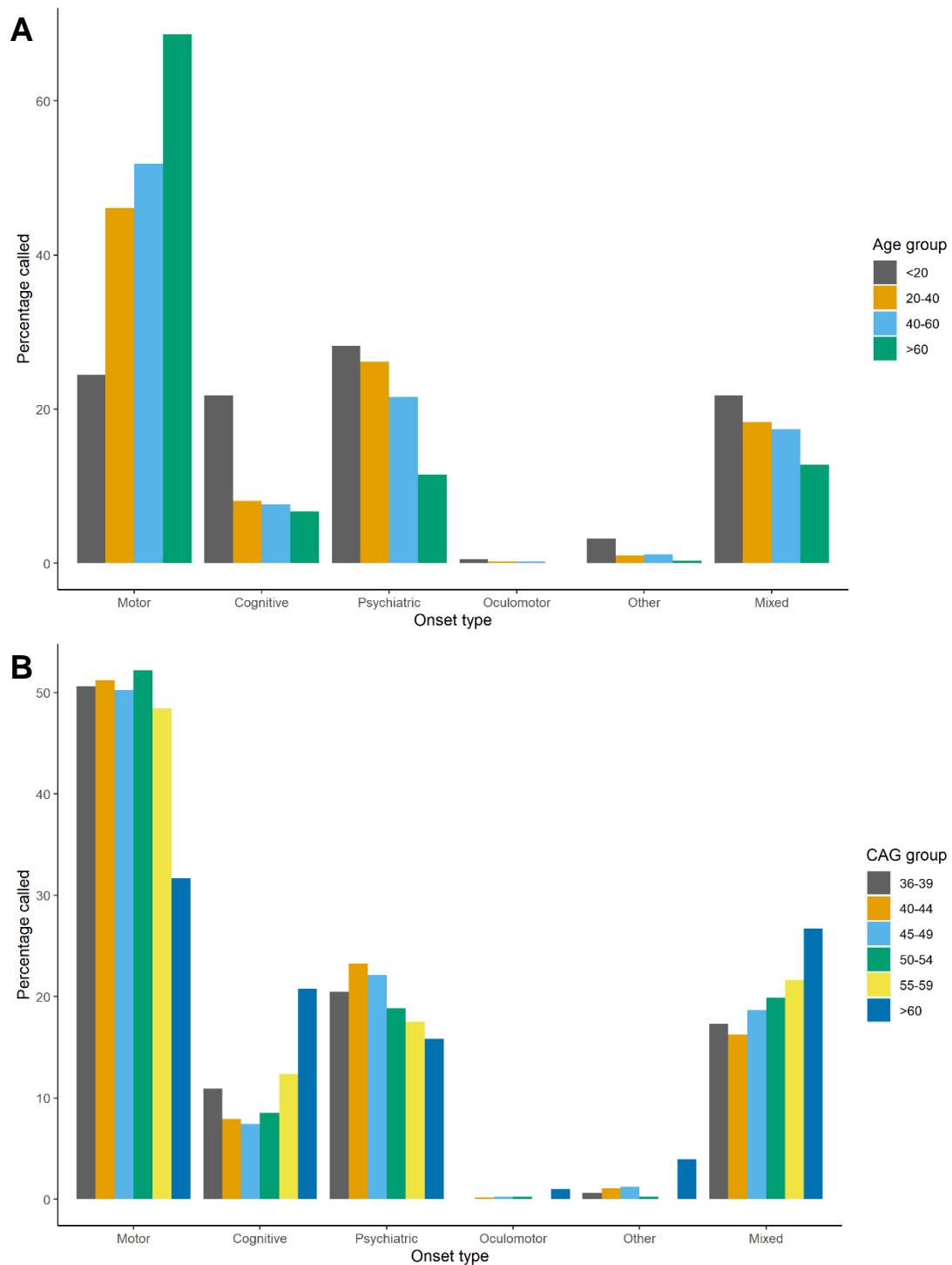
Figure 1. The initial symptom of HD varies by age and CAG length. All included individuals had a pathogenic CAG length (36-93) and confirmed HD onset age determined by a rating clinician. **(A)** Frequency of different onset types in four age groups, chosen to show juvenile HD and then 20 year bins for 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.
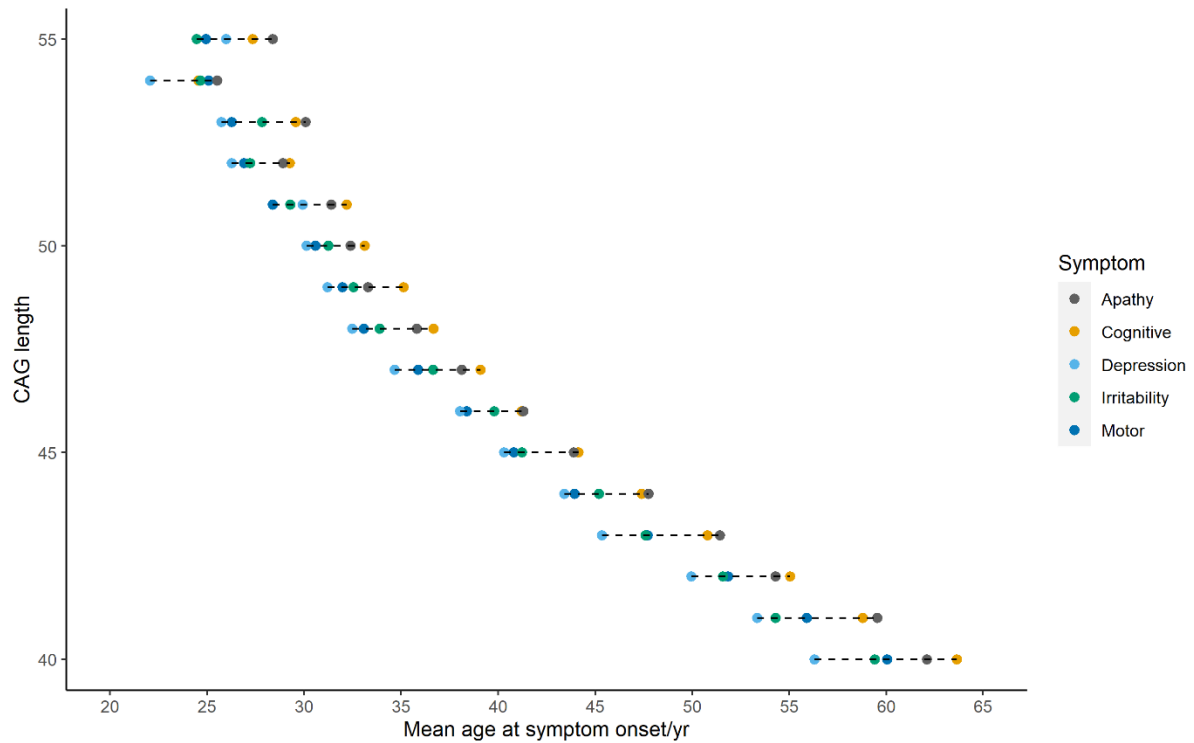
Figure 2. Mean ages at onset for motor and psychiatric symptoms at different CAG repeat lengths. Shown are the mean symptom ages as recorded by the HD Clinical Characteristics Questionnaire for apathy (N = 2739), cognitive impairment (N = 3069), depression (N = 3399), irritability (N = 3117) and motor 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%	5.29×10^{-1}
Cognitive	1584	1132	58.32%	1688	1187	58.71%	7.66×10^{-1}
Apathy	1456	1259	53.63%	1495	1374	52.11%	2.56×10^{-1}
Depression	1582	1135	58.23%	2025	853	70.36%	**2.57×10^{-21}**
POB	1005	1711	37.00%	1038	1834	36.14%	5.04×10^{-1}
Irritability	1706	1006	62.91%	1634	1240	56.85%	**4.03×10^{-6}**
VAB	947	1769	34.87%	777	2100	27.01%	**1.99×10^{-10}**
Psychosis	319	2396	11.75%	325	2549	11.31%	6.06×10^{-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* < 6.25×10^{-3}, multiple testing correction). POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

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

Table 2. 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 ($P < 6.25 \times 10^{-3}$) 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	*P*	β	*P*	β	*P*	β	*P*
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	*1.79×10^{-2}*	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	*9.91×10^{-3}*
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	*P*	β	*P*	β	*P*	β	*P*
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	*4.01×10^{-2}*	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	*1.06×10^{-2}*	-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.