

Epidemiologic characteristics of a Hungarian subpopulation of Huntington's Disease patients

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Abstract

Background: recent advances in the therapeutic options may prevent deterioration related to Huntington's disease (HD) even at the presymptomatic stage. However, a well-characterized patient population is essential for screening and outcome monitoring as well. Accordingly, the aim of this study was to describe the characteristics of a Hungarian subpopulation of HD patients and mutation carriers diagnosed at the University of Szeged.

Methods: we conducted a search for International Classification of Diseases (ICD) code G10H0 in the local medical database for the period between 1 January 1998 and 31 December 2018.

Results: we identified 90 HD cases (male: 45, female: 45) and 34 asymptomatic carriers (male: 15, female: 19). The median age of onset was 45 years (range: 16-79). There were 3 cases of juvenile (3.3%), and 7 of late disease onset (7.8%). The median repeat length was 43 (range: 36-70) for the pathological and 19 for the non-pathological alleles (range: 9-35). 17.5% of the pathological alleles was in the decreased penetrance range, while 7% of non-pathological alleles was intermediate.

Conclusions: the genetic and clinical features of the population examined in present study was in line with the previous Hungarian study as well as with international literature, the exceptions being the higher ratio of reduced penetrance and intermediate alleles.

1. Introduction:

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterised by choreiform movements, cognitive dysfunction, behaviour and mood problems (1-4). The worldwide prevalence of HD is estimated to be 2.71/100.000, with a significantly higher prevalence (5.7/100.000) and incidence (0.11–0.8/100.000) in Europe and North America compared to Asian populations (prevalence: 0.4/100.000, incidence: 0.046–0.16/100.000) (2, 5). The age of disease onset is widely variable, the average is estimated to be between 30–50 years (1, 3, 4, 6, 7), but it can occur during early childhood as well as above 60 years (3, 4, 8). Cases where the disease manifests itself before the age of 20 are called juvenile type HD, whereas cases presenting symptoms after the age of 60 are termed late onset HD (8–11). Juvenile HD accounts for approximately 5% of all HD cases, and are usually characterised by large repeat numbers and paternal transmission (10, 12). Some of these patients present atypical symptoms like rigidity, brady-hypokinesia, postural instability and dysarthria, a phenotype referred to as the Westphal-variant (13). The frequency of late-onset HD varies widely in different studies with a range between 4.4–25% (9, 14). In these cases, the course of the disease tends to be mild, and repeat lengths are usually below 50 (9, 14). Regarding disease course, HD is a progressive condition resulting in death within 10–20 years (11), the juvenile onset being associated with shorter and the late onset with longer disease duration (3, 12).

HD is caused by a CAG trinucleotide repeat expansion in the first exon of the IT-15 gene, located on chromosome 4p16.3, and shows an autosomal dominant pattern of inheritance (3, 6–8, 11, 15). Repeat

length of 26 or less is considered normal (3, 8, 16). The repeats falling between 27 and 35 are referred to as intermediate alleles (or large normal alleles), which are not considered to be pathogenic but due to meiotic instability, they are prone to expansion, often leading to the development of HD in the next generation (3, 16, 17). In some cases, however, the presence of these alleles have been associated with subtle HD-like symptoms (16, 18). If the expansion exceeds 35 repeats, it becomes pathogenic, with the range 36–39 showing decreased penetrance, and a length of 40 or longer showing full penetrance (3, 4, 8). The age of onset and the CAG repeat length of the pathological allele is known to have a strong inverse correlation, though it is widely debated in literature whether repeat length by itself can be used to accurately predict disease onset and duration (3, 19). Several studies suggest that the age of onset can be influenced by other genetic factors, including the length of the non-pathological allele (3, 20). HD is characterised by genetic anticipation, the phenomenon that each successive generation demonstrates an earlier age of onset. It is based on the meiotic instability of the mutation, and is usually associated with paternal transmission (3, 8).

The aim of the current study was to evaluate the characteristics of a Hungarian subpopulation of HD patients and asymptomatic carriers regarding genetic and clinical features and to compare the obtained results with those of a previous study published from the same University in 1999 (15) and also with available international literature data.

2. Patients And Methods:

We performed a search for International Classification of Diseases (ICD) code G10H0 in the medical database of Department of Neurology, University of Szeged, Hungary, for the period between 1 January 1998, and 31 December 2018. We also revised the medical archives of our out-patient unit for the same time interval. Case assessment was conducted by reviewing medical records for patient history and genetic findings. HD was defined by the presence of a pathological mutation in the IT-15 gene (CAG repeat length of 36 or above) and related unequivocal neurological and/or psychiatric symptoms. A mutation carrier was defined by having a pathological allele but no evidence of clinical symptoms. The time of diagnosis was established by the occurrence of symptoms together with the date of the genetic testing, or, when not available, the first reference in records as genetically defined case. Regarding paternal or maternal inheritance, the presence of HD in the affected ancestors was based on at least clinical data. We assembled a control group ($n = 62$, male: 32, female: 30), consisting of unaffected relatives of HD patients, and individuals with symptoms similar to that of HD, but no pathological expansion in the IT-15 gene.

All statistical calculations were performed with the use of the freely available R software (R Development Core Team). We first checked the distribution of data populations with the Shapiro–Wilk test. To determine correlations, Pearson's or Spearman's tests were applied when the data had Gaussian or non-Gaussian distribution, respectively. Furthermore, we applied linear regression models to find out if there is a difference or interaction between the different variables.

3. Results:

Based on medical records between 1 January 1998 and 31 December 2018 we identified 90 cases of HD (male: 45, female: 45) and 34 asymptomatic carriers (male: 15, female: 19). The age of onset was available in 79 of the HD cases (male: 40, female: 39) and the median for that variable was 45 years (range: 16–79 years), 43.5 years in males (range: 18–79 years), and 45 in females (range 16–78 years). We identified 3 juvenile onset cases (3.3% of all cases) including 2 male patients with disease onsets at 18 and 19 years and repeat lengths of 52 and 59, respectively, one of them having a history of learning difficulties and behaviour disorder since early childhood. The third case was a female patient with a repeat length of 70, presenting atypical symptoms such as rigidity, cognitive dysfunction, hypokinesia, postural instability, dysarthria and dysphagia at the age of 16. All these patients inherited the condition from their fathers. There were 7 late-onset cases (7.8% of all cases), 1 male and 6 females, their age ranging from 61–79 years (median: 62), and their repeat sizes were between 37 and 45 (median: 40). The inheritance was known in only 2 of these cases, both of them had maternal transmission.

The median time between disease onset and the date of diagnosis was 3.5 years (range: 0–20 years).

The frequencies of all alleles in HD, carrier and control groups are presented in Fig. 1.

Exact CAG repeat length of pathological alleles were available in 86 HD cases (male: 42, female: 44) and in 34 carriers, whereas sizes of normal alleles were known in 75 HD patients and 31 carriers. The parameters (median, range) and distribution of pathological and non-pathological alleles in each group is described in Table 1. The repeat length of pathological alleles ranged between 36–70 in the HD and 36–52 in the carrier group with medians of 45 and 41. The median repeat length of non-expanded alleles was 19 with a range of 9–35. Regarding alleles in the non-expanded range, there was no statistical difference between HD, carrier and control groups. Regarding the age of onset, pathological, and non-expanded allele length, there was no significant difference between the genders in either group (Table 1).

Table 1
Distribution of CAG repeat lengths in the pathological and non-pathological ranges by groups and genders

	HD group	Carrier group	Control group (Alleles [individuals])	All pathological alleles	All non-pathological alleles
CAG repeats of pathological range (≥ 36)					
N (male/female)	86 (42/44)	34 (15/19)	-	120 (57/63)	-
Median (male/female)	45 (45/43.5)	41 (42/41)	-	43 (42/44)	-
Range (male/female)	36–70 (38–59/36–70)	36–52 (36–52/36–49)	-	36–70 (36–59/36/70)	-
CAG repeats of decreased penetrance (36–39)					
N (male/female)	12 (3/9)	9 (2/7)	-	21 (5/16)	-
Percent of respective group members	13.3%	26.5%	-	17.5%	-
CAG repeats of non-pathological range (< 36)					
N (male/female)†	75 (34/41)	30 (13/17)	124 (64/60) [62(32/30)]	-	229 (111/118)
Median (male/female)	18 (18/19)	19 (19/19)	20 (20/19)	-	19 (19/19)
Range (male/female)	9–28 (10–28/9–27)	14–24 (16–23/14–24)	10–35 (10–33/11/35)	-	9–35 (10–33/9–35)
CAG repeats of intermediate range (27–35)					
N (male, female)	3 (2/1)	0	13 (7/6)	-	16 (9/7)
Percent of respective group members	4%	0	10.5% [21%]	-	7%

†The repeat number of the normal allele was not available in all HD cases and carriers.

The age of onset showed a strong inverse correlation with the pathological CAG repeat length ($r_s = -0.575$; $p < 0.0001$), whereas no statistically significant correlation was found between the age of onset and the size of non-expanded alleles ($r = -0.62$; $p = 0.17$) (Fig. 2).

Alleles of decreased penetrance were identified in 9 carriers (26.5%, male: 2, female: 7) and 12 HD cases (13.3%, male: 3, female: 9), representing 17.5% of pathological alleles. In this group of HD patients, the

mean age of onset was 53.5 years (range: 39–78 years). Out of these 21 individuals, an affected parent was known in 11 cases (mother: 5, father: 6).

We identified 16 individuals – 3 in the HD and 13 in the control group – carrying intermediate alleles. These intermediate alleles represented approximately 10.5% of control group alleles, 7% of all non-pathological and 4.6% of all alleles assessed in this study. The 13 individuals carrying intermediate alleles (male: 7, female: 5) represented 21% of all controls. No individuals with 2 intermediate alleles were found. Eight of these controls presented with HD-like symptoms, such as chorea, perioral dyskinesia, and cognitive decline (5 males with repeat lengths of 27, 28, 28, 30, 33, and 3 females with repeat lengths of 28, 28, 35, respectively). Three of them had additional symptoms such as ataxia, dysphagia, dysarthria and convulsions. One person showed atypical extrapyramidal signs (myoclonus, cervical dystonia). Evidence for alternative diagnosis (alcohol and medication abuse) was provided only in one of these cases. Only one individual had a positive family history: a woman with alleles of 15 and 35, who presented with minor signs of movement disorder showing no progression during follow-up examinations. Her mother was diagnosed with HD (there is no evidence of genetic confirmation) and she had several other relatives with similar symptoms.

Fifty-two HD patients were found to have a positive family history. There were 25 patients with paternal and 27 with maternal inheritance. Regarding the carrier group, evidence of an affected parent was found in 26 (14 with maternal and 12 with paternal inheritance) out of 34 cases. Though the median age of onset was lower in cases of paternal (38.5, range: 16–57 years) than in that of maternal transmission (44.5, range: 24–79 years), and the median repeat length was higher in case of paternal (46, range: 38–70) compared to maternal inheritance (43, range: 37–58), the difference was not statistically significant ($p = 0.0612$ for age of onset and $p = 0.1$ for pathological allele size) (Fig. 3–4).

4. Discussion:

In recent years, there have been major advances regarding molecular therapeutic options in HD. As a prelude to joining international clinical trials, the detailed characterization of target patient populations is essential, enabling clinicians to estimate and better understand differences in therapeutic response (21–23).

Accordingly, in this retrospective study, we aimed at the characterization of 90 HD cases (male: 45, female: 45), and 34 carriers. In age of onset, pathological, and non-expanded allele lengths, there was no significant difference between genders in either group. However, regarding late-onset cases, and those with decreased penetrance alleles, there was a marked female dominance (7:1 and 16:5, respectively). This predominance may be related to their higher life expectancy at birth: during the period in question, the life expectancy of women was by approximately 7.7 years (range: 6.5–9 years) higher, according to the data of the Hungarian Central Statistical Office (24).

The median age of onset (45 years) was close to the European Huntington's Disease Network's estimates for Central Europe (47 years) but it was lower than those of Northern (50 years) or Southern Europe

(49 years) as well as that of United Kingdom (49 years) (4, 6, 11).

The ratio of juvenile onset cases (3.3%) was slightly lower than the 5% described in other studies (9, 14). All of these patients had a repeat length above 50 and a positive family history where the affected parent was the father. One patient with juvenile onset presented with the atypical Westphal phenotype (13). 7 patient of late disease onset was identified, representing 7.8% of all cases, which is well within the range (4.4–25%) reported previously (9, 14). Each of these patients had a repeat length below 46, and evidence of an affected parent was present in only 2 out of 7 cases.

Compared to the previous study from Hungary (median: 43, range: 37–70) and also to the international literature (median: 42–44, range: 36–121), we found that the pathological repeat lengths of the HD patients and asymptomatic carriers was similar (6, 7, 15, 25, 26). Alleles with decreased penetrance were found in 9 carriers (26.5%) and 12 HD patients (13.3%), representing approximately 17.5% of all pathological alleles found in this study, which is higher than the data reported by the European Huntington's Disease Network (3.1% for all participants, 1.8% for Central, 10% for Northern and 2.2% for Southern Europe) (6). As expected, the median age of onset (53.5 years) of patients in this range was higher compared to that of the whole HD group (45 years) (17, 27). The frequency of intermediate alleles either in the control group alleles (10.5%) or in all non-expanded alleles from the three groups (7%) was higher than those reported from most populations (0.45-6%), the exceptions being the findings of 2 Brazilian cohorts with frequencies of 7-8.7% (16, 18, 21, 28, 29). In light of that there are several reports associating intermediate alleles to HD-like clinical and pathological findings, the assessment of these alleles gains increasing attention despite the still controversial data (16, 17, 29). In the current study we identified 8 individuals out of 13 controls with intermediate alleles presenting with symptoms similar to that of HD, although in the lack of further clinical data or pathological confirmation it is unclear whether there is a causative relationship between these alleles and the presenting symptoms.

The median length of non-expanded CAG repeat alleles (19) was similar to that found in the previous Hungarian study (18) and those reported from other Caucasian populations (17.1–19.3), but higher than in Asian or African ethnic groups (16.2–17.7), (15, 21).

The strong inverse correlation between age of onset and pathological repeat size was established in the current study as well ($r_s = -0.575$; $p < 0.0001$). However, there was no significant association between the age of onset and the length of the non-pathological allele. It has been demonstrated that the expanded allele explains about 66-67.3% of the variance in age of onset, whereas the effect of the non-expanded allele is relatively small (approximately 1%) (3, 20). Furthermore, it was proposed that the effect of the normal alleles becomes evident among individuals with large pathological repeat lengths (20), which population accounts for only a small proportion of patients in our study (25.6% with repeat sizes above 46 and only 8% exceeding 50). Although the median age of onset was lower by approximately 6 years and the median repeat size was larger by 3 in cases of paternal transmission, the difference was not statistically significant. However, all cases of juvenile onset were of paternal inheritance. For a more precise assessment of parental transmission and genetic anticipation, the examination of parent-

offspring pairs would be advisable as introduced in other studies (3, 8, 15). Unfortunately, the medical records serving as the basis of this study were not sufficient for the reliable assessment of such relations within our patient population.

In conclusion, the genetic and clinical features of the populations examined in the present study were in accordance with the previous Hungarian study as well as with international literature data, except the higher frequency of intermediate alleles and individuals with reduced penetrance alleles.

Abbreviations

HD

Huntington's Disease

ICD

International Classification of Diseases

Declarations

Ethics approval and consent to participate: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, as well as approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged (registration number is 44/2016). Informed consent was obtained from all participants.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: Katalin Despotov has received support for congress participation from Teva, and speaker honoraria from Novartis. Dénes Zádori received <1000 EUR honoraria for lectures, travel expenses and registration fees for conferences, educational grants from Hungarian subsidiaries of Abbvie, Abbott, Allergan, Goodwill Pharma, Ipsen, Krka, Medis, Medtronic, Sandoz, TEVA and UCB. Regarding this study the authors did not receive any corporate funding. Gábor Veres, Katalin Jakab, Gabriella Gárdián, Eszter Tóth, Tamás Zs Kincses, László Vécsei, András Ajtay, Dániel Bereczki, Péter Klivényi declared no conflict of interest.

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Authors contributions: KD collected and analyzed the data and was a major contributor in writing the manuscript. DZ interpreted the data and contributed to writing the manuscript. PK helped analysing the

data and contributed to revising the manuscript. GV was conducting the statistical analysis of the data. KJ, GG, ET, LV, TZSK, DB, AA performed data analysis of the patients. All authors read and approved the final manuscript.

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Figures

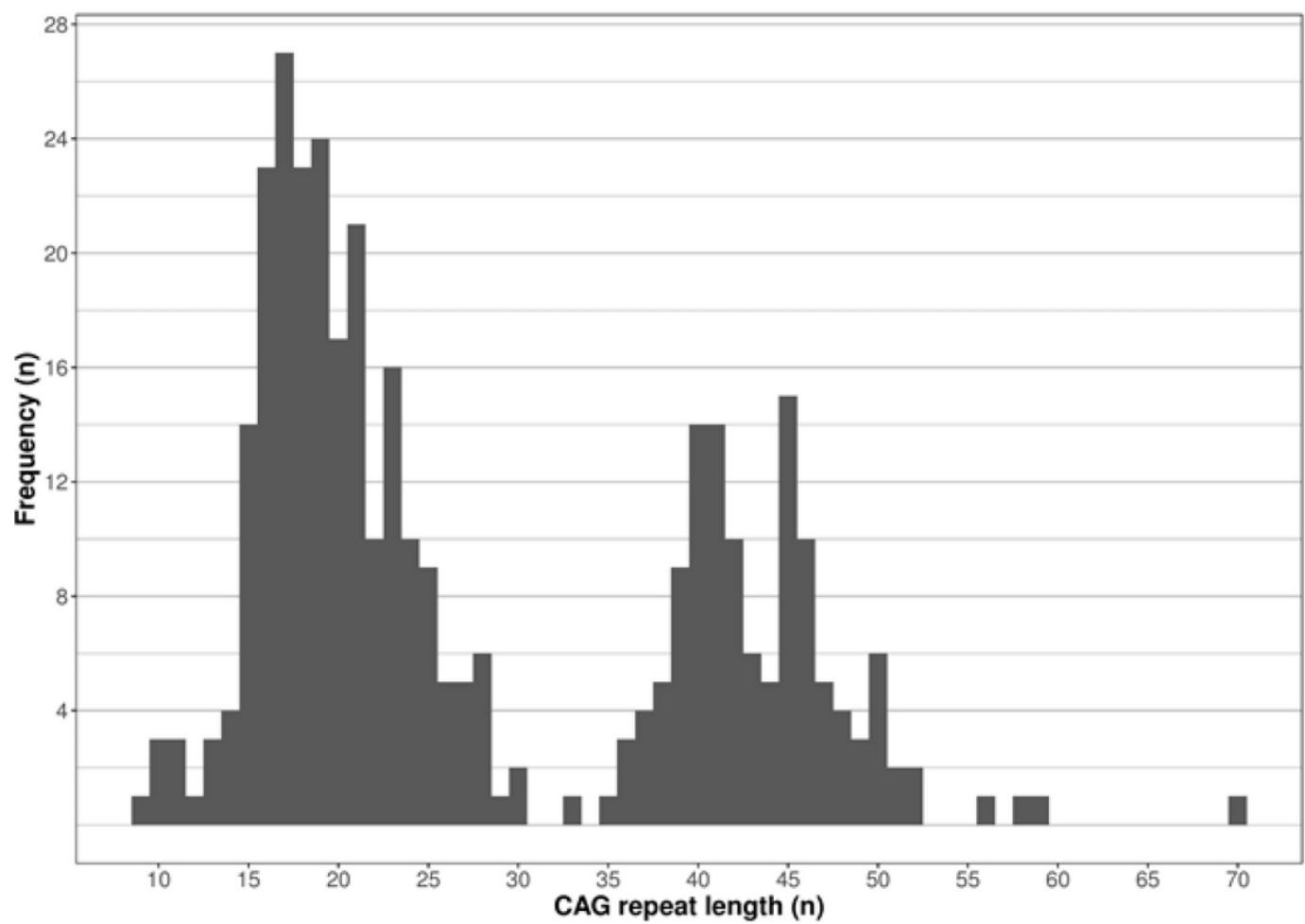


Figure 1

Allele frequencies of HD (n=86), carrier (n=34) and control groups (n=62).

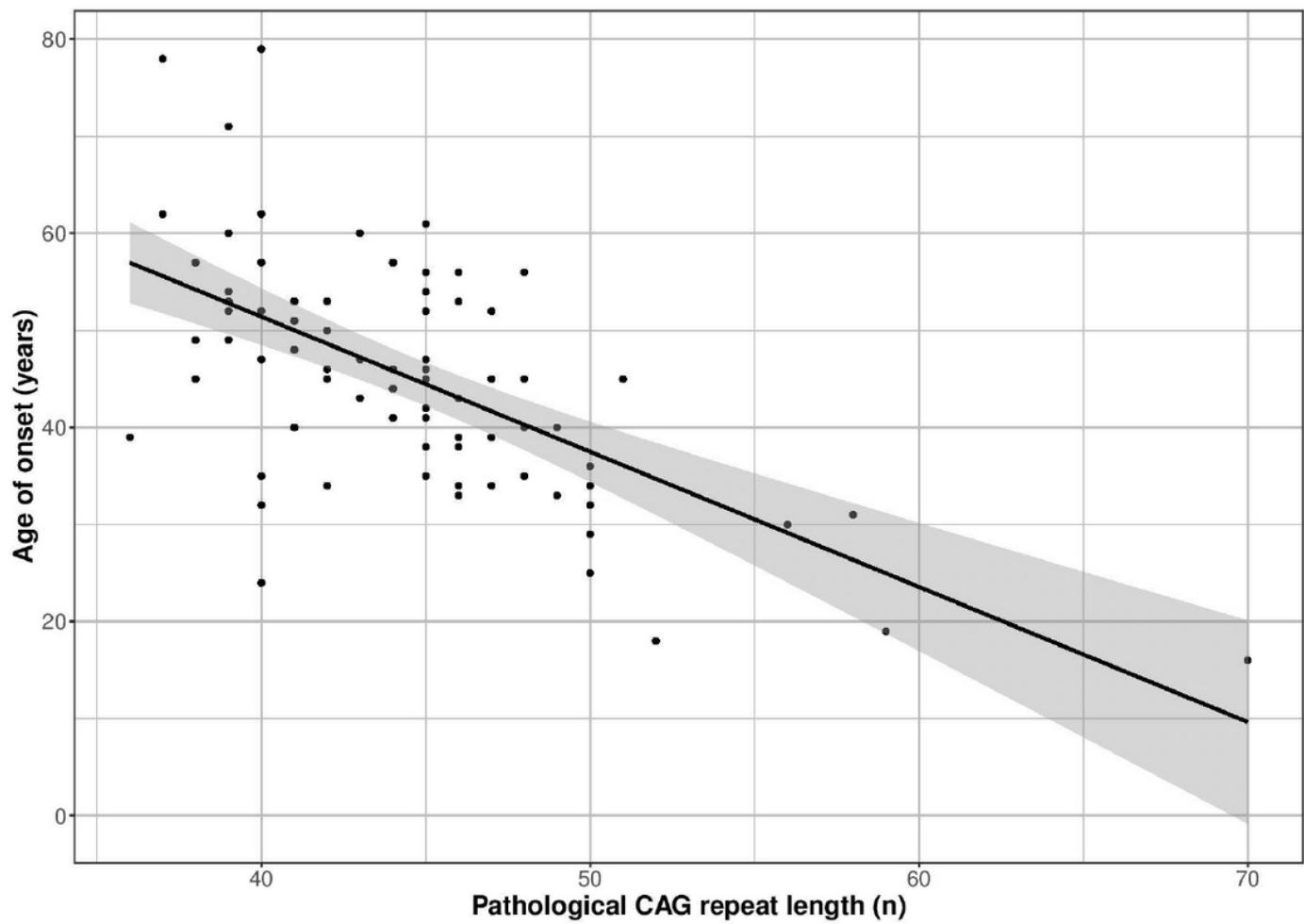


Figure 2

Correlation between the age of onset and pathological CAG repeat length in HD patients. The gray zone represents 95% confidence interval.

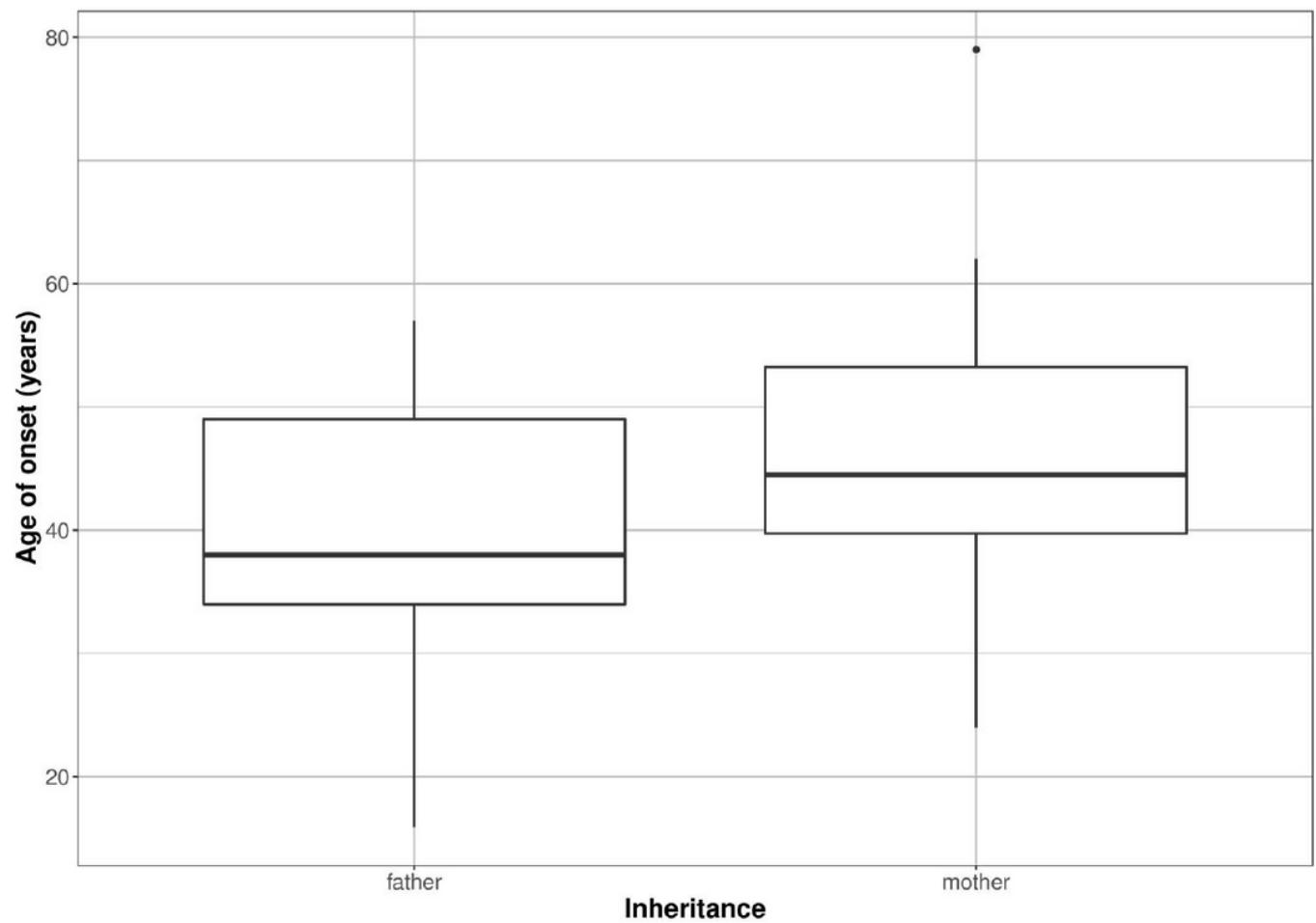


Figure 3

Comparison of paternal (n=25) and maternal (n=27) inheritance in term of age of onset. The data are presented as median, IQR, minimum-maximum.

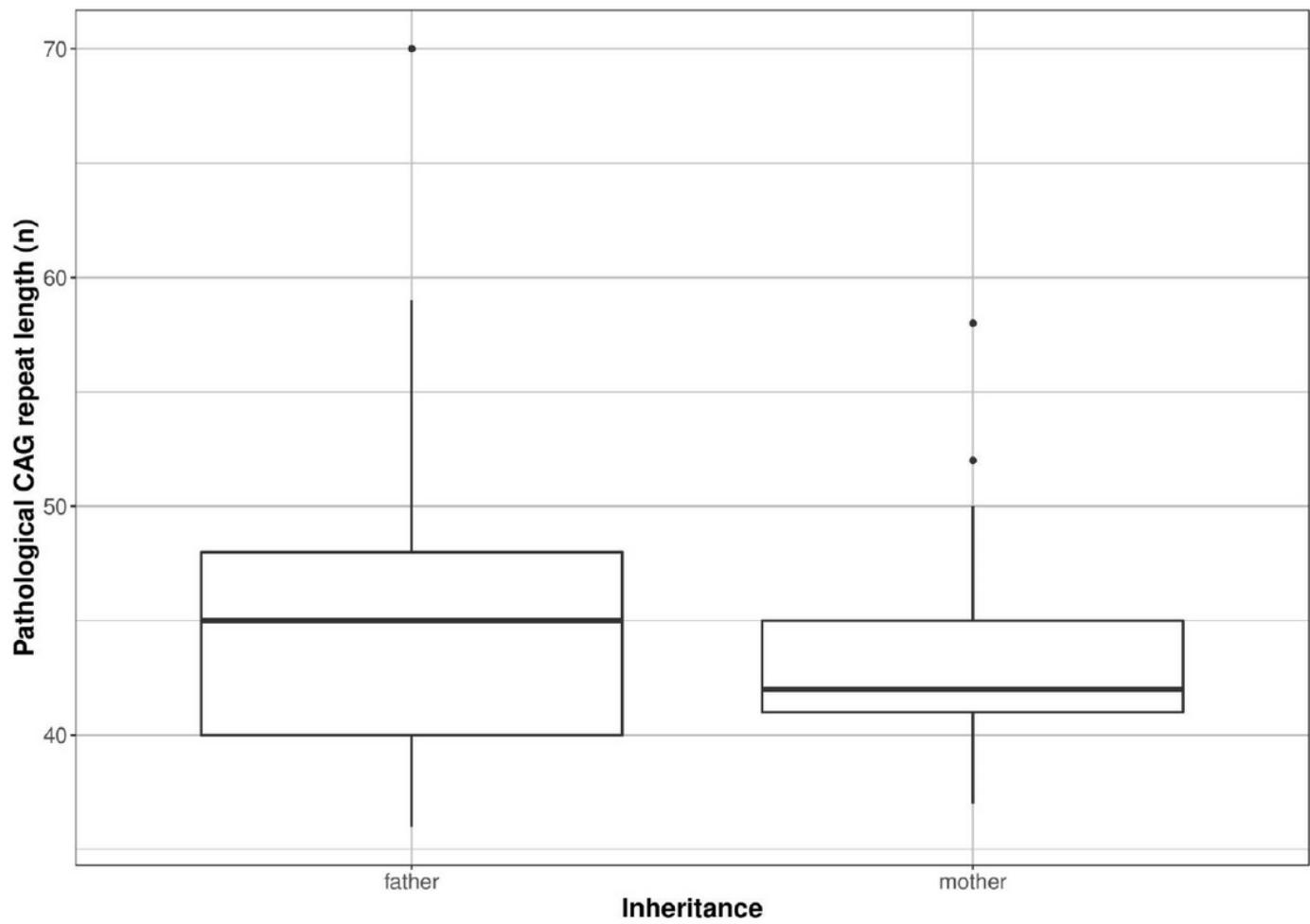


Figure 4

Comparison of paternal (n=25) and maternal (n=27) inheritance in term of pathological CAG repeat length. The data are presented as median, IQR, minimum-maximum.