NULL HYPOTHESIS   CLASS OF EVIDENCE

Clinical manifestations of homozygote allele carriers in Huntington disease

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Abstract

Objective
Because patients homozygous for Huntington disease (HD) receive the gain-of-function mutation in a double dose, one would expect a more toxic effect in homozygotes than in heterozygotes. Our aim was to investigate the phenotypic differences between homozygotes with both alleles ≥36 CAG repeats and heterozygotes with 1 allele ≥36 CAG repeats.

Methods
This was an international, longitudinal, case-control study (European Huntington's Disease Network Registry database). Baseline and longitudinal total functional capacity, motor, cognitive, and behavioral scores of the Unified Huntington's Disease Rating Scale (UHDRS) were compared between homozygotes and heterozygotes. Four-year follow-up data were analyzed using longitudinal mixed-effects models. To estimate the association of age at onset with the length of the shorter and larger allele in homozygotes and heterozygotes, regression analysis was applied.

Results
Of 10,921 participants with HD (5,777 female [52.9%] and 5,138 male [47.0%]) with a mean age of 55.1 ± 14.1 years, 28 homozygotes (0.3%) and 10,893 (99.7%) heterozygotes were identified. After correcting for multiple comparisons, homozygotes and heterozygotes had similar age at onset and UHDRS scores and disease progression. In the multivariate linear regression analysis, the longer allele was the most contributing factor to decreased age at HD onset in the homozygotes ($p < 0.0001$) and heterozygotes ($p < 0.0001$).

Conclusions
CAG repeat expansion on both alleles of the *HTT* gene is infrequent. Age at onset, HD phenotype, and disease progression do not significantly differ between homozygotes and heterozygotes, indicating similar effect on the mutant protein.

Classification of evidence
This study provides Class II evidence that age at onset, the motor phenotype and rate of motor decline, and symptoms and signs progression is similar in homozygotes compared to heterozygotes.

Glossary

BMI = body mass index; **CI** = confidence interval; **EHDN** = European Huntington's Disease Network; **HD** = Huntington disease; **SNP** = single nucleotide polymorphism; **TFC** = total functional capacity; **TMS** = total motor score; **UHDRS** = Unified Huntington's Disease Rating Scale.

The presence of 36 or more CAG trinucleotide repeats in the *HTT* gene nearly ensures the development of Huntington disease (HD) as an autosomal dominantly transmitted disorder. Because homozygote patients (i.e., with 2 mutant alleles) for HD receive the gain-of-function mutation in a double dose, one would expect a more toxic effect in homozygotes than in the heterozygotes (i.e., with one mutant allele), similar to other poly CAG diseases.[1,2] In this regard, some publications in animal models and small HD human retrospective studies have reported a more aggressive HD progression and brain atrophy in homozygotes.[2,3] In contrast, other authors have reported an indistinguishable phenotype in HD homozygotes and heterozygotes.[4–8] Given these contradictory data and the sparse longitudinal information, we aimed to further investigate the clinical differences between HD homozygotes (with both alleles ≥36 CAG repeats) and heterozygotes (with one allele ≥36 CAG repeats) in terms of age at onset, phenotypic presentation, and disease progression.

Methods

Design

This was an international, retrospective–longitudinal, case–control study.

Sample characteristics and ethics

Clinical and sociodemographic data were obtained from patients enrolled in the European Huntington's Disease Registry Database (European Huntington's Disease Network [EHDN]).[9] For this observational study, participants provided written, informed consent following the International Conference on Harmonization–Good Clinical Practice guidelines.[10] For participants who lacked capacity to consent, study sites followed country-specific guidelines for signing consent forms. Minors agreed with both parents authorizing for them. Ethical approval was collected from the local ethics committee for each study site contributing to EHDN Registry.[9]

Participants and clinical assessments

Data of individuals from the European Huntington's Disease Registry Database, from July 1998 to December 2016, with a larger allele ≥36 CAG repeats within the Huntingtin gene were included in this study. Data collection adhered to a standard protocol including electronic case report forms, and used identical study protocols of assessment and sampling of biomaterials.

Demographics, number of years of education, and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) were extracted from the EHDN registry. Motor and psychiatric signs were scored using the Unified Huntington's Disease Rating Scale (UHDRS).[11] For motor and behavior UHDRS, higher scores indicated worse motor and higher psychiatric impairment. For cognition, we used the cognitive UHDRS composite score (UHDRS total correct for letter fluency, Symbol Digit Modalities Test, and Stroop subscores for word reading, color identification, naming, and interference), with lower scores indicating worse performance.[12] Disease stage was obtained from total functional capacity (TFC) scores, with higher scores indicating better functional status.[13] Patients were followed up on a yearly basis according to the EHDN Registry protocol.[9,12] Study site raters were annually trained, evaluated, and certified to lessen interrater and intrarater variability. Data entry was reviewed online and an on-site by monitors fluent in the language of the study site.[9,12] The *HTT* CAG genotyping was performed at each local genetic laboratory. In addition, fresh blood samples were donated by patients and sent to the central laboratory in Milan, Bio-Rep, to be reanalyzed. Clinically significant discrepancies, defined as crossing the boundary at 35–36 or 39–40 CAG repeat lengths, or measurement errors (±1 for CAG repeat lengths ≤42 and ±3 for CAG repeat lengths ≥43), were brought to the attention of the local site investigator and subsequently addressed.

Data management

HD homozygotes were defined as carriers of 2 alleles with ≥36 CAG repeats, while HD heterozygotes were individuals with the longer allele ≥36 CAG repeats and the shorter allele <36 CAG repeats. Demographics, CAG repeat length, and clinical information including total motor score (TMS), cognitive and behavior UHDRS scores, and TFC information at baseline and after 4 years of follow-up were collected from the EHDN database. With the motor UHDRS, different domain subscores were calculated: chorea (sum of the chorea items [face, buccolingual, upper and lower extremities scores]), dystonia (sum of the trunk, upper and lower extremities scores), bradykinesia (sum of the finger taps, pronate/supinate, rigidity of each extremity, and body bradykinesia scores), gait impairment (sum of gait, tandem, and retropulsion scores), and oculomotor performance (sum of ocular pursuit, saccade initiation, and saccade velocity). To deal with missing values, case-wise deletions were adopted.

Statistical analysis

Analysis was done using IBM-SPSS 21 software (SPSS Inc., Chicago, IL), following the Reporting of Observational Studies in Epidemiology guidelines.[14] Normal distribution of variables was analyzed using the Kolmogorov-Smirnov test. Descriptive analysis of the participants' characteristics was

performed in terms of frequencies (percentage), mean/median values with the corresponding SD or interquartile range, as appropriate, and 95% confidence intervals (CI).

Clinical characteristics were analyzed in a cross-sectional and longitudinal manner. Baseline differences between HD homozygotes and the total sample of HD heterozygous were first evaluated. To balance differences in sample sizes, a post hoc secondary analysis was carried out, comparing homozygotes with a subset of heterozygotes, paired by age and CAG larger allele (1:3). In addition, because aging might worsen the UHDRS scores, especially bradykinesia and gait scores, independently of the genetic status,[15] a comparative analysis between homozygotes and heterozygotes was conducted including young and older participants. All homozygote and heterozygote participants were classified as older (>51 years old) or younger participants (≤51 years old), based on the median age of homozygotes at registry entry. Differences were analyzed using the χ^2, Phi, and Cramer tests (categorical variables), and Mann-Whitney U tests (nonparametric for quantitative variables). A significance level of $\alpha = 0.004$, 2-sided tests, was applied after post hoc Bonferroni multiple comparison adjustments.

To analyze the association between age, length of the larger and shorter alleles, BMI, and UHDRS outcome measures, correlations were calculated using Spearman (nonparametric) correlation coefficients. To analyze the relationship between age at onset and the length of the larger and shorter alleles in the homozygote and heterozygote groups, a multivariate linear regression analysis was conducted.

For follow-up data, linear mixed-effects models[16] were constructed to investigate the course of different outcomes over a 4-year period. To account for the correlation between repeated measurements on the same participant, a random intercept and random time effect (slope) per participant was used. For all analyses, an unstructured covariance for the random intercepts and random slopes was used. Differences in the rate of progression (i.e., slope) between homozygotes and heterozygotes were compared.

Data availability statement

We used the same methodology as that described in a previous study.[15] The European HD Registry is a large, prospective study observing the natural course, clinical spectrum, and management of HD in 140 centers from 17 European countries and 3 other countries.[9,12] More information on the Registry can be found at euro-hd.net/html/registry. This study is registered with ClinicalTrials.gov, number NCT01590589.

Results

As of December 2016, of 10,921 participants with HD (5,777 female [52.9%] and 5,138 male [47.0%]) with a mean age of 55.1 ± 14.1 years, 28 homozygotes (0.3%) and 10,893

(99.7%) heterozygotes were identified. The median CAG repeat lengths of the longer and shorter alleles were 45 (42; 47) and 38 (37;40), respectively, for the homozygote group, and 43 (44;45) and 18 (17;20), respectively, for the heterozygote group (table 1).

At baseline, clinical characteristics of homozygotes and heterozygotes were not significantly different, although homozygotes showed a trend for lower age at HD onset and lower BMI (table 1 and figure 1). Similar results were obtained in the post hoc comparative analysis between homozygotes and the age-larger allele-paired heterozygotes, with a trend for greater ocular disturbances in homozygotes (table 1).

After stratification of participants by age, the median CAG repeats of the longer allele in the younger group was 47 (45; 55) among homozygotes (n = 14) and 45 (43;49) among heterozygotes (n = 4,138), while in the older group, it was 43 (40;45) and 42 (41;44) for homozygotes (n = 14) and heterozygotes (n = 6,757), respectively. No significant differences in BMI, TMS, Cognitive, Behavior-UHDRS, and TFC scores were observed in the young or old group, except for a trend for lower age at HD onset in young homozygotes compared to young heterozygotes (27.0 [16.7;36.5] vs 34.0 [28.0;39.0], $p = 0.04$) and greater gait UHDRS scores in old homozygotes compared to old heterozygotes (5.0 [4.0;9.2] vs 4.0 [2.2;7.0], $p = 0.01$).

The length of the longer allele was correlated with age at HD onset in both homozygotes ($r_s = -0.86$, $p < 0.0001$) and heterozygotes ($r_s = -0.76$, $p < 0.0001$), while correlation with BMI was only seen in homozygotes ($r_s = -0.50$, $p = 0.01$). The length of the shorter allele did not have a significant effect on cognitive, behavior, or motor (including bradykinesia, chorea, gait, and dystonia UHDRS) scores, in either group. Likewise, the number of years of education did not show a significant correlation with age at HD onset among heterozygotes or homozygotes.

In the multivariate linear regression analysis, using the smaller and longer alleles as the independent variables, the length of the longer allele contributed most to earlier age at HD onset in the homozygote and heterozygote groups (table 2). According to these models, in heterozygotes, with 1-unit CAG repeat increase in the longer allele, age at HD onset decreased 1.90 years, 95% CI −1.94; −1.86 ($p < 0.0001$). Likewise, in homozygotes, for 1-unit CAG repeat increase in the longer allele, age at HD onset decreased 1.72 years, 95% CI −2.36; −1.07 ($p < 0.0001$). These models explained 44.8% and 61.7% of the variability of age at HD onset in the heterozygote and homozygote groups, respectively.

TMS, cognitive, behavior UHDRS, BMI, and TFC follow-up data are shown in boxplots (figure 2). Overall, no significant differences were observed in homozygotes compared to heterozygotes in terms of outcome variables over the course of 4 years (table 3).

Table 1 Baseline characteristics of homozygotes and heterozygotes with Huntington disease (HD)

	Homozygotes, n = 28	Heterozygotes, n = 10,893	p Value[a]	Heterozygotes_p, n = 65	p Value[b]
Age, y	51.5 (36.7–71.7), 28	55.0 (45.0–65.0), 10,886	0.31	52.0 (39.5–71.5), 65	0.76
Female	19 (67.9), 28	5,758 (52.9), 10,893	0.12	38 (58.5), 65	0.48
Shorter allele, CAG repeats	38 (37–40), 28	18 (17–20), 10,893	<0.0001	18 (17–21), 65	<0.0001
Longer allele, CAG repeats	45 (42–47), 28	43 (41–46), 10,893	0.03	45 (41–47), 65	0.37
Age at onset, y	39.5 (23.7–53.0), 20	46.0 (37.0–56.0), 8,442	0.04	44.5 (34.7–58.0), 46	0.13
HD duration, y	12.5 (6.0–16.0), 20	10.0 (6.0–15.0), 8,478	0.35	12.0 (9.0–16.2), 46	0.98
Education, y	10.0 (9.0–13.0), 27	11.0 (9.0–14.0), 10,391	0.12	12.0 (10.0–14.0), 65	0.01
BMI	22.1 (21.0–23.6), 25	23.5 (21.2–26.5), 10,817	0.04	23.2 (20.9–26.7), 59	0.13
TFC	9.5 (4.5–12.7), 28	10.0 (6.0–13.0), 10,717	0.50	11.0 (7.0–13.0), 65	0.15
TMS-UHDRS	35.0 (8.2–57.7), 28	27.0 (9.0–46.0), 10,445	0.46	21.5 (4.0–45.0), 64	0.20
Chorea-UHDRS	6.5 (0.2–10.7), 28	5.0 (1.0–10.0), 10,576	0.55	4.0 (0.0–9.0), 65	0.33
Bradykinesia-UHDRS	8.0 (3.2–16.7), 28	7.0 (2.0–12.0), 10,535	0.44	6.0 (1.0–11.0), 65	0.28
Dystonia-UHDRS	1.0 (0.0–5.7), 28	0.0 (0.0–3.0), 10,562	0.35	1.0 (0.0–2.0), 65	0.12
Gait-UHDRS	4.0 (0.0–6.7), 28	3.0 (0.0–5.0), 10,542	0.23	1.5 (0.0–4.7), 65	0.15
Ocular-UHDRS	6.0 (1.5–16.5), 28	6.0 (1.2–11.0), 10,569	0.31	4.0 (0.0–10.0), 65	0.06
Cognitive-UHDRS	226.0 (142.0–269.0), 9	174.0 (122.0–241.0), 4,102	0.34	210.0 (127.0–302.0), 35	0.71
Behavior-UHDRS	13.0 (4.0–27.0), 21	12.0 (5.0–21.0), 6,753	0.81	8.0 (3.0–15.0), 47	0.51

Abbreviations: BMI = body mass index; Heterozygotes_p = age-larger allele-paired heterozygotes; TFC = total functional capacity; TMS = total motor score; UHDRS = Unified Huntington's Disease Rating Scale.
A significance level of α = 0.004, 2-sided tests was applied after post hoc Bonferroni multiple comparisons adjustments. Values are expressed as median (interquartile range), n; or n (%), N.
[a] p Value relates to the homozygotes vs heterozygotes comparison.
[b] p Value relates to homozygotes vs age-larger allele-paired heterozygotes. Baseline comparison values were compared using the Mann-Whitney U test.

Discussion

In this longitudinal analysis of the EHDN registry, after correcting for multiple comparisons, homozygote HD carriers had a similar age at onset, phenotype, and disease progression compared to heterozygotes. These findings suggest that, overall, the shorter expanded allele does not have a significant and major influence in determining either the age at onset or the phenotypic expression and progression of HD.

In HD animal models and some CAG triplet diseases in humans, including spinal and bulbar muscular atrophy and dentatorubral-pallidoluysian atrophy, homozygotes have consistently shown more aggressive neurodegeneration compared to heterozygotes.[17,18] In other polyQ diseases, however, the effect of a second expanded allele remains unclear. Single reports and small series of homozygotes for spinocerebellar ataxia type 6 and 3 suggest a gene dose effect on age at onset and increased severity of the phenotype.[19,20] For HD, assessment of double dose gene effect in the phenotype has been extremely challenging, given the rare occurrence of homozygotes. While some publications in HD have reported an indistinguishable phenotype in homozygotes and heterozygotes,[4,7,8] other studies have observed a nonchoreiform phenotype presentation, more frequently in homozygotes, with a significant increase in severity of progression of motor and psychiatric manifestations, indicating that homozygotes may present with a wider spectrum of neurologic symptoms, other than chorea, compared to heterozygotes.[2,21] Supporting findings included marked cerebellum atrophy in neuroimaging in 3 homozygotes and widespread brain atrophy at autopsy of one homozygote patient with HD.[2] Our study, however, cannot confirm this difference in phenotype, as clinical characteristics of homozygotes were similar to heterozygotes. Even more, we did not observe a different clinical profile between younger and older homozygotes, except for a trend for greater gait impairment in the old group. Homozygotes (especially young homozygotes) had lower age at HD onset than heterozygotes, but they also had higher median CAG repeats of the longer allele, which may partially account for an earlier initiation of symptoms. Of note, homozygotes also showed a trend for lower BMI compared to heterozygotes. Explaining hypothesis includes that homozygotes might be at risk for a greater hypermetabolic state that may precede the occurrence of motor symptoms and contribute to weight loss.[22,23]

Figure 1 The relationship between expanded alleles CAG repeat length and age at onset of Huntington disease
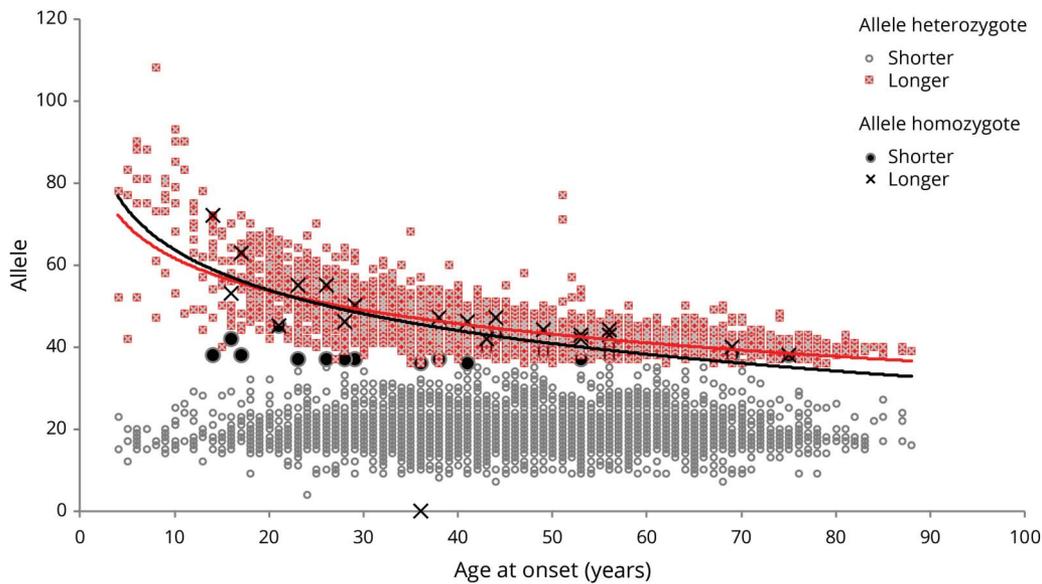
The minimal adequate model for this heterozygote and homozygote dataset is shown as black (homozygotes) and red (heterozygotes) lines.

Heterozygote individuals with clinically diagnosed HD experience a steady progressive decline in the cardinal features of the disease.[24,25] In our study, heterozygotes had a similar rate of decline compared to homozygotes in terms of BMI, TFC, TMS, behavior, and cognitive UHDRS scores. In contrast, Squitieri et al.[2] observed a faster rate of progression in disability, measured by independence and the physical disability scales, in 8 homozygotes compared to 75 heterozygotes. Given the different methodology used in that study,[2] our results are not comparable. Available clinimetric data show that in the overall HD population, items measured by the TMS-UHDRS, the only recommended rating scale to measure the severity of motor signs in HD that cover all motor domains in HD,[26] have variable weights at different HD stages. It seems that bradykinesia and dystonia are predominant in patients with greater CAG repeats and younger onset of HD compared to lower CAG repeats in the larger allele. Instead, chorea is predominant in earlier stages of manifest, adult HD, tends to plateau, and decreases later, and parkinsonian features become progressively more severe and are more clinically significant in later stages of the disease.[27] Interestingly, we found a similar motor phenotype progression in homozygotes compared to heterozygotes in terms of choreiform and nonchoreiform manifestations over time, except for a trend

for greater gait impairment in older homozygotes compared with heterozygotes in post hoc analysis. However, the scarce and relatively short longitudinal clinical information on homozygotes limits the clinical relevance of these observations.
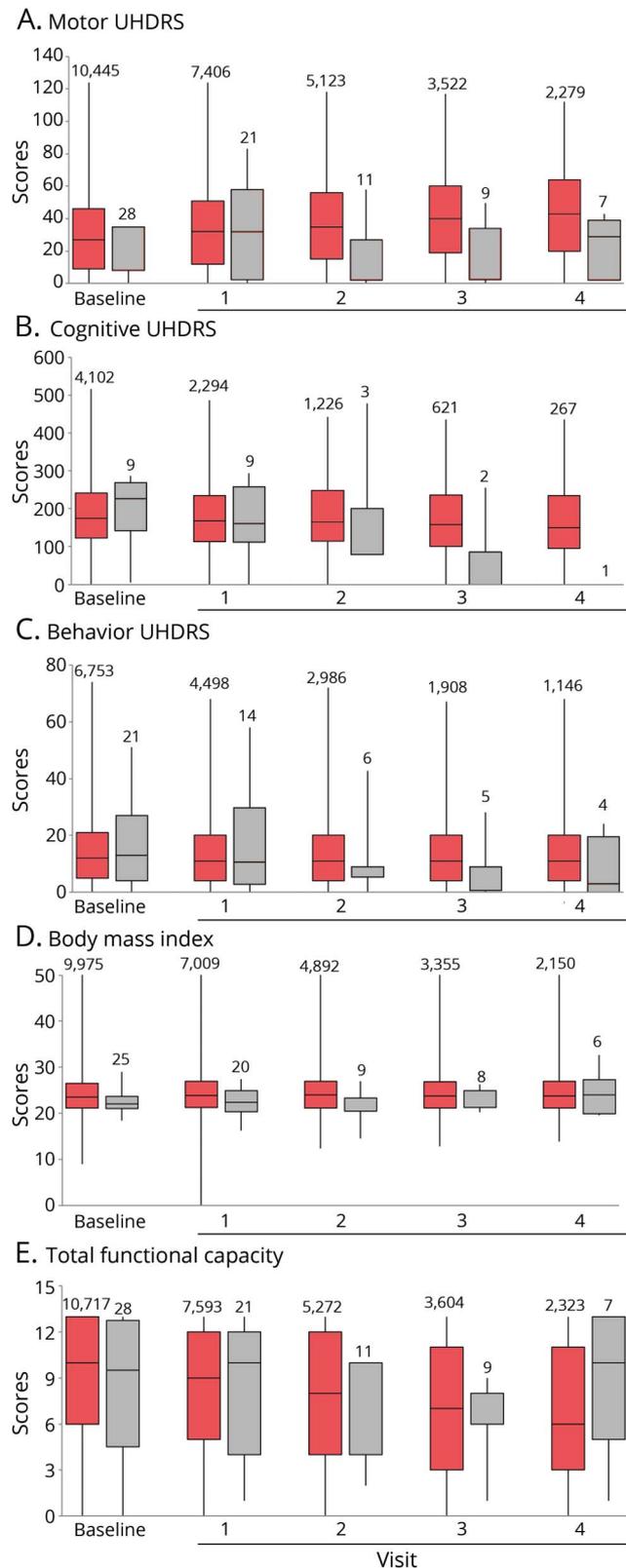
In previous studies on HD homozygotes, the most frequent variable of disease severity was the difference in age at HD onset. In agreement with other studies, the length of the longer allele was the most contributing and consistent factor associated with age at HD onset in both homozygotes and heterozygotes.[2,4,5,7,8,28] These results suggest that CAG repeat expansion in HD determines age at onset in a fully dominant fashion.[28,29] Age at HD onset in our homozygote participants was similar to that of the Lee et al.[28] study, but lower than reported by Squitieri et al.[2] It should be mentioned, however, that this difference might be due to the greater expansion in the longer allele in our homozygote sample, compared to the Squitieri et al.[2] study. In any case, the small number of homozygotes in both studies[2,28] does not allow us to draw definitive conclusions.

The underlying mechanisms of the lack of a significant expression of a double mutant gene dosage in HD are not well-understood. On one hand, it has been proposed that biallelic

Table 2 Multivariate lineal regression analysis of clinical variables associated with age at Huntington disease onset

	Homozygotes, corrected R^2 = 65.7, n = 20, n (95% confidence interval), *p* value	Heterozygotes, corrected R^2 = 48.7, n = 8,442, B (95% confidence interval), *p* value
Shorter allele	−1.44 (−3.65 to 0.76), 0.18	0.01 (−0.04 to 0.07), 0.15
Longer allele	−1.72 (−2.36 to −1.07), <0.0001	−1.90 (−1.94 to −1.86), <0.0001

Figure 2 Follow-up data

A. Motor UHDRS

B. Cognitive UHDRS

C. Behavior UHDRS

D. Body mass index

E. Total functional capacity

Follow-up data for motor Unified Huntington's Disease Rating Scale (UHDRS) (A), cognitive UHDRS (B), behavior UHDRS (C), body mass index (D), and total functional capacity (E). Number of participants participating in each visit is shown. Homozygotes are represented in gray boxes and heterozygotes in red boxes. The dark line represents the median of the outcome variable, the bottom of the box indicates the 25th percentile, and the top the 75th percentile.

Table 3 Slope differences for the homozygotes vs heterozygotes

	Slope difference (SE)	p Value
TFC	−0.9 (0.6)	0.40
TMS-UHDRS	4.1 (4.2)	0.36
Chorea-UHDRS	0.2 (0.8)	0.78
Bradykinesia-UHDRS	1.0 (1.1)	0.37
Dystonia-UHDRS	0.5 (0.3)	0.44
Ocular-UHDRS	1.3 (1.0)	0.19
Cognitive-UHDRS	17.0 (26.4)	0.53
Behavior-UHDRS	1.5 (2.1)	0.47
BMI	−1.5 (1.2)	0.18

Abbreviations: BMI = body mass index; TFC = total functional capacity; TMS = total motor score; UHDRS = Unified Huntington's Disease Rating Scale. Shown are parameter estimates from the linear mixed models. The difference between homozygotes and heterozygotes is expressed as a slope. p Values relates to the difference in the homozygotes compared to heterozygotes.

mutation in HD might be deleterious in patients, due to lack of protective function of the wild-type huntingtin or mitochondria impairment.[2,30,31] On the other hand, the level of mutant huntingtin protein produced from a single allele apparently exceeds any minimum threshold required to trigger pathogenesis (at a rate determined primarily by its CAG repeat length), and that hypothetically neither additional mutant protein nor the absence of any normal protein further alters the rate of pathogenesis leading to motor onset.[28] In spite of that, it is also important to consider the potential modifying effect of genetic factors on HD clinical course, beside the CAG repeat length of the *HTT* gene. In a recent genome-wide disease progression association study, single nucleotide polymorphism (SNP) encoding an amino acid change (Pro67Ala) in MSH3[32] was shown to have an effect on disease progression. Each copy of the minor allele at this SNP was associated with a 0.4 units per year (95% CI 0.16–0.66) reduction in the rate of change of the TMS-UHDRS, and a reduction of 0.12 units per year (95% CI 0.06–0.18) in the rate of change of TFC in heterozygotes.[32] In this scenario, identification and assessment of individual genetic and environmental factors should contribute to define the possible effect of the second expanded allele on the variance of HD phenotype and progression.

The main limitations of this study are the small sample of homozygotes, the limited clinical relevance of statistically significant results obtained in post hoc analysis, and the lack of biological data including measurement of mutant huntingtin protein levels and other genetic modifiers, neuroimaging, and postmortem pathologic results in the homozygotes supporting our data. Likewise, we cannot rule out that homozygotes have a significant, distinct motor or cognitive phenotype that

cannot be adequately captured by the UHDRS, or detected due to sample selection/attribution bias (loss of follow-up in participants with more severe cognitive or motor decline), or limited statistical power. In addition, participants with HD in our study are very likely to be on medication, a factor that could modify the phenotypic expression and outcome measures. Consequently, the HD clinical manifestations and progression in this study may not reflect that of the broader HD population (homozygotes and heterozygotes) who may have less access to such care. However, despite the above limitations, this study documents the clinical profile and disease progression using the largest HD homozygote multicenter sample so far described. Of note, these observational data were obtained from a database without any prespecified hypotheses at the time of data collection, which may preclude sample selection bias.

The results of this study extend previous reports examining the natural history of HD, highlighting the importance of an observational, longitudinal disease registry. Homozygosity in HD does not seem to modify significantly the age at onset, clinical phenotype, or disease progression, except for subtle clinical differences. Environmental factors and compensatory genetic factors might counteract the possible effect of the mutation in a double dose. This speculative hypothesis could be an area for future therapeutic investigation.

Author contributions

E. Cubo: study concept, design and writing the manuscript. M.A. Ramos-Arroyo: interpretation, critical revision of the manuscript. S.-I. Martinez-Horta: interpretation, critical revision of the manuscript. A. Martinez-Descalls: critical revision of the manuscript. S. Calvo, F. Sampedro Santalo: data management and analysis. C. Gil-Polo, D. Diaz, A. Gutierrez, I. Muñoz, K. Llano, N. Mariscal, L. Aguado: interpretation and critical review of the manuscript.

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