ORIGINAL ARTICLE

Clinical and genetic characteristics of late-onset Huntington's disease in a large European cohort

Martina Petracca[1] | Sonia Di Tella[2] | Marcella Solito[1] | Paola Zinzi[1,3] | Maria Rita Lo Monaco[4,5] | Giulia Di Lazzaro[1,6] | Paolo Calabresi[1,7] | Maria Caterina Silveri[2,5] | Anna Rita Bentivoglio[1,7]

[1]Movement Disorders Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[2]Department of Psychology, Università Cattolica del Sacro Cuore, Milan, Italy

[3]Clinical Psychology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[4]Geriatric Day-Hospital, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[5]Medicine of the Aging, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[6]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

[7]Institute of Neurology, Università Cattolica del Sacro Cuore, Rome, Italy

Correspondence
Martina Petracca, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, L.go Agostino Gemelli 8, 00168 Rome, Italy.
Emails: martina.petracca@policlinicogemelli.it; martina.petracca@gmail.com

Abstract

Background and purpose: Huntington's disease (HD) is an autosomal dominant condition caused by CAG-triplet repeat expansions. CAG-triplet repeat expansion is inversely correlated with age of onset in HD and largely determines the clinical features. The aim of this study was to examine the phenotypic and genotypic correlates of late-onset HD (LoHD) and to determine whether LoHD is a more benign expression of HD.

Methods: This was a retrospective observational study of 5053 White European HD patients from the ENROLL-HD database. Sociodemographic, genetic and phenotypic variables at baseline evaluation of subjects with LoHD, common-onset HD (CoHD) and young-onset HD (YoHD) were compared. LoHD subjects were compared with healthy subjects (HS) aged ≥60 years. Differences between the CoHD and LoHD groups were also explored in subjects with 41 CAG triplets, a repeat number in the lower pathological expansion range associated with wide variability in age at onset.

Results: Late-onset HD presented predominantly as motor-onset disease, with a lower prevalence of both psychiatric history and current symptomatology. Absent/unknown HD family history was significantly more common in the LoHD group (31.2%) than in the other groups. The LoHD group had more severe motor and cognitive deficits than the HS group. Subjects with LoHD and CoHD with 41 triplets in the larger allele were comparable with regard to cognitive impairment, but those with LoHD had more severe motor disorders, less problematic behaviors and more often an unknown HD family history.

Conclusions: It is likely that cognitive disorders and motor symptoms of LoHD are at least partly age-related and not a direct expression of the disease. In addition to CAG-triplet repeat expansion, future studies should investigate the role of other genetic and environmental factors in determining age of onset.

KEYWORDS
41 CAG triplets, age of onset, allele expansion, Enroll-HD, late-onset Huntington's disease

INTRODUCTION

Huntington's disease (HD) is a rare heredo-neurodegenerative autosomal dominant disorder that is characterized by abnormal involuntary movements (most characteristically chorea), loss of motor control, progressive cognitive impairment and psychiatric disorders. HD is caused by cytosine-adenine-guanine (CAG) triplet-repeat expansions in exon 1 of the huntingtin gene (IT15), which is located on chromosome 4p16.3 [1,2]. CAG is the genetic code for the amino acid glutamine; the mutant alleles produce a sequence of 36 or more glutamines in the N-terminus of the Huntingtin protein (Htt), which results in selective neural cell death in the basal ganglia and cerebral cortex [3]. There is international agreement that disease onset should be defined as the time when motor signs occur, although the disease may manifest years earlier with psycho-cognitive symptoms. The age of onset of HD varies greatly. It usually occurs in middle adulthood, that is, between 35 and 55 years of age, but the disease can manifest at any age from 1 to 80 years. In a smaller percentage (approximately 10%–25%), patients experience initial symptoms after the age of 50 years; onset at the age of over 80 years has also been reported [4,5]. Current studies typically set a threshold at 60 years of age to define late-onset HD [6–13]. However, this age limit is arbitrary; in fact, "biological age" has more relevance than chronological age because the continuum of change between extremes of good health and loss of independence occurs in a wide time frame. Recent approaches have been exploring the overlap between the hallmarks of biological aging (i.e., genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction) and neurodegenerative disorders such as HD, and the subject of how aging may contribute to HD onset and progression is currently under debate [14,15].

Before the advent of genetic testing, epidemiological studies estimated that late-onset HD (LoHD) was present in 10%–25% of subjects [16,17]. In recent studies conducted in a larger European cohort, the percentage of tardive onset has been estimated at approximately 11% [11]. The clinical features of LoHD largely overlap with those of the common-onset phenotype (CoHD). The clinical characteristics of LoHD are slower disease progression, mild choreic symptoms [11] and less severe and slower cognitive decline [9,16–21]. Preponderant maternal transmission and attenuated chorea have also been hypothesized by some authors [20,22] but not confirmed by others [8,23,24]. However, it is common belief that disease progression is generally slower and less disabling because it is probably associated with a lower number of CAG repeats in the expanded allele [7,25]. As in other triplet diseases, age of onset correlates inversely with CAG-repeat length, which accounts for approximately 50% to 70% of the variability [26], with the higher variability being observed for 40–42 repeats [27,28]. Other genetic and environmental factors have been found to modulate the onset and the course of the disease [18,26,27,29,30]. In particular, in 2015, an initial combination of three genome-wide association studies (GWAS) carried out by the GeM-HD Consortium identified genome-wide significant loci on chromosomes 8 and 15 [31]. The modifier gene on chromosome 15 has been confirmed recently as FAN1 [32], involved in the repair of DNA damage, while the responsible gene on chromosome 8 is RRM2B, which encodes the small subunit of a heterotetrameric ribonucleotide reductase. A third GWAS locus suggested to be significant on chromosome 3 was confirmed in targeted follow-up of the original study [33]. Furthermore, a smaller GWAS of the TRACK-HD study participants identified MSH3, another mismatch repair gene, as an HD modifier [34] and three more DNA repair loci (PMS1, PMS2 and LIG1) have recently been identified as modifiers of onset in HD in a large cohort [35]. Taken together, these findings show that DNA repair/maintenance mechanisms play an important role in HD pathogenesis [35,36].

In conclusion, to date there is no definitive description of the genetic and phenotypical characteristics of tardive HD patients and the factors determining age of onset. In particular, it is not yet completely clear whether LoHD is characterized by an overall more benign disease expression.

The present study aimed to define the genetic and phenotypical profile of subjects with LoHD. Subjects were selected from a large cohort of HD patients and studied comprehensively with standardized tools (the ENROLL-HD database). We focused on subjects who were over 60 years of age at disease onset.

Consistent with the study aims, the following analyses were carried out:

(i) The clinical, behavioral and cognitive characteristics of White European subjects with LoHD were compared with those of subjects with onset in other age ranges;

(ii) The subgroup of LoHD patients in the initial stage of the disease (i.e., Shoulson Stage I, based on a Unified Huntington's Disease Rating Scale [UHDRS] total functional score of 11–13) [37] was compared to the group of healthy subjects (HS) enrolled as non-consanguineous family controls aged ≥60 years;

(iii) The phenotypic characteristics of patients with the same number (41) of CAG triplets (low-range CAG triplet repeats associated with wide variability in age of onset) [28] divided on the basis of age at motor onset into two groups, LoHD and CoHD, were compared with the aim of determining which factors in addition to CAG triplet repeats influence the onset of the disease. This information is of great clinical relevance because it suggests the possibility of intervention with the aim of postponing the onset of symptoms for as long as possible.

MATERIALS AND METHODS

Participants

Study subjects were enrolled from the participants in the multicentric, global, longitudinal, observational study of HD families, Enroll-HD (https://enroll-hd.org/) [38].

We used baseline data obtained from the Enroll-HD database (July 2012–October 2018) in the *Fourth Periodic Data Set* (PDS4) released on December 31, 2018.

Eligible participants were White European motor-manifest adults with CAG ≥ 36 and motor signs compatible with clinically definite disease diagnosis (UHDRS, Motor Diagnostic Confidence Level = 4). Data were collected from 123 study sites located in 13 European countries.

Patients with HD were divided by age of onset into four groups based on the most recent classifications [10–12]: LoHD (≥ 60 years); common/typical adult-onset (CoHD; 30–59 years, CoHD), young adult-onset (YoHD; 20–29 years,) and juvenile/pediatric-onset (JHD; <20 years, excluding minors, we included subjects aged 18–19 years at the baseline visit). We preferred age at motor onset to age at diagnosis, as the latter is usually postponed from one to a few years compared to the actual onset. The identification of age of motor onset was retrieved from the HD Clinical Characteristics Questionnaire (HDCCQ), which was administered at baseline by a healthcare professional and which collects retrospective information about the prevalence and onset of eight symptoms commonly observed in HD [39], asking whether the participant has ever had the symptom (yes or no) and, if yes, the age at which the symptom was first experienced. Symptoms included were as follows: motor, cognitive impairment, apathy, depression, perseverative/obsessive behavior, irritability, violent or aggressive behavior, psychosis.

For further analysis, a subgroup of subjects with LoHD at early stage (Shoulson stage I) [37] was selected and compared to a group of ≥60 years HS from nonconsanguineous family controls (i.e. spouse) who were not blood related to HD patients.

Finally, for phenotypical comparisons, HD patients with 41 CAG repeats were extracted from the dataset and clustered into two groups, namely, a CoHD and an LoHD group, on the basis of age at onset.

Outcome measures

We analyzed the genetic, sociodemographic, clinical, neuropsychological and behavioral variables of HD patients that were reported at the enrollment baseline visit in the Enroll-HD database (for further details, see Table S1). We also analyzed the Burden of Pathology (BOP) score, an index of lifelong exposure to mutant Huntingtin, calculated using the formula based on age and CAG repeat length: age $\times$ (CAG-35.5) [40].

Statistical analyses

Statistical analyses were carried out using the Statistical Package for Social Science (SPSS) version 24.0 and R Studio version 1.4.1106. Summary statistics are expressed as means and standard deviations or percentages for categorical variables. Categorical variables were compared with chi-squared statistics and continuous variables with independent samples *t*-tests or corresponding non-parametric

independent samples Mann–Whitney *U*-tests, depending on data distribution. Neuropsychological data were analyzed using analysis of covariance (ANCOVA) by inserting age, education level (according to the International Standard Classification of Education, ISCED) and disease duration as covariates or education level (ISCED)[1] and BOP score as covariates.

To prevent false-positive significant results, we set the statistical significance threshold at a *p* value <0.005 in the analysis performed on the whole sample of adult HD motor-manifest subjects, whereas a *p* value <0.05 was set for the analyses conducted on subsamples. In post hoc analyses, Bonferroni's correction was adopted to adjust *p* values when comparing more than two groups.

RESULTS

Phenotypic and genetic characteristics of the four patient groups

The complete original dataset included 15,301 participants. We excluded non-European, non-White European subjects, non-motor-manifest patients (or presenting prodromal non-specific neurological signs with a diagnostic confidence level <4), gene-negative subjects, family control subjects and minors (age <18 years at baseline). The final sample included 5053 adult motor-manifest subjects: 663 in the LoHD, 3960 in the CoHD, 368 in the YoHD and 62 in the JHD group. Due to the small number of juvenile/pediatric-onset subjects aged >18 years at baseline, the JHD group was not included in further analyses (Figure 1).

Table 1 summarizes the descriptive data of the three HD subgroups and the between-group comparisons.

The LoHD presented significantly fewer CAG triplets in the expanded allele and a lower BOP score than the other two HD groups. Regarding the UHDRS, despite the significantly shorter disease duration, the LoHD group presented comparable severity of motor symptoms and functional impairment (total motor score [TMS]; total functional capacity [TFC]) with respect to CoHD and YoHD.

Absent/unknown HD family history was significantly more common in LoHD patients (31.2%) than in the other groups (CoHD = 10%; YoHD = 3.2%) and paternal inheritance was significantly less common in that group than in any other group (Figure 2a). Expansion of the non-pathological allele was not different among the groups.

According to the rater's opinion, the initial major symptom was primarily motor in all groups, with a higher frequency in the LoHD group compared to the CoHD and YoHD groups; the frequency of cognitive disorders at onset was slightly lower in those with LoHD compared to CoHD, but was similar to that in the YoHD group. Psychiatric/behavioral disorders at onset did not differentiate the subgroups in the rater's opinion (Figure 2b).

In the psychiatric anamnesis, however, subjects with LoHD reported significantly less frequent history of alcohol/substance abuse, suicidal behavior/ideation, apathy, depression and irritability and obsessive/compulsive disorders than those with CoHD; alcohol/

FIGURE 1 Flowchart of selection of PDS4 Enroll-HD participants included in the study. Abbreviations: Co, common onset; DCL, diagnostic confidence level; HD, Huntington's disease; HS, healthy subjects; J, juvenile-pediatric onset; Lo, late onset; PDS4, Fourth Periodic Data Set; UHDRS, Unified Huntington's Disease Rating Scale; Yo, young adult age onset
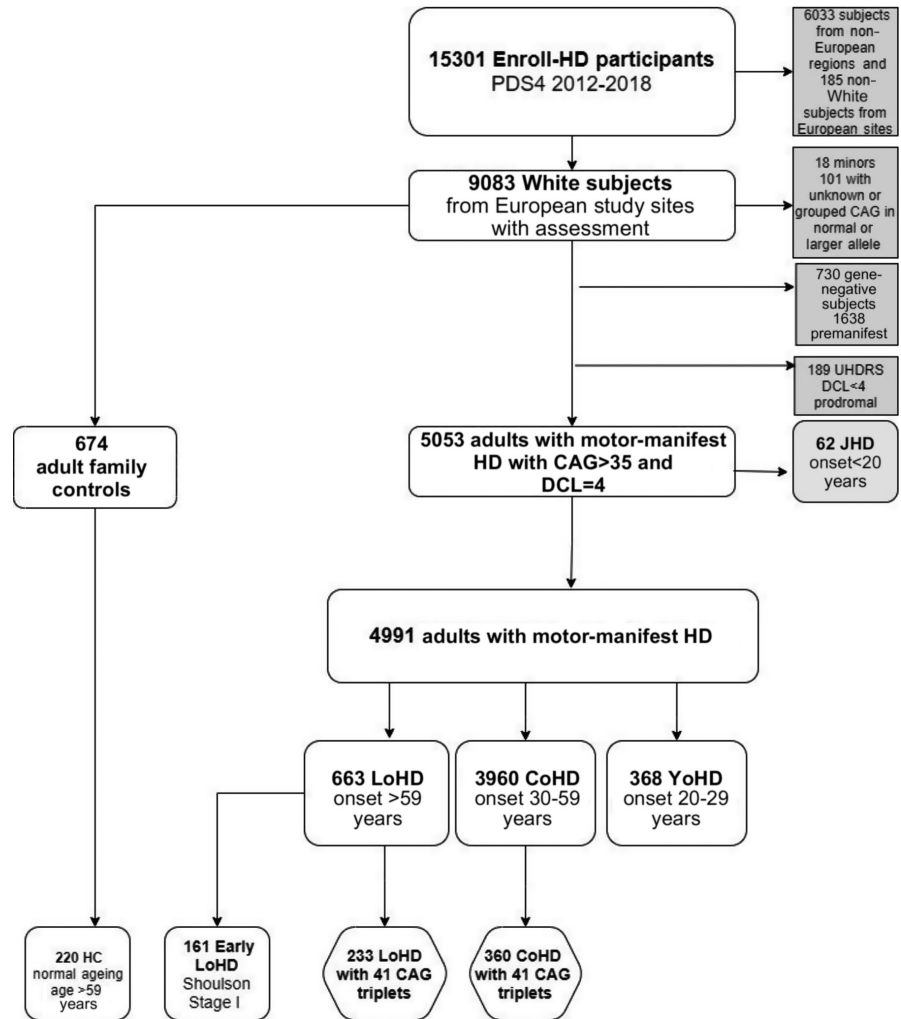
substance abuse, suicidal behavior/ideation were also reported significantly less frequently in the LoHD compared to the YoHD group. With respect to the behavioral and psychiatric disorders in the last month before baseline, the Problem Behaviors Assessment questionnaire short version (PBA-s) [39,41,42] showed a lower irritability subscore in the LoHD than the CoHD group.

In the neuropsychological assessment, the LoHD group performed worse than the CoHD group on the Mini-Mental State Examination (MMSE) and the Symbol Digit Modality Test after controlling for confounding factors (Table 1). When BOP score was also introduced into the analysis, subjects with LoHD had the lowest scores on almost all tasks (except for the Trail-Making Test [TMT] part A, correct number of answers) compared to the other two groups and the CoHD group performed worse than the YoHD group (Table 1).

Demographic, cognitive and behavioral differences between subjects with LoHD in early stages and subjects with normal aging

The subgroup of subjects with early-stage LoHD with a TFC score in the range of 11–13 (Shoulson's stage I) [37] and aged ≥60 years

(N = 161) were compared with HS aged ≥60 years (N = 220). Sociodemographic, clinical and genetic characteristics are detailed in Table 2. Subjects with LoHD were older and had a lower body mass index than controls. As expected, those with LoHD presented with lower motor performance (TMS-UHDRS) and residual functional capacity scores (TFC-UHDRS) than the HS group and had a higher number of CAG repeats. No differences were observed between the two groups with respect to psychiatric history in terms of alcohol and drug abuse. On the PBA-s, the LoHD group had a higher apathy, irritability and executive (perseverative/obsessive symptoms) domain score than the HS group.

With respect to the neuropsychological examination, the LoHD group performed worse on all tasks.

Comparison between CoHD and LoHD subjects with 41 CAG triplets

It is known that, in HD, CAG-repeat length is inversely correlated with age of onset but does not fully account for age of onset variability. In order to investigate other factors potentially able to shape this variable, subjects (N = 593) with the same number of

TABLE 1 Sociodemographic and clinical variables of subgroups of HD patients with different age of onset from Enroll-HD PDS4 ($N = 4991$)

	HD groups based on motor-onset age			Pairwise comparisons	
	LoHD	CoHD	YoHD	LoHD vs CoHD	LoHD vs YoHD
	(n = 663)	(n = 3960)	(n = 368)	p value	p value
Female, %	50.7	51.2	51.4	Ns[a]	Ns[a]
Age, years	71.6 (5.6)	52.7 (9.1)	33.2 (6.4)	<0.001[b]	<0.001[b]
Age at motor onset, years	65.1 (4.7)	45.4 (7.8)	25.4 (2.6)	<0.001[b]	<0.001[b]
Educational level (ISCED)	2.9 (1.4)	3.2 (1.2)	3.1 (1.1)	<0.001[c]	Ns[c]
CAG larger allele (n repeats)[f]	40.8 (1.2)	43.7 (2.5)	50.7 (4.3)	<0.001[b]	<0.001[b]
CAG normal allele (n repeats)	18.2 (3.1)	18.2 (2.9)	18.1 (3.0)	Ns[b]	Ns[b]
Penney BOP score	375.8 (78.7)	418.9 (91.7)	493.5 (128.4)	<0.001[b]	<0.001[b]
BMI, kg/m^2	24.6 (4.1)	24.5 (4.7)	23.4 (4.8)	Ns[b]	<0.001[b]
UHDRS TMS	41.2 (18.7)	41.2 (22.8)	44.6 (25.9)	Ns[b]	Ns[b]
UHDRS TFC score	7.4 (3.7)	7.7 (3.9)	7.3 (4.2)	Ns[b]	Ns[b]
Disease duration, years	6.5 (4.1)	7.3 (5.2)	7.7 (6.0)	<0.001[b]	<0.001[b]
Inheritance, %					
Maternal	38.8	45.4	46.2	0.001[a]	Ns[a]
Paternal	30.0	44.6	48.6	<0.001[a]	<0.001[a]
Absent/Unknown	31.2	10.0	5.2	<0.001[a]	<0.001[a]
Initial major symptom in rater's opinion, %					
Motor	60.0	50.8	50.9	<0.001[a]	0.004[a]
Cognitive	3.5	6.0	5.4	0.009[a]	Ns[a]
Psychiatric/behavioral	18.4	21.4	19.6	Ns	Ns[a]
Other/Unknown	0.4	1.1	1.6	Ns[a]	Ns[a]
Mixed (motor plus other)	17.7	20.7	22.5	Ns	Ns[a]
Psychiatric anamnesis presence, %					
Alcohol abuse history	4.2	8.1	9.2	0.001[a]	0.001[a]
Drug use/ abuse history	1.2	5.2	13.0	<0.001[a]	<0.001[a]
Suicidal behaviour/ideation	21.5	32.2	31.7	<0.001[a]	<0.001[a]
Apathy	64.6	71.2	66.0	0.001[a]	Ns[a]
Depression	63.5	76.0	67.7	<0.001[a]	Ns[a]
Irritability	64.7	73.3	67.7	<0.001[a]	Ns[a]
Psychosis	13.1%	14.3%	16.9%	Ns[a]	Ns[a]
Ossessions/Compulsions	51.6	57.6	55.0	0.004[a]	Ns[a]
PBA-s baseline domain score					
Depression	4.8 (6.0)	5.5 (6.5)	5.1 (6.2)	Ns	Ns[b]
Irritability/ aggression	2.9 (4.3)	3.7 (5.2)	3.7 (5.4)	<0.001[b]	Ns[b]
Psychosis	0.3 (1.5)	0.4 (1.9)	0.6 (2.8)	Ns[b]	Ns[b]
Apathy	4.1 (4.9)	4.3 (4.8)	3.9 (4.8)	Ns	Ns[b]
Obsessions/compulsions	3.4 (5.3)	4.1 (5.9)	4.2 (6.4)	0.002[b]	Ns[b]
Neuropsychological tests, estimated marginal means (SE)					
Age, ISCED and disease duration as covariate					
MMSE (0–30)	23.3 (0.3)	24.3 (0.1)	24.2 (0.4)	0.002[d]	Ns[d]
Symbol Digit Modality Test (0–110)	18.3 (0.6)	20.6 (0.2)	20.7 (0.8)	0.001[d]	Ns[d]
Categorial fluency (animals)	10.8 (0.3)	11.3 (0.1)	10.9 (0.3)	Ns[d]	Ns[d]

TABLE 1 (Continued)

	HD groups based on motor-onset age			Pairwise comparisons	
	LoHD	CoHD	YoHD	LoHD vs CoHD	LoHD vs YoHD
	(n = 663)	(n = 3960)	(n = 368)	p value	p value
Phonological fluency (letters)	18.2 (0.7)	19.1 (0.2)	18.5 (0.9)	Ns[d]	Ns[d]
Stroop Color Naming Test (0–100)	37.1 (0.9)	38.3 (0.3)	38.6 (1.1)	Ns[d]	Ns[d]
Stroop Word Reading Test (0–100)	50.9 (1.2)	51.8 (0.4)	50.7 (1.5)	Ns[d]	Ns[d]
Stroop Interference Test (0–100)	20.1 (0.6)	21.8 (0.2)	22.0 (0.8)	Ns[d]	Ns[d]
TMT – part A (time, 0–240 s)	84.9 (3.6)	82.6 (1.1)	85.6 (4.4)	Ns[d]	Ns[d]
TMT – part A (correct, 0–25)	23.8 (0.3)	23.8 (0.1)	23.1 (0.4)	Ns[d]	Ns[d]
TMT – part B (time, 0-240 s)	177.9 (4.6)	164.7 (1.3)	154.2 (5.6)	Ns[d]	Ns[d]
TMT – part A (correct, 0–25)	18.7 (0.6)	19.9 (0.2)	19.9 (0.7)	Ns[d]	Ns[d]
ISCED and disease burden score as covariates					
MMSE (0–30)	22.9 (0.2)	24.3 (0.1)	25.0 (0.3)	<0.001[e]	<0.001[e]
Symbol Digit Modality Test (0–110)	15.6 (0.5)	20.6 (0.2)	25.4 (0.6)	<0.001[e]	<0.001[e]
Categorial fluency (animals)	9.8 (0.2)	11.3 (0.1)	13.0 (0.3)	<0.001[e]	<0.001[e]
Phonological fluency (letters)	17.1 (0.5)	19.0 (0.2)	20.9 (0.7)	0.001[e]	<0.001[e]
Stroop Color Naming Test (0–100)	34.1 (0.7)	38.3 (0.3)	44.4 (0.9)	<0.001[e]	<0.001[e]
Stroop Word Reading Test (0–100)	47.1 (0.9)	51.8 (0.4)	58.1 (1.2)	<0.001[e]	<0.001[e]
Stroop Interference Test (0–100)	16.5 (0.5)	21.9 (0.2)	27.0 (0.6)	<0.001[e]	<0.001[e]
TMT – part A (time, 0-240 s)	101.3 (2.7)	81.9 (1.1)	64.2 (3.6)	<0.001[e]	<0.001[e]
TMT – part A (correct, 0–25)	23.1 (0.2)	23.9 (0.1)	23.9 (0.3)	Ns[e]	Ns[e]
TMT – part B (time, 0-240 s)	192.3 (3.4)	164.2 (1.3)	135.2 (4.5)	<0.001[e]	<0.001[e]
TMT – part A (correct, 0–25)	16.7 (0.5)	20.0 (0.2)	22.3 (0.6)	<0.001[e]	<0.001[e]

Data are mean and standard deviation unless otherwise specified. Between-group comparisons are also reported (significant $p < 0.005$).

Abbreviations: BMI, body mass index; BOP, Burden of Pathology; ISCED, International Standard Classification of Education; MMSE, Mini-Mental State Examination; PBA-s, Problem Behaviors Assessment questionnaire short version; TFC, total functional capacity; TMT, Trail-Making Test; UHDRS, Unified Huntington's Disease Rating Scale.

[a]Chi-squared test.

[b]Independent samples t-test.

[c]Independent samples Mann–Whitney U test.

[d]Post hoc comparisons of ANCOVA including age, ISCED and disease duration as covariates.

[e]Post hoc comparisons of parametric ANCOVA including ISCED and disease burden score as covariates.

[f]Five patients with CAG repeat >70 not included.

triplet repeats (41 CAG triplets) were split into two subgroups: 233 LoHD$_{41CAG}$ vs. 360 CoHD$_{41CAG}$. Sociodemographic, clinical and neuropsychological variables were compared in subjects with a potentially comparable genetic status but different ages of onset (Table 3). As expected, at the baseline visit, subjects in the LoHD$_{41CAG}$ subgroup were older than those in the CoHD$_{41CAG}$ subgroup, and their age at motor onset was higher. Subjects in the LoHD$_{41CAG}$ subgroup had worse motor performance (TMS) and functional capacity (TFC) and shorter disease duration. Pure motor onset was slightly significantly more frequent in those with LoHD$_{41CAG}$ (Figure 2b). Despite the same number of CAG repeats, absent or unknown family history was more frequent in LoHD$_{41CAG}$, but maternal or paternal inheritance did not differentiate the groups (Figure 2b). The length of the non-pathological allele was not different between the two groups.

Furthermore, according to the psychiatric anamnesis, subjects in the LoHD$_{41CAG}$ subgroup reported a history of depression and suicidality ideation/behavior less often than those in the CoHD$_{41CAG}$ subgroup and less severe current depression and anxiety symptoms on the PBA-s. In the neuropsychological assessment significant differences emerged only on the Stroop Interference Test and the TMT part B (correct responses), with worse performance in the LoHD$_{41CAG}$ subgroup when correcting for confounding factors.

DISCUSSION

This study focused on the LoHD population and was aimed at dissecting the correlated genotype–phenotype complexity in this subpopulation. Out of 5053 White adults with motor-manifest HD, 13%
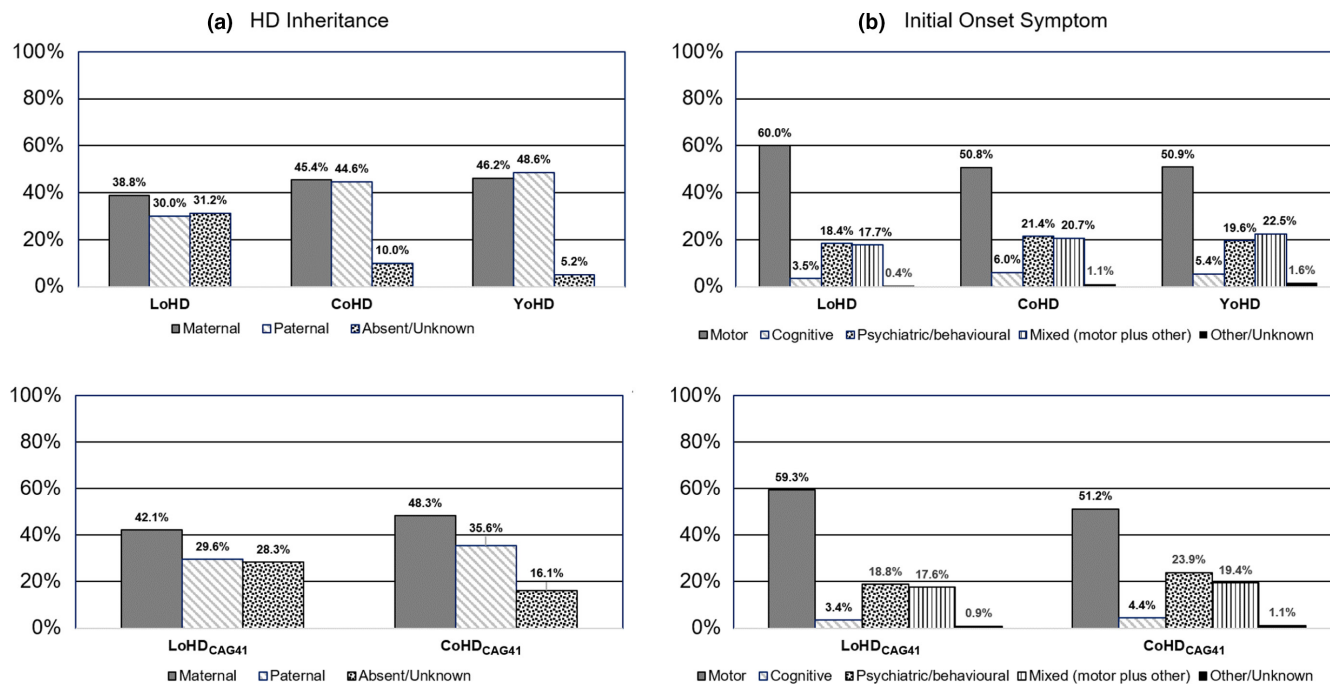
FIGURE 2 Inheritance (a) and initial major symptoms in rater's opinion (b) of subgroups of Huntington's disease (HD) patients with different age of onset (top; common onset HD [CoHD], late-onset HD [LoHD], young adult-onset HD [YoHD]) and of patients with 41 CAG repeats with CoHD and LoHD (bottom; CoHD$_{41CAG}$ and LoHD$_{41CAG}$) [Colour figure can be viewed at wileyonlinelibrary.com]

had late-onset HD, which was consistent both with previous reports, showing that in 4.4%–12.5% of HD subjects the disease manifests at the age of over 60 years [10] and with the percentage (11%) reported in the Registry cohort, which comprised European subjects (including non-White subjects) [11].

A negative correlation between CAG expansion and age of onset accounts for 50%–70% of the age variation [43]. As expected, our LoHD group showed fewer triplet repeats than the CoHD and YoHD groups, in line with data from other studies conducted in same-age groups [7,10]. Furthermore, the significantly shorter disease duration in subjects with LoHD compared to the other groups corroborates what has already been observed [7,8,44].

Late-onset HD significantly differed from CoHD and YoHD regarding absent /unknown family history (31.2% vs. 10% and 5.2%, respectively), confirming data reported in previous studies [9–11]. It has been proposed that a possible explanation for missing HD history is that these subjects may have had a parent with a mild phenotype caused by reduced penetrance allelic copy or a parent with a non-pathogenetic permutated allele that further expanded in successive generations [11].

It is noteworthy that we did not find any difference between the LoHD and CoHD groups, either in the whole sample of patients or in the subsample of those with CAG41 triplets, in the expansion of the non-pathological allele. In agreement with our data, no difference was documented between the CoHD and LoHD groups in a large European cohort from Registry [11,39].

Subjects with LoHD presented with motor onset more frequently than the other groups [7,8,11] and with cognitive onset slightly less frequently than the CoHD group. At the baseline visit, TMS and TFC

did not differentiate the groups despite different disease duration (shorter in the LoHD group), further suggesting that motor symptoms are characteristic of this group. While our data are consistent with those reported in previous studies showing more severe motor disorders in individuals with LoHD [11,12], they are in contrast with others that report lower severity of motor symptoms, particularly chorea [11]. This is coherent with clinical observations of patients with longer disease duration in which chorea is replaced by a rigid-akinetic phenotype.

In line with recent data [12,13], the anamnestic presence of psychic and behavioral disorders was less significant in the LoHD group compared to the other groups as was the detection of current psychiatric symptoms at baseline.

Regarding cognitive impairment, the global measure (MMSE) and a few executive tasks were more impaired in subjects with LoHD than in those with CoHD and were overall comparable in the LoHD and YoHD groups. However, it is likely that the origin of the cognitive impairment is different in LoHD and YoHD, that is, correlated to aging in LoHD [45] and to the disease in YoHD. Consistent with this, introducing BOP score as a covariate in the statistical comparisons, that is, controlling for general effects of the disease, performance on the cognitive tasks clearly reflected the age of the subjects, with lower scores in older subjects (LoHD) and higher scores in younger subjects (YoHD).

Thus, the hypothesis that LoHD might correspond to less severe disease expression [7,21] is at least partially supported. However, subjects with early-stage LoHD (Shoulson stage I) already showed clear signs of a widespread cognitive disorder compared to HS aged ≥60 years, as well as behavioral manifestations

TABLE 2 Sociodemographic and clinical variables of subjects with late-onset Huntington's disease in the early stage of disease (Shoulson stage I) and family non-blood-related healthy subjects, aged ≥ 60 years (total subjects = 381)

	Early-stage (Shoulson stage I) LoHD ≥60 (*n* = 161)	Healthy subjects ≥60 (*n* = 220)	*p* value
Female, %	42.9	56.4	**0.009**[a]
Age, years	69.3 (5.3)	66.5 (5.2)	**<0.001**[b]
Educational level (ISCED)	3.4 (1.4)	3.1 (1.3)	**<0.028**[c]
Age at motor onset, years	64.8 (4.4)		
CAG larger allele (*n* repeats)	40.6 (1.0)	19.5 (3.1)	**<0.001**[b]
CAG normal allele (*n* repeats)	18.3 (2.8)	16.6 (2.1)	**<0.001**[b]
Penney BOP score	352.0 (66.8)		
BMI, kg/m^2	24.9 (4.0)	28.0 (4.4)	**<0.001**
UHDRS total motor score	24.9 (10.9)	1.9 (2.7)	**<0.001**[b]
UHDRS total functional capacity	12.0 (0.8)	12.7 (0.7)	**<0.001**[b]
Disease duration, years	4.4 (3.5)		
Psychiatric anamnesis, %			
Alcohol abuse history	0.6	2.3	Ns[a]
Drug use/ abuse history	0	0.9	Ns[a]
PBA-s baseline domain score			
Depression	4.1 (5.8)	4.2 (5.1)	Ns[b]
Irritability/ Aggression	2.5 (3.8)	1.3 (2.8)	**0.001**[b]
Psychosis	0.2 (1.2)	0 (0)	Ns[b]
Apathy	1.4 (2.9)	0.7 (2.0)	**0.005**[b]
Executive	1.5 (2.9)	0.7 (2.0)	**0.002**[b]
Neuropsychological Tests estimated marginal means (standard error)			
MMSE (0–30)	26.9 (0.2)	29.0 (0.2)	**<0.001**[d]
Symbol Digit Modality Test (0–110)	26.6 (0.8)	38.0 (0.6)	**<0.001**
Categorial fluency (animals)	14.5 (0.4)	20.0 (0.3)	**<0.001**[d]
Phonological fluency (letters)	26.3 (1.1)	34.7 (0.8)	**<0.001**[d]
Stroop Color Naming Test (0–100)	48.8 (1.0)	64.8 (0.8)	**<0.001**[d]
Stroop Word Reading Test (0–100)	68.4(1.3)	87.3(1.1)	**<0.001**[d]
Stroop Interference Test (0–100)	23.6(0.8)	33.2(0.6)	**<0.001**[d]

(Continues)

TABLE 2 (Continued)

	Early-stage (Shoulson stage I) LoHD ≥60 (*n* = 161)	Healthy subjects ≥60 (*n* = 220)	*p* value
TMT – part A (time, 0-240s)	66.1(2.7)	42.1(2.1)	**<0.001**[d]
TMT – part A (correct, 0–25)	24.9(0.2)	24.6(0.2)	Ns[d]
TMT – part B (time, 0-240s)	138.6(5.1)	95.9(3.8)	**<0.001**[d]
TMT – part B (correct, 0–25)	22.6(0.5)	23.5(0.4)	Ns[d]

Note: Mean and standard deviation are reported unless otherwise specified. Between-group comparisons are also reported (significant *p* < 0.05 in bold).

Abbreviations: BMI, body mass index; BOP, Burden of Pathology; ISCED, International Standard Classification of Education; MMSE, Mini-Mental State Examination; PBA-s, Problem Behaviors Assessment questionnaire short version; TMT, Trail-Making Test.

[a]Chi-squared test.

[b]Independent samples *t*-test.

[c]independent samples Mann–Whitney *U*-test.

[d]ANCOVA including age, sex and ISCED as covariates.

and motor disorders. Thus, although part of the symptomatology can be attributed to aging at both the cognitive and motor level, tardive HD is a highly disabling condition, completely different from normal aging.

Even if some differences in phenotypic expression between LoHD and CoHD are cancelled out when subjects with the same low number of triplets are considered, in our population, some elements of diversity remain, namely, greater behavioral impairment in those with CoHD and cognitive impairment in LoHD, respectively. More frequent motor onset was also confirmed in the LoHD group.

It is quite interesting to note that despite the same allele expansion, greater difficulty in identifying positive family history in LoHD was confirmed, with a consistently greater presence of cases with absent or unknown inheritance (28.3 vs. 16.1) in this group. Thus, our data on subjects with an equal number of triplets differ in some respects from the data reported in a recent work [28]. In conclusion, what we see in the phenotypical expression of LoHD is probably the combined effects of disease- and age-related factors [46]. As recently investigated, genetic modifiers independent of CAG length contribute to age of onset [36]; furthermore, the intervention of epigenetic and environmental factors cannot be excluded. Cognitive impairment in LoHD is only partly determined by the disease; in fact, there may also be age-related factors [46]. There is evidence of an age-related decline at a more rapid rate in HD, with aging exacerbating cerebral damage in HD. In some brain regions, HD seems to be associated with an accelerated epigenetic age and an overlap between the cellular mechanism of aging and

TABLE 3 Sociodemographic, clinical and neuropsychological variables of subjects with common-onset Huntington's disease (HD) with 41 CAG triplets and subject with late-onset HD with 41 CAG triplets (total subjects with 41CAG = 593)

	LoHD	CoHD	Ns[a]
	Onset ≥ 60 years	Onset 30–59 years	
	(n = 233)	(n = 360)	p- value
Female, %	54.1%	53.3%	Ns[a]
Age, years	70.6 (4.7)	60.1 (7.6)	<0.001[b]
Age at motor onset, years	64.2 (3.5)	52.0 (6.1)	<0.001[b]
Educational level (ISCED)	3.0 (1.4)	3.3 (1.3)	0.009[c]
CAG normal allele (n repeats)	18.2 (3.1)	17.9 (2.8)	Ns[b]
Penney BOP score	388.3 (25.8)	330.7 (41.8)	<0.001[b]
BMI, kg/m^2	24.7 (3.9)	25.4 (4.7)	Ns[b]
UHDRS total motor score	42.7 (19.1)	33.6 (19.4)	<0.001[b]
UHDRS total functional capacity	7.4 (3.7)	8.7 (3.6)	<0.001[b]
Disease duration, years	6.4 (3.8)	8.1 (5.8)	<0.001[b]
Inheritance, %			
Maternal	42.1	48.3	Ns[a]
Paternal	29.6	35.6	Ns[a]
Absent/Unknown	28.3	16.1	<0.001
Initial major symptom in rater's opinion, %			
Motor	59.3	51.2	Ns[a]
Cognitive	3.4	4.4	Ns[a]
Psychiatric/behavioural	18.8	23.9	Ns[a]
Other/Unknown	0.9	1.1	Ns[a]
Mixed (motor plus other)	17.6	19.4	Ns[a]
Psychiatric anamnesis presence, %			
Alcohol abuse history	4.8	5.3	Ns[a]
Drug use/ abuse history	0.9	3.6	0.038[a]
Suicidal behaviour/ideation	23.7	36.7	0.001[a]
Depression	69.5	79.7	0.005[a]
Irritability	66.5	71.7	Ns[a]
Psychosis	13.3	17.5	Ns[a]
Apathy	66.1	67.8	Ns[a]
Executive	51.9	53.9	Ns[a]
PBA-s baseline domain score			
Depression	4.4 (5.4)	5.9 (6.9)	0.005[b]
Irritability/ aggression	2.9 (4.3)	3.2 (4.6)	Ns[b]
Psychosis	0.2 (1.2)	0.3 (1.8)	Ns[b]
Apathy	4.3 (5.1)	4.0 (4.8)	Ns[b]
Obsessive/compulsive symptoms	3.1 (4.9)	3.6 (5.6)	Ns[b]
Neuropsychological tests estimated marginal means (standard error)			
MMSE (0–30)	24.1 (0.5)	25.3 (0.3)	Ns[d]
Symbol Digit Modality Test (0–110)	21.3 (0.9)	22.4 (0.7)	Ns[d]
Categorial fluency (animals)	11.7 (0.5)	12.2 (0.3)	Ns[d]
Phonological fluency (letters)	21.2 (1.2)	22.1 (0.8)	Ns[d]
Stroop Color Naming Test (0–100)	38.2 (1.4)	41.6 (1.1)	Ns[d]
Stroop Word Reading Test (0–100)	53.3 (1.9)	56.5 (1.4)	Ns[d]

TABLE 3 (Continued)

	LoHD	CoHD	Ns[a]
	Onset ≥ 60 years	Onset 30–59 years	
	(n = 233)	(n = 360)	p- value
Stroop Interference Test (0–100)	20.2 (1.0)	23.7 (0.8)	**0.023**[d]
Trail Making Test – part A (time, 0-240 s)	84.0 (5.3)	73.2 (3.5)	Ns[d]
Trail Making Test – part A (correct, 0–25)	23.8 (0.5)	24.0 (0.3)	Ns[d]
Trail Making Test – part B (time, 0-240 s)	166.4 (7.2)	162.6 (4.8)	Ns
Trail Making Test – part B (correct, 0–25)	18.7 (0.8)	21.4 (0.6)	**0.020**[d]

Note: Mean and standard deviation represented, unless otherwise specified.

Abbreviations: BMI, body mass index; BOP, Burden of Pathology; ISCED, International Standard Classification of Education; MMSE, Mini-Mental State Examination; PBA-s, Problem Behaviors Assessment questionnaire short version.

[a]Chi-squared test.

[b]Independent samples *t*-test.

[c]Independent samples Mann–Whitney *U*-test.

[d]ANCOVA including age, educational level, disease duration as covariates.

the pathogenesis of HD has been widely described [47]. Therefore, it is possible that, in the elderly, the effects of brain damage interact with age-related fragility, contributing to a greater impact on cognitive dysfunction. Similar considerations can be taken into account with regard to motor and functional impairment. From this point of view, it is possible to conclude that the late-onset disease is more benign, as some of the symptoms can be attributed to the "age factor". In this regard, it is also significant that some of the clinical manifestations persist in those with LoHD, even when they are compared to subjects with CoHD but the same allele expansion, supporting the hypothesis that additional factors concur in the phenotypical expression. In 2018, Morrison and Delatycki [48] suggested that, out of the 30% of factors not related to triplet size, 10% are environmental, providing a possible chance for intervention to postpone the age of onset of HD and slow its progression. Lifestyle interventional treatments, including diet, physical exercise, maintaining/improving social relationships, psychobehavioral support to minimize stress impact and enhance coping strategies, will possibly impact healthspan and phenotypical expression of the disease in HD subjects [49,50].

The strength of our study is the large number of subjects and variables considered. However, we also acknowledge some limitations. First, this was a cross-sectional observational study that focused on the baseline visit but did not cover disease progression, which could be an important driver of diversity between LoHD and CoHD [8]. In fact, many other useful observations can be drawn from the longitudinal observation of the evolution of symptoms to answer the questions we have posed. A longitudinal approach will be followed in future studies. Experimental designs constructed to disentangle age-related from disease-derived factors could also help to better define clinical pictures in patients with late-onset disease, as well as in the search for genetic and familial factors not expressed by the triplet repeat expansions in exon 1 of the huntingtin gene (IT15).

Finally, identification of any environmental factors with a role in modulating age of onset would have great clinical importance; in fact, this could suggest important strategies and interventions for delaying disease onset as much as possible, increasing the healthspan of HD mutation carriers.

CONFLICT OF INTEREST
The authors declare no potential conflicts of interest related to this manuscript and did not receive financial or material support for this research. Financial disclosures for all authors for the preceding 12 months are as follows. M.P. received honoraria for an advisory board from Zambon and fee for scientific meeting from Merz, Ipsen and Bial. A.R.B. received speaker honoraria from Allergan, Ipsen, Merz, UCB Pharma, Bial, Chiesi, AbbVie, Zambon, Ralpharma and Boston. G.D.L. received a fellowship research grant from EAN. P.C. received research support, speaker honoraria, and support to attend national and international conferences (not related to the present study) from Abbvie, Bial, Bayer Schering, Biogen-Dompè, Biogen-Idec, Eisai, Lilly, Lundbeck, Lusofarmaco, Merck-Serono, Novartis, Sanofi-Genzyme, Teva, UCB Pharma and Zambon. All other authors have no disclosures to report.

AUTHOR CONTRIBUTIONS
Martina Petracca: Data curation (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). **Sonia Di Tella:** Data curation (equal); Formal analysis (equal); Methodology (equal); Software (lead); Writing – original draft (equal); Writing – review and editing (equal). **Marcella Solito:** Conceptualization (equal); Data curation (equal); Methodology (equal). **Paola Zinzi:** Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (equal). **Maria Rita Lo Monaco:** Conceptualization (equal); Data curation (equal); Formal

analysis (equal); Methodology (equal); Writing – original draft (equal). **Giulia Di Lazzaro:** Data curation (equal); Methodology (equal). **Paolo Calabresi:** Supervision (equal); Writing – review and editing (equal). **Maria Caterina Silveri:** Conceptualization (equal); Supervision (equal); Writing – review and editing (equal). **Anna Rita Bentivoglio:** Conceptualization (equal); Methodology (equal); Supervision (equal); Writing – review and editing (equal).

INFORMED CONSENT

This study did not require institutional review board (IRB) approval because it utilized pre-collected, deidentified data from the Enroll-HD database. Each study site that collected data received its own approval for the study from the local or national coordinator Site IRB and all participants, or their authorized representative in case of inability, gave their written informed consent for participation in the study and the distribution of de-identified data for research purposes.

DATA AVAILABILITY STATEMENT

Details regarding Enroll-HD are accessible at website https://enroll-hd.org/Enroll-HD. Dataset access can be requested by qualified researchers at https://enroll-hd.org/for-researchers/

ORCID

Martina Petracca https://orcid.org/0000-0001-8033-3785
Sonia Di Tella https://orcid.org/0000-0002-2248-5120
Marcella Solito https://orcid.org/0000-0002-9120-058X
Paola Zinzi https://orcid.org/0000-0001-5379-4674
Maria Rita Lo Monaco https://orcid.org/0000-0002-1457-7981
Giulia Di Lazzaro https://orcid.org/0000-0003-2413-1788
Paolo Calabresi https://orcid.org/0000-0003-0326-5509
Maria Caterina Silveri https://orcid.org/0000-0002-0019-6838
Anna Rita Bentivoglio https://orcid.org/0000-0002-9663-095X

ENDNOTE

[1] ISCED: Educational Levels coded internationally as: 0, preprimary; 1, primary; 2, lower secondary; 3, upper secondary, 4, postsecondary, 5, first-stage tertiary, 6, second-stage tertiary.

REFERENCES

1. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature*. 1983;306(5940):234-238. doi:10.1038/306234a0
2. MacDonald M, Ambrose C, Duyao M, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72(6):971-983. doi:10.1016/0092-8674(93)90585-e
3. Estrada-Sánchez AM, Rebec GV. Role of cerebral cortex in the neuropathology of Huntington's disease. *Front Neural Circuits*. 2013;7:19. doi:10.3389/fncir.2013.00019
4. Gómez-Tortosa E, del Barrio A, García Ruiz PJ, et al. Severity of cognitive impairment in juvenile and late-onset Huntington disease. *Arch Neurol*. 1998;55(6):835-843. doi:10.1001/archneur.55.6.835
5. Langbehn DR, Hayden MR, Paulsen JS. CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. *Am J Med Genet: Part B Neuropsychiatr Genet*. 2010;153B(2):397-408. doi:10.1002/ajmg.b.30992
6. Alonso ME, Ochoa A, Boll MC, et al. Clinical and genetic characteristics of Mexican Huntington's disease patients. *Mov Disord*. 2009;24(13):2012-2015. doi:10.1002/mds.22737
7. Lipe H, Bird T. Late onset Huntington disease: clinical and genetic characteristics of 34 cases. *J Neurol Sci*. 2009;276(1–2):159-162. doi:10.1016/j.jns.2008.09.029
8. Koutsis G, Karadima G, Kladi A, Panas M. Late-onset Huntington's disease: diagnostic and prognostic considerations. *Parkinsonism Relat Disord*. 2014;20(7):726-730. doi:10.1016/j.parkreldis.2014.03.017
9. Cornejo-Olivas MR, Inca-Martinez MA, Espinoza-Huertas K, et al. Clinical and molecular features of late onset Huntington disease in a Peruvian cohort. *J Huntington's Dis*. 2015;4(1):99-105. doi:10.3233/JHD-140119
10. Chaganti SS, McCusker EA, Loy CT. What do we know about Late Onset Huntington's Disease? *J Huntington's Dis*. 2017;6(2):95-103. doi:10.3233/jhd-170247
11. Oosterloo M, Bijlsma EK, van Kuijk SM, Minkels F, de Die-Smulders CE. Clinical and genetic characteristics of late-onset Huntington's disease. *Parkinsonism Relat Disord*. 2019;61:101-105. doi:10.1016/j.parkreldis.2018.11.009
12. Kwa L, Larson D, Yeh C, Bega D. Influence of age of onset on Huntington's disease phenotype. *Tremor Other Hyperkinet Mov*. 2020;10:21. 10.5334/tohm.536
13. Ranganathan M, Kostyk SK, Allain DC, Race JA, Daley AM. Age of onset and behavioral manifestations in Huntington's disease: an Enroll-HD cohort analysis. *Clin Gene*. 2021;99(1):133-142. doi:10.1111/cge.13857
14. Machiela E, Southwell AL. Biological aging and the cellular pathogenesis of Huntington's disease. *J Huntington's Dis*. 2020;9(2):115-128. doi:10.3233/jhd-200395
15. Azam S, Haque ME, Balakrishnan R, Kim IS, Choi DK. The ageing brain: molecular and cellular basis of neurodegeneration. *Front Cell Dev Biol*. 2021;9:683459. doi:10.3389/fcell.2021.683459
16. Harper PS. *Huntington's Disease*. Major Problems in Neurology (31), 2nd, London, Philadelphia: WB Saunders Company Ltd; 1996.
17. Hayden MR. Living with Huntington's chorea: The social perspective. *Huntington's Chorea*. New York: Springer; 1981:123-135. https://link.springer.com/book/10.1007/978-1-4471-1308-9
18. Kremer B, Squitieri F, Telenius H, et al. Molecular analysis of late onset Huntington's disease. *J Med Genet*. 1993;30(12):991-995. doi:10.1136/jmg.30.12.991
19. Faught E, Falgout JC, Leli DA. Late-onset variant of Huntington's chorea. *South Med J*. 1983;76(10):1266-1270. doi:10.1097/00007611-198310000-00018
20. Myers RH, Sax DS, Schoenfeld M, et al. Late onset of Huntington's disease. *J Neurol Neurosurg Psychiatry*. 1985;48(6):530-534. doi:10.1136/jnnp.48.6.530
21. Britton JW, Uitti RJ, Ahlskog JE, Robinson RG, Kremer B, Hayden MR. Hereditary late-onset chorea without significant dementia: genetic evidence for substantial phenotypic variation in Huntington's disease. *Neurology*. 1995;45(3 Pt 1):443-447. doi:10.1212/wnl.45.3.443
22. Farrer LA, Conneally PM. A genetic model for age at onset in Huntington disease. *Am J Hum Genet*. 1985;37(2):350-357.
23. Adams P, Falek A, Arnold J. Huntington disease in Georgia: age at onset. *Am J Hum Genet*. 1988;43(5):695-704.
24. Went LN, Vegter-van der Vlis M, Bruyn GW. Paternal transmission in Huntington's disease. *Lancet*. 1984;323(8386):1100-1102. doi:10.1016/S0140-6736(84)92510-8
25. Rosenblatt A, Kumar BV, Mo A, Welsh CS, Margolis RL, Ross CA. Age, CAG repeat length, and clinical progression in Huntington's disease. *Mov Disord*. 2012;27(2):272-276. doi:10.1002/mds.24024
26. Myers RH. Huntington's disease genetics. *NeuroRx*. 2004;1(2):255-262. doi:10.1602/neurorx.1.2.255

27. 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 USA*. 2004;101(10):3498-3503. doi:10.1073/pnas.0308679101

28. Capiluppi E, Romano L, Rebora P, et al. Late-onset Huntington's disease with 40–42 CAG expansion. *Neurol Sci*. 2020;41(4):869–876. 10.1007/s10072-019-04177-8

29. Gusella JF, MacDonald ME. Huntington's disease: the case for genetic modifiers. *Genome Med*. 2009;1(8):80. 10.1186/gm80

30. Metzger S, Walter C, Riess O, et al. The V471A polymorphism in autophagy-related gene ATG7 modifies age at onset specifically in Italian Huntington disease patients. *PLoS One*. 2013;8(7):e68951. doi:10.1371/journal.pone.0068951

31. Consortium GMoHsDG-H. Identification of genetic factors that modify clinical onset of Huntington's disease. *Cell*. 2015;162(3):516-526. doi:10.1016/j.cell.2015.07.003

32. Kim KH, Hong EP, Shin JW, et al. Genetic and Functional analyses point to FAN1 as the source of multiple huntington disease modifier effects. *Am J Hum Genet*. 2020;107(1):96-110. doi:10.1016/j.ajhg.2020.05.012

33. Lee JM, Chao MJ, Harold D, et al. A modifier of Huntington's disease onset at the MLH1 locus. *Hum Mol Genet*. 2017;26(19):3859-3867. doi:10.1093/hmg/ddx286

34. Moss DJH, 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(9):701-711. doi:10.1016/s1474-4422(17)30161-8

35. Consortium GMoHsDG-H. CAG repeat not polyglutamine length determines timing of Huntington's disease onset. *Cell*. 2019;178(4):887-900.e14. doi:10.1016/j.cell.2019.06.036

36. Gusella JF, Lee JM, MacDonald ME. Huntington's disease: nearly four decades of human molecular genetics. *Hum Mol Genet*. 2021;30(R2):R254-R263. doi:10.1093/hmg/ddab170

37. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. *Neurology*. 1979;29(1):1-3. doi:10.1212/wnl.29.1.1

38. 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(2):212-224. doi:10.1002/mdc3.12388

39. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. *PLoS Curr*. 2011;2:RRN1184. 10.1371/currents.RRN1184

40. Penney JB Jr, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann Neurol*. 1997;41(5):689-692. doi:10.1002/ana.410410521

41. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. *Neuropsychiatry Neuropsychol Behav Neurol*. 2001;14(4):219-226.

42. Kingma EM, van Duijn E, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. *Gen Hosp Psychiatry*. 2008;30(2):155-161. doi:10.1016/j.genhosppsych.2007.11.005

43. Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet*. 1993;4(4):398-403. doi:10.1038/ng0893-398

44. Foroud T, Gray J, Ivashina J, Conneally PM. Differences in duration of Huntington's disease based on age at onset. *J Neurol Neurosurg Psychiatry*. 1999;66(1):52-56. doi:10.1136/jnnp.66.1.52

45. Baake V, Reijntjes R, Dumas EM, Thompson JC, Roos RAC. Cognitive decline in Huntington's disease expansion gene carriers. *Cortex*. 2017;95:51-62. doi:10.1016/j.cortex.2017.07.017

46. James CM, Houlihan GD, Snell RG, Cheadle JP, Harper PS. Late-onset Huntington's disease: a clinical and molecular study. *Age Ageing*. 1994;23(6):445-448. doi:10.1093/ageing/23.6.445

47. Horvath S, Langfelder P, Kwak S, et al. Huntington's disease accelerates epigenetic aging of human brain and disrupts DNA methylation levels. *Aging*. 2016;8(7):1485-1512. doi:10.18632/aging.101005

48. Morrison PJ, Delatycki MB. Ameliorating the age at onset and disease progression in Huntington disease. *Neurology*. 2018;90(24):1087-1088. doi:10.1212/wnl.0000000000005670

49. Mo C, Hannan AJ, Renoir T. Environmental factors as modulators of neurodegeneration: insights from gene-environment interactions in Huntington's disease. *Neurosci Biobehav Rev*. 2015;52:178-192. doi:10.1016/j.neubiorev.2015.03.003. Epub 2015 Mar 10 PMID: 25770041.

50. Queen NJ, Hassan QN 2nd, Cao L. Improvements to healthspan through environmental enrichment and lifestyle interventions: where are we now? *Front Neurosci*. 2020;12(14):605. doi:10.3389/fnins.2020.00605

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Petracca M, Di Tella S, Solito M, et al. Clinical and genetic characteristics of late-onset Huntington's disease in a large European cohort. *Eur J Neurol.* 2022;29:1940–1951. doi:10.1111/ene.15340