The Cerebellum (2019) 18:896–909
https://doi.org/10.1007/s12311-019-01073-x

ORIGINAL PAPER

Application of Quantitative Motor Assessments in Friedreich Ataxia and Evaluation of Their Relation to Clinical Measures

Christian Hohenfeld[1,2] · Imis Dogan[1,2] · Robin Schubert[3] · Claire Didszun[1,2] · Ludger Schöls[4,5] · Matthis Synofzik[4,5] · Ilaria A. Giordano[6,7] · Thomas Klockgether[6,7] · Jörg B. Schulz[1,2] · Ralf Reilmann[3,4,8] · Kathrin Reetz[1,2]

Published online: 22 August 2019

Abstract

Friedreich's ataxia (FRDA) is a rare autosomal-recessive slowly progressive neurodegenerative disorder. As common clinical measures for this devastating disease lack sensitivity, we explored whether (a) the quantitative motor assessments of the Q-Motor battery can enhance clinical characterisation of FRDA; (b) clinical measures can predict Q-Motor outcomes and (c) Q-Motor is sensitive to longitudinal change. At baseline 29 patients and 23 controls and in a 1-year follow-up 14 patients and 6 controls were included. The Q-Motor included lift (manumotography), finger tapping (digitomotography) and pronate/supinate (dysdiadochomotography) tasks. To model responses, a search of generalised linear models was conducted, selecting best fitting models, using demographic and clinical data as predictors. Predictors from selected models were used in linear mixed models to investigate longitudinal changes. Patients with FRDA performed worse than controls on most measures. Modelling of the pronate/supinate task was dominated by SCAFI (SCA functional index) subtasks, while tapping task and lift task models suggested a complex relationship with clinical measures. Longitudinal modelling implied minor changes from baseline to follow-up, while clinical scales mainly showed no change in this sample. Overall Q-Motor likely has favourable properties for assessing distinct motor aspects in severe FRDA as it can be administered in wheelchair-bound patients. Further longitudinal research is warranted to fully characterise its relation to routinely used measures and scales for FRDA.

Keywords Cerebellar ataxia · Friedreich ataxia · Upper extremity · Motor activity

Ralf Reilmann and Kathrin Reetz shared last authorships

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12311-019-01073-x) contains supplementary material, which is available to authorized users.

✉ Kathrin Reetz
kreetz@ukaachen.de

[1] Department of Neurology, RWTH Aachen University, Pauwelsstraße 30, 52074 Aachen, Germany

[2] JARA-Brain Institute Molecular Neuroscience and Neuroimaging, Forschungszentrum Jülich GmbH/RWTH Aachen University, Aachen, Germany

[3] George-Huntington-Institute, Technology-Park, Münster, Germany

[4] Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

[5] German Centre for Neurodegenerative Diseases (DZNE), Tübingen, Germany

[6] Department of Neurology, University Hospital Bonn, Bonn, Germany

[7] German Centre for Neurodegenerative Diseases (DZNE), Bonn, Germany

[8] Department of Clinical Radiology, University of Münster, Münster, Germany

Introduction

Friedreich ataxia (FRDA) is a neurodegenerative spinocerebellar ataxia. It is caused by a mutation of the Frataxin gene, containing an expanded GAA-repeat in the first intron [1]. It is a rare disease with an estimated prevalence of no more than 1:20,000 [2]; however, it is the most common hereditary ataxia.

As FRDA is of a multisystem nature, symptoms of FRDA affect a multitude of domains. Core symptoms involve slowly progressing ataxia of stance and gait, areflexia, sometimes vestibular dysfunction and dysarthria. Further, commonly observed symptoms are scoliosis, heart disease—primarily cardiomyopathy—and congenital deformations of the feet [3]. Abnormal eye movements, urinary dysfunction and diabetes are additionally associated with FRDA. The onset of disease is typically around adolescence, but can be variable [4–6]. There is evidence that onset and progression of the disease are dependent on the amount of GAA-repeats on the Frataxin gene [6, 7], with higher amounts of GAA-repeats leading to earlier onset and more severe clinical presentation.

Several measures for clinical characterisation of the spinocerebellar ataxias are available (see for example [7–10]). However, a thorough clinical assessment is often strenuous for affected patients especially if severity of symptoms is critical. Additionally, it has been shown that the Scale for the Assessment and Rating of Ataxia (SARA) [8] and Composite Cerebellar Functional Severity Score (CCFS) [11] measurements have limitations due to ceiling effects if patients are too severely affected [12]. Additionally, clinical measures often are not very sensitive in FRDA and require large sample sizes to detect change [7], which is even complicated further by the fact that FRDA only progresses slowly. Assessment of upper limb motor function in FRDA found a decline over 1 year for the non-dominant hand in the 9-hole peg test as well as the box and block test [13]. However, the state of lacking data are an issue with the SCAFI, as FRDA patients eventually become wheelchair-bound [14] and consequently can no longer perform the 8-m walk test. There is one study that examined clinical instruments the literature regarding systematic assessments of upper limb motor measures in FRDA is still limited. Thus, new ways to characterise symptoms of the disease and related disease progression should be explored, in particular for the upper limb.

The Q-Motor assessments were originally developed to characterise motor impairment in the neurodegenerative movement disorder Huntington's disease [15–17], but has also been used in other diseases such as multiple sclerosis [18, 19], Parkinson's disease [20, 21], myasthenia [22] and Alzheimer's disease [23]. Q-Motor measures have further been implemented in more than ten clinical trials in Huntington's disease, though specific implementations and inclusion of subtasks vary [17]. So far, other quantitative motor assessments in spinocerebellar ataxias characterising functional limitations mainly used tasks, which require tracking and reaching movements, as performance therein should be especially impaired in spinocerebellar disease [24–27]. These studies showed that patients with spinocerebellar ataxias display reduced velocity, accuracy and steadiness of movement compared to healthy individuals, all features that could be captured by Q-Motor tasks. However, there is a lack of longitudinal data, systematically tracking progression in both clinical scales and quantitative motor tasks at the same time. In addition, the relevance and real-world generalisability of upper limb motor assessments like the Q-Motor was for example demonstrated in Huntington's disease in which *reach-to-eat* movements are impaired [28] and in Parkinson's disease, in which computer keyboard interaction difficulties are indicative of early stages of the disease [29].

To the best of our knowledge, this study describes the first application of the Q-Motor tasks to FRDA. The present implementation includes (i) a lift task (manumotography), (ii) pronate/supinate task (dysdiadochomotography) and (iii) a speeded finger tapping task (digitomotography). As a variety of objective measures can be derived from these tasks, we sought to investigate whether measures from the Q-Motor battery could provide insight into state of disease and progression beyond what is routinely used to characterise the severity of FRDA. In addition to an explorative approach, we hypothesised that the Q-Motor measures could be validated against standard FRDA instruments, and additionally lead to more fine-grained insight regarding disease severity.

Methods

Subjects

Data was collected in the context of European Friedreich's Ataxia Consortium for Translational Studies (EFACTS, www.e-facts.eu) at study sites in Aachen, Bonn and Tübingen (all in Germany), with Q-Motor examinations all being done at the Aachen site. The present subsample of the cohort included 29 patients (15 female, 14 male; mean age 31.8 years, standard deviation [SD] = 14.1) and 23 healthy control subjects (12 female, 11 male; mean age 33.1 years, SD = 11.4). The subset for which 12-month follow-up data was available encompassed 14 patients and 6 controls (Table 1).

The Edinburgh Handedness Inventory (EHI) [30] was administered to characterise subjects' handedness. Both patients and healthy subjects were primarily characterised as having a right-hand dominance, with only two patients and one control subject being left-hand dominant. Participants were clinically examined using the SARA [8], Inventory of Non-Ataxia Signs (INAS) [10] and the SCA Functional Index (SCAFI)

Table 1 Sample characteristics

	Patients		Controls	
	Baseline	Follow-up	Baseline	Follow-up
Sample size *n* (typical/late onset)	29 (24/5)	14 (11/3)	23	6
Female *n*	15	7	12	4
Male *n*	14	7	11	2
Dominant hand *n* L/R	2/27	2/12	1/22	1/5
GAA-repeats allele 1				
Mean ± SD	508.74 ± 266.30	441 ± 242.99	n/a	n/a
Median ± MAD	512 ± 296.52	431 ± 189.03		
GAA-repeats allele 2				
Mean ± SD	810.83 ± 218.56	723.3 ± 207.89	n/a	n/a
Median ± MAD	814.63 ± 215.00	717 ± 237.22		
Age				
Mean ± SD	31.76 ± 14.05	34.07 ± 11.36	33.17 ± 11.28	33.83 ± 8.98
Median ± MAD	30 ± 17.91	32.5 ± 13.34	30 ± 8.89	30.5 ± 6.67
Age of onset				
Mean ± SD	16.64 ± 8.11	17.21 ± 7.53	n/a	n/a
Median ± MAD	13.5 ± 7.41	17.5 ± 8.89		
SARA				
Mean ± SD	18.69 ± 9.34	16.5 ± 7.61	0.04 ± 0.21	0 ± 0
Median ± MAD	16.5 ± 12.60	15.25 ± 6.67	0 ± 0	0 ± 0
SCAFI PATA				
Mean ± SD	21.65 ± 4.27	23.5 ± 3.88	36.21 ± 5.99	32.67 ± 4.17
Median ± MAD	21 ± 3.71	24.5 ± 4.08	37 ± 6.67	34.25 ± 2.22
SCAFI 9HPT				
Mean ± SD	68.54 ± 47.04	51.33 ± 14.96	18.50 ± 2.33	19.74 ± 2.17
Median ± MAD	49.38 ± 21.18	52.25 ± 18.90	18.1 ± 2.95	19.39 ± 2.54
SCAFI 8mw				
Mean ± SD	14.30 ± 18.98	11.48 ± 9.11	4.02 ± 0.54	4.47 ± 0.73
Median ± MAD	6.55 ± 3.78	8.23 ± 3.86	3.9 ± 0.30	4.33 ± 0.63
SCAFI total z				
Mean ± SD	− 0.43 ± 0.45	− 0.35 ± 0.40	1.23 ± 0.43	0.90 ± 0.38
Median ± MAD	− 0.46 ± 0.55	− 0.39 ± 0.47	1.27 ± 0.51	1.05 ± 0.25
ADL				
Mean ± SD	11.21 ± 6.97	12.29 ± 5.37	0 ± 0	0 ± 0
Median ± MAD	10 ± 11.08	12.5 ± 5.19	0 ± 0	0 ± 0
INAS count				
Mean ± SD	5.56 ± 2.83	6 ± 2.55	0.07 ± 0.267	0 ± 0
Median ± MAD	5 ± 2.97	6 ± 2.97	0 ± 0	0 ± 0

For all considered clinical measures, descriptives are given where *SD*, standard deviation and *MAD*, median absolute deviation. Where either no data is available for controls or control data is all zero, no statistic for the entire sample is reported. SCAFI values from the *total* column were used in z-scaling of values

[9]. An overview of demographics and clinical scores is given in Table 1.

Prior to participation, all subjects were informed about the purpose of the study and its procedures, and written informed consent was given. All procedures were reviewed and approved by the local ethics committee at RWTH Aachen University and followed the declaration of Helsinki [31].

Quantitative Motor Assessment

Quantitative motor assessments were performed using a Q-Motor device provided by the George-Huntington-Institute (GHI, Münster, Germany) containing a pre-calibrated force transducer and an electro-magnetic position sensor to capture information about velocity, angle and force of movements and

grip. Data was recorded using the dedicated software for the Q-Motor battery, accompanying the device.

Subjects underwent three different motor tasks. First, a speeded tapping task (digitomotography) in which one should tap repeatedly and as quickly as possible on the sensor using the index finger [32]; second a pronate/supinate alternating hand tapping task (dysdiadochomotography) in which one should change the orientation of the hand repeatedly while touching a surface after each orientation change [17]; and finally a lift task in which an object of 250 g weight should be held in the air without aid as stable as possible at a marked location 10 cm above the table in front of the subject, using the precision-grip with thumb and index finger of one hand (manumotography) [33]. Each tapping trial lasted 10 s and each lift trial 20 s and five trials were performed for each condition with each hand. Beginning and end of each trial was signalled by an auditory cue.

Scores from left and right hand were associated to dominant and non-dominant hand based on EHI results. If a subject had an EHI result in the range that would be considered ambidextrous, the general tendency (i.e. the sign of the EHI result) for left or right was used for creating these scores. An overview of all Q-Motor measures is given in Supplementary Table 1.

Data Analysis

Q-Motor raw data was transferred online to GHI and analysed after quality control using automated pre-defined algorithms [17]. The Q-Motor team at GHI was blinded to the clinical status of subjects and extracted Q-Motor measures were transferred to Aachen for consecutive statistical analysis. This analysis was carried out using the statistical software and programming language R version 3.4 [34]. To assess the quality of modelling, threshold for statistical significance was set at $p < 0.05$ for individual predictors, but models were additionally examined using Akaike's Information Criterion corrected for small sample sizes (AICC) [35, 36] and root mean squared residual errors (RMSE). Due to the exploratory nature of the analysis, we did not apply corrections for multiple testing. As we were aiming at a first insight into the Q-Motor in FRDA, we decided to make the trade-off to accept type I errors in favour of avoiding type II errors.

As a first step, Q-motor values were compared between patients and controls using *t* tests to investigate whether there is at all a difference in results between both groups. For each of the Q-Motor variables then an exploratory analysis was conducted, aiming to find a model based on pre-selected variables that best describes the data of patients (the analysis was limited to patients due to the lack of variance in data from controls). By this, we aimed to characterise Q-Motor in the context of established clinical measures as we were interested if and to which extent the variation of Q-motor variables could be modelled by FRDA-related measures including demographics and age of onset. Furthermore, Q-Motor variables were chosen as dependent variables to limit the space of possible predictors (nine clinical and demographic variables compared to > 40 Q-Motor variables). For modelling, generalised linear models were employed using log-transformed dependent variables to avoid predictions of negative values as well as the Gaussian error distribution with its canonical identity link function. The space of predictors to search included SARA sum score, INAS count, SCAFI z-scores for each task (8 m walk, 9-hole peg test and PATA), ADL (activities of daily living) sum score, gender, age and age of onset. To avoid overfitting, interactions between predictors were not considered, leading to a space of 512 models to search in, which were evaluated based on AICC values. The model space search was done using the glmulti R package version 1.0.7 [37]. To further assess the model fit, residuals were inspected visually for patterns along fitted values, distribution of quantiles against theoretical (standard normal) quantiles and also whether there were individual cases with high leverage per Cook's distance.

After best fitting models for each variable were selected, they were entered into a fivefold cross-validation. This method was chosen, as the data set did not allow for *hard* splitting of the sample into a training and validation data set due to the small sample size and additional missing data points (for a discussion of accuracy estimation methods see [38]). Root mean squared errors of the best fitting model on the entire dataset were here compared to the root mean squared errors of the fivefold cross-validation including bias correction, to gain insight into the model's performance in predicting values.

In a next step, longitudinal effects were investigated, again in patients only, due to lack of variance and few data points in controls. For this purpose, random effects for subjects were introduced into linear mixed models (LMM) with a fixed effect structure as suggested by the GLM for each variable. For each model, the Satterthwaite approximation [39] was applied, allowing for calculations of *p* values characterising the influence of individual predictors. However, the results from this approach should be interpreted with caution [40]. To obtain more information about the influence of time on Q-Motor measures, we calculated an analysis of deviance between LMM including the enumeration of the time point and LMM excluding that information. In addition, where one of the two aforementioned measures suggested an effect over time, we also calculated the conditional R^2 (below $R^2_{c\_time}$ written as for the model including the longitudinal predictor and $R^2_{c\_all}$ for the model not including such a predictor) statistic for both models [41] allowing assessment of the additional explained variance due to the inclusion of a longitudinal predictor.

Finally, we also looked for differences in means between baseline and 1-year follow-up for clinical scales in patients to

enable comparing potential progress in Q-Motor measures with potential progress in clinical scales. To do so, paired *t* tests were computed between clinical scores (SARA, ADL, INAS, SCAFI subtasks) for all patients where a follow-up was available.

Results

Q-Motor Group Differences

Under the null hypothesis, *t* tests showed group differences for all means of Q-Motor measures from all three tasks. The only exception in this regard was the force during the speeded finger tapping task for both hands (dominant: $t(48.188) = -0.714$, $p = .479$, $d = -0.199$; non-dominant: $t(48.921) = -0.239$, $p = .812$, $d = -0.066$). A full overview of tests for difference in means is given in Table 2 and mean scores per measure are visualised in Fig. 1.

Correlations of Q-Motor Data with Clinical Measures

Across all time points in summary, in patients with FRDA for the lift task predominantly correlations with $|r| < .15$ were found for all included measures, except for age of onset. Here, earlier age at disease onset was related to lower grip force (dominant hand: $r = .575$, $t(38) = 4.339$, $p < .001$; non-dominant hand: $r = .523$, $t(39) = 3.839$, $p < .001$) and inversely related to grip force variation (dominant hand: $r = -.301$, $t(38) = -1.948$, $p = .059$; non-dominant hand: $r = -.297$, $t(37) = -1.942$, $p = .006$), variation of orientation-index (dominant hand: $r = -.330$, $t(38) = -2.152$, $p = .038$, non-dominant hand: $r = -.433$, $t(37) = -2.924$, $p = .006$) and position-index (dominant hand: $r = -.338$, $t(38) = -2.212$, $p = .034$, non-dominant hand: $r = -.338$, $t(38) = -2.152$, $p = .033$). For the tapping task, strong correlations were found for all variables except for force which showed strong correlations with age of onset only. The same was generally true for the pronate/supinate task. For controls, mostly no correlations were found, likely due to a lack of variance in clinical measures. However, some relationships were found between the SCAFI and the pronate/supinate task in controls. See Fig. 2 for a summarising visualisation of correlations.

Exhaustive Generalised Linear Model Search

The best fitting models for each Q-Motor measure are given in Table 3. All of the considered predictors were included at least once and complexity between models differed. Noticeable patterns include that tasks from the SCAFI were predictors in almost all models. Furthermore, age of onset occurred as predictor mainly for the lift task and the tapping task, while gender effects were chiefly found for the tapping task. GLM results are additionally visualised in Fig. 3. Performance of models in predicting Q-Motor values as measured by root mean squared errors is given in Supplementary Table 2.

Longitudinal Modelling

Analyses of deviance suggested few changes over time in Q-Motor measures when comparing models respecting time and those that did not. For the lift task, a better model fit was found for grip force of the non-dominant hand ($\chi^2(1) = 10.6$, $p = .001$, $R^2_{c\_all} = .812$, $R^2_{c\_time} = .936$), reflecting in a significant effect for time ($estimate = 0.308$, $error = 0.128$, $t(12.136) = 2.405$, $p = .033$). Statistical significance was slightly missed for modelling of the orientation-index of the dominant hand after including time as a factor ($\chi^2(1) = 3.447$, $p = .063$, $R^2_{c\_al} = .676$, $R^2_{c\_time} = .853$). For the speeded finger tapping task, analyses of deviance suggested no better fits of either model, and no individual significant influences by time were found.

Modelling of the responses to the pronate/supinate task suggested a better fit when including time for the inter-tap-interval of the non-dominant hand ($\chi^2(1) = 12.37$, $p < .001$, $R^2_{c\_all} = .755$, $R^2_{c\_time} = .939$). A slightly better fit of the model respecting time was found for the force of the dominant hand ($\chi^2(1) = 3.095$, $p = .079$, $R^2_{c\_all} = .635$, $R^2_{c\_time} = .718$). Considering individual effects, influence of time was suggested for inter-tap-interval of the non-dominant hand ($estimate = 0.189$, $error = 0.058$, $t(17.123) = 3.274$, $p = .004$, $R^2_{c\_all} = .755$, $R^2_{c\_time} = .939$), inter-peak-interval of the dominant hand ($estimate = 0.120$, error = 0.050, $t(29.850) = 2.411$, $p = .023$, $R^2_{c\_all} = .932$, $R^2_{c\_time} = .946$) and inter-onset-interval of the dominant hand ($estimate = 0.124$, $error = 0.049$, $t(30.683) = 2.523$, $p = .017$, $R^2_{c\_all} = .930$, $R^2_{c\_time} = .950$). A visualisation of Q-Motor responses in patients from baseline to follow-up for measures with changes characterised by $p < .05$ is given in Fig. 4 (a complete visualisation of longitudinal changes can be found in Supplementary Fig. 1).

Clinical Scales

In patients, no differences in means were found from baseline to 1-year follow-up for the ADL ($t(12) = -0.291$, $p = .776$, $d_z = -0.026$), INAS ($t(11) = -1.694$, $p = .118$, $d_z = -0.475$) and any of the SCAFI tasks (8 m walk: $t(7) = 0.301$, $p = .772$, $d_z = 0.051$; 9-hole peg test: $t(12) = -1.214$, $p = .248$, $d_z = -0.082$; PATA: $t(12) = -0.421$, $p = .681$, $d_z = -0.089$). A change in scores was however found for the SARA reflecting an improvement of scores from baseline to follow-up ($t(12) = 2.498$, $p = .028$, $d_z = 0.114$). However, this change was mainly driven by one subject with an unusually large improvement between time points; excluding that subject form the analysis from the analysis negates that difference ($t(12) = 0.228$, $p = .821$, $d_z = 0.093$).

Table 2 Comparison of means between patients and controls for all available Q-Motor measures

Measure	Unit	*t*	df	95% CI Lo	95% CI Up	Mean ± SD Ctrl	Mean ± SD Pat	*p*	*d*
Lift task (manumotography), dominant hand									
Grip force	*N*	− 2.39	43.97	− 3.58	− 0.30	5.47 ± 2.26	7.41 ± 3.37	.02	− 0.67
Grip force coeffvar	%	− 3.58	31.50	− 8.02	− 2.20	5.52 ± 2.35	10.63 ± 6.84	< .01	− 0.98
Orientation-index	°/s	− 3.48	33.18	− 6.26	− 1.64	3.43 ± 1.96	7.38 ± 5.34	< .01	− 0.94
Position-index	cm/s	− 5.02	27.28	− 1.53	− 0.64	0.74 ± 0.20	1.83 ± 1.08	< .01	− 1.32
Lift task (manumotography), non-dominant hand									
Grip force	*N*	− 2.63	42.79	− 4.75	− 0.63	5.82 ± 2.61	8.50 ± 4.49	.01	− 0.73
Grip force coeffvar	%	− 4.22	36.50	− 6.18	− 2.17	4.85 ± 2.01	9.03 ± 4.66	< .01	− 1.13
Orientation-index	°/s	− 4.12	25.84	− 18.62	− 6.22	3.98 ± 1.74	16.40 ± 15.24	< .01	− 1.08
Position-index	cm/s	− 5.84	27.90	− 2.24	− 1.08	0.72 ± 0.30	2.38 ± 1.41	< .01	− 1.54
Speeded finger tapping (digitomotography), dominant hand									
Tap-duration	s	− 8.36	33.76	− 0.12	− 0.08	0.08 ± 0.02	0.18 ± 0.06	< .01	− 2.17
Tap-duration SD		− 4.88	29.78	− 0.03	− 0.01	0.01 ± < 0.01	0.03 ± 0.02	< .01	− 1.25
Tap-force	%	− 0.71	48.19	− 6.28	2.99	31.65 ± 7.93	33.3 ± 8.51	.48	− 0.20
Frequency	Hz	11.96	48.94	2.02	2.84	5.10 ± 0.67	2.67 ± 0.79	< .01	3.31
Inter-onset-interval	s	− 8.15	30.32	− 0.26	− 0.16	0.2 ± 0.03	0.41 ± 0.13	< .01	− 2.10
Inter-onset-interval SD		− 3.95	31.35	− 0.04	− 0.01	0.02 ± 0.01	0.05 ± 0.03	< .01	− 1.02
Inter-peak-interval	s	− 8.14	30.30	− 0.26	− 0.16	0.2 ± 0.03	0.41 ± 0.13	< .01	− 2.09
Inter-peak-interval SD		− 4.39	31.11	− 0.04	− 0.02	0.02 ± 0.01	0.05 ± 0.03	< .01	− 1.13
Inter-tap-interval	s	− 6.64	31.91	− 0.16	− 0.08	0.12 ± 0.02	0.23 ± 0.09	< .01	− 1.71
Inter-tap-interval SD		− 2.61	32.52	− 0.03	< − 0.01	0.02 ± 0.01	0.04 ± 0.031	.01	− 0.68
Speeded finger tapping (digitomotography), non-dominant									
Tap-duration	s	− 9.21	31.13	− 0.15	− 0.10	0.09 ± 0.02	0.22 ± 0.07	< .01	− 2.37
Tap-duration SD		− 4.91	29.95	− 0.03	− 0.01	0.02 ± 0.01	0.04 ± 0.03	< .01	− 1.26
Tap-force	%	− 0.24	48.92	− 5.25	4.14	32.36 ± 7.34	32.91 ± 9.34	.81	− 0.07
Frequency	Hz	14.49	45.65	2.02	2.67	4.66 ± 0.44	2.32 ± 0.71	< .01	3.90
Inter-onset-interval	s	− 8.73	28.12	− 0.32	− 0.20	0.22 ± 0.02	0.48 ± 0.16	< .01	− 2.23
Inter-onset-interval SD		− 4.42	32.18	− 0.05	− 0.02	0.03 ± 0.01	0.06 ± 0.04	< .01	− 1.14
Inter-peak-interval	s	− 8.72	28.11	− 0.32	− 0.20	0.22 ± 0.02	0.48 ± 0.16	< .01	− 2.23
Inter-peak-interval SD		− 5.22	33.09	− 0.05	− 0.02	0.02 ± 0.01	0.06 ± 0.03	< .01	− 1.35
Inter-tap-interval	s	− 7.44	28.85	− 0.17	− 0.10	0.13 ± 0.02	0.26 ± 0.10	< .01	− 1.90
Inter-tap-interval SD		− 3.64	37.14	− 0.03	− 0.01	0.02 ± 0.01	0.04 ± 0.02	< .01	− 0.96
Pronate/supinate task (dysdiadochomotography), dominant hand									
Tap-duration	s	− 6.83	30.67	− 0.22	− 0.12	0.10 ± 0.03	0.26 ± 0.13	< .01	− 1.76
Tap-duration SD		− 7.35	30.62	− 0.10	− 0.05	0.02 ± 0.01	0.10 ± 0.05	< .01	− 1.89
Tap-force	%	− 5.54	48.56	− 20.06	− 9.37	32.41 ± 8.08	47.13 ± 10.89	< .01	− 1.51
Frequency	Hz	10.04	44.12	1.34	2.02	3.31 ± 0.63	1.63 ± 0.55	< .01	2.86
Inter-onset-interval	s	− 7.37	30.12	− 0.49	− 0.28	0.31 ± 0.06	0.70 ± 0.27	< .01	− 1.89
Inter-onset-interval SD		− 7.41	28.61	− 0.19	− 0.11	0.04 ± 0.02	0.19 ± 0.11	< .01	− 1.90
Inter-peak-interval	s	− 7.39	30.13	− 0.49	− 0.28	0.31 ± 0.06	0.70 ± 0.27	< .01	− 1.90
Inter-peak-interval SD		− 7.15	28.63	− 0.20	− 0.11	0.04 ± 0.02	0.20 ± 0.11	< .01	− 1.83
Inter-tap-interval	s	− 6.70	30.67	− 0.29	− 0.15	0.22 ± 0.04	0.44 ± 0.17	< .01	− 1.73
Inter-tap-interval SD		− 7.49	28.17	− 0.14	− 0.08	0.03 ± 0.01	0.14 ± 0.08	< .01	− 1.91
Pronate/supinate task (dysdiadochomotography), non-dominant hand									
Tap-duration	s	− 8.47	31.04	− 0.25	− 0.15	0.11 ± 0.03	0.31 ± 0.12	< .01	− 2.18
Tap-duration SD		− 5.82	31.73	− 0.10	− 0.05	0.03 ± 0.02	0.1 ± 0.07	< .01	− 1.50
Tap-force	%	− 6.46	48.35	− 18.53	− 9.74	31.57 ± 7.47	45.71 ± 8.13	< .01	− 1.80
Frequency	Hz	11.23	46.85	1.36	1.95	3.15 ± 0.53	1.49 ± 0.52	< .01	3.16
Inter-onset-interval	s	− 8.28	29.75	− 0.54	− 0.33	0.33 ± 0.06	0.76 ± 0.27	< .01	− 2.13

Table 2 (continued)

Measure	Unit	*t*	df	95% CI Lo	95% CI Up	Mean ± SD Ctrl	Mean ± SD Pat	*p*	*d*
Inter-onset-interval SD		− 6.93	28.47	− 0.20	− 0.11	0.05 ± 0.02	0.20 ± 0.12	< .01	− 1.77
Inter-peak-interval	s	− 8.28	29.73	− 0.54	− 0.33	0.33 ± 0.06	0.76 ± 0.27	< .01	− 2.13
Inter-peak-interval SD		− 7.26	28.52	− 0.19	− 0.11	0.05 ± 0.02	0.19 ± 0.11	< .01	− 1.86
Inter-tap-interval	s	− 6.97	30.30	− 0.30	− 0.17	0.22 ± 0.04	0.45 ± 0.17	< .01	− 1.79
Inter-tap-interval SD		− 7.20	27.89	− 0.15	− 0.08	0.04 ± 0.01	0.16 ± 0.09	< .01	− 1.84

Note that for all tests except force of the speeded tapping task, difference between patients and controls was significant at $p \leq .05$. Abbreviations: *df*, degrees of freedom; *95 CI*, 95% confidence interval around the difference in means; *Lo*, lower bound; *Up* upper bound; *SD* standard deviation; *d*, Cohen's *d*; *Ctrl*, controls; *Pat*, patients

Discussion

Our first results show that patients with FRDA performed worse than controls in all three applied tasks of the Q-Motor assessment. Modelling of Q-Motor responses did indicate at associations between common clinical rating scores and performance of patients in these tasks as well as some changes in outcomes after 1 year, but complexity and quality of models varied. In particular prospectively, the Q-Motor assessment could be of complementary clinical and of high scientific interest in the detailed characterisation of FRDA, especially as it focuses strongly on characterisation of upper limb movements and thus can also be applied in patients where the disease progressively leads to dependence on a wheelchair.

One study investigating upper limb motor performance in FRDA using a reaching task reported considerably impaired performance in patients compared to controls and also correlations between clinical scales and motor performance [42]. While results from that study and the present work are limited in comparability due to very different implementations, the overall findings are nonetheless congruent by showing that quantification of upper limb movements is highly discriminative between healthy subjects and patients of FRDA, and that this quantification might provide useful information when clinical measures reach limitations like the afore mentioned ceiling effects [12]. Further, it should be pointed out that quantitative measures overcome limitations of objectivity in numerous clinical measures, as many clinical scales rely on examiners making choices based on some criteria, which is more prone to error and bias than standardised quantitative measures. Considering previous work assessing clinical tools for upper limb motor performance in FRDA [13], a stronger change over time is suggested than what was demonstrated here, but this might be in part due to the much larger sample size in that work.

Previous works on quantitative motor tasks in different diseases have suggested that measures of variability in motor tasks are more suited for characterisation of symptom severity

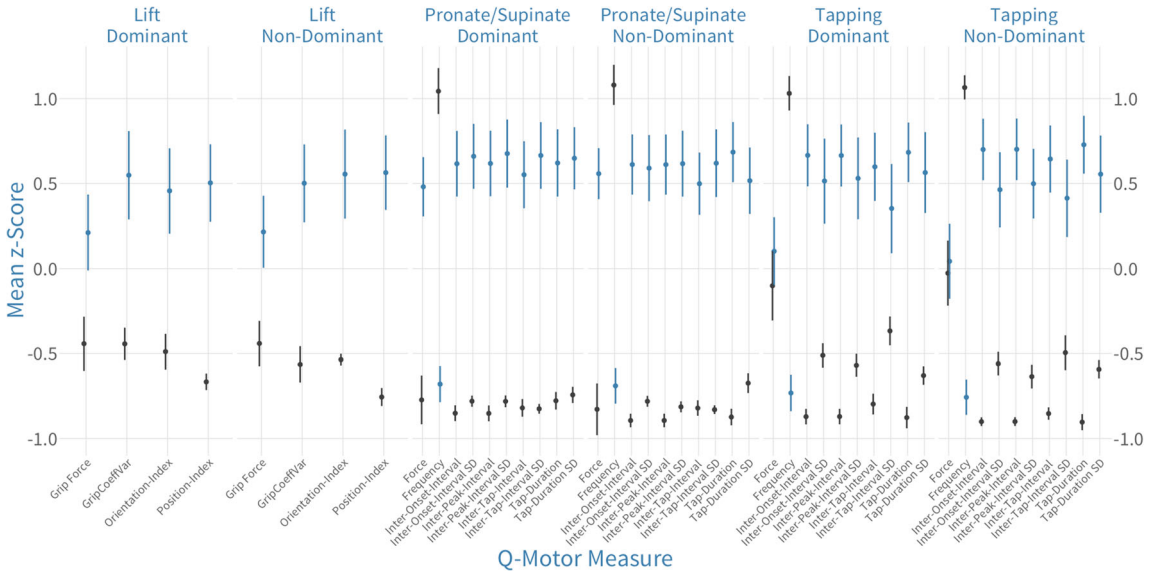

Fig. 1 Overview of all Q-Motor measures between FRDA patients and controls at the baseline examination. Data are split up by task and hand dominance. The difference in means assessed with Welch's *t* test results in $p \leq .05$ where error bars (indicating the standard error of the mean) do not overlap. Blue points indicate patients, black points indicate controls. To avoid issues due to differing scales between variables, all data were z-transformed by each measure before plotting

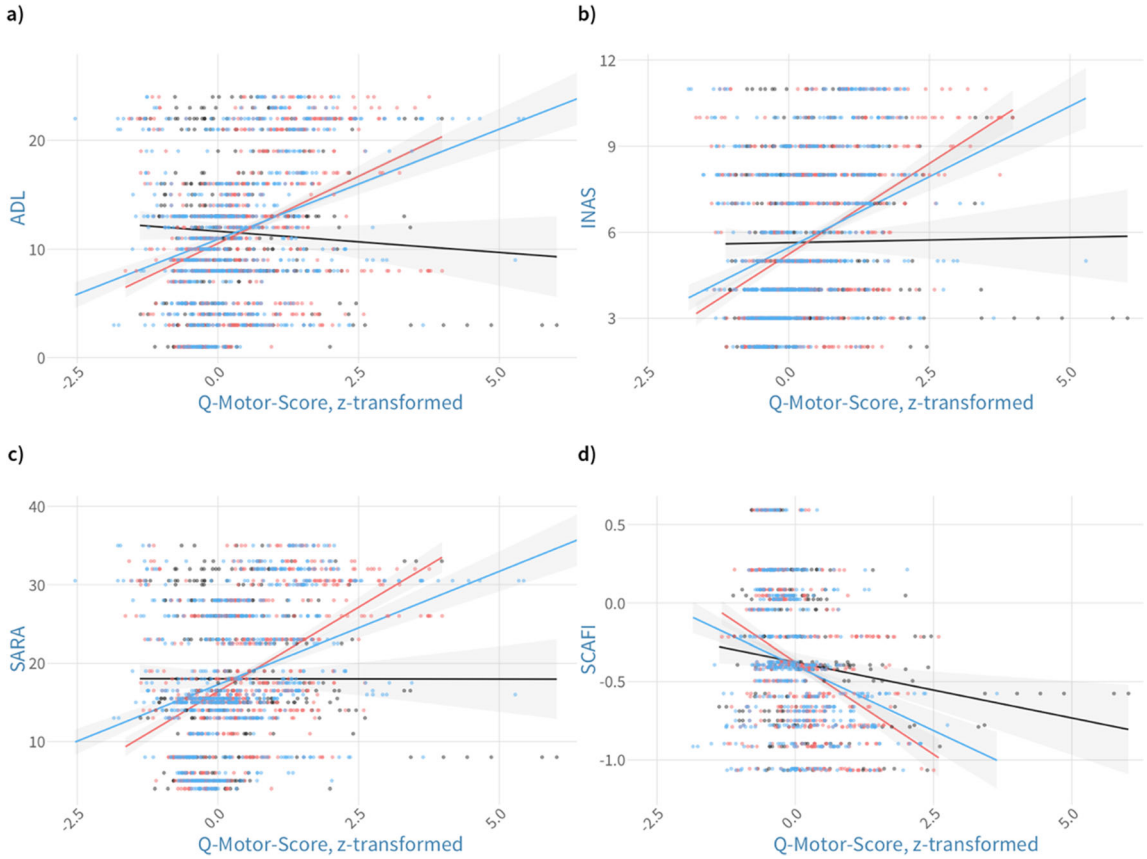

Fig. 2 Relation between Q-Motor and clinical measures in patients. All Q-Motor variables are shown together; thus, there are several points for each subject in each panel (one for each Q-Motor measure). Regression lines indicate the relation between clinical measures and averaged z-transformed Q-Motor measures. The shade around each regression line shows the 95% confidence interval. Panels are **a** for the activities of daily living (ADL) questionnaire; **b** the Inventory of Non-Ataxia Signs (INAS) count; **c** the Spinocerebellar Ataxia Functional Index (SCAFI) overall z-score and **d** the Scale for the Assessment and Rating of Ataxia (SARA) sum score

than averaged measures in a motor task. This means the variability of intervals between consecutive taps conveys more information than the average interval [18, 43]. Regarding the Q-Motor lift task, previous works have also indicated that variability measures related better than averaged measures to clinical measures [15, 33]. The picture is less clear here with FRDA, as for the lift task, there does not seem to be a difference in model complexity and accuracy that would suggest better suitability of variability measures. Future studies on Q-Motor in FRDA should investigate the information content of measures of variability compared to averaged measures.

Generally, in the present data, the lift task displayed interesting characteristics. On the one hand, correlations with clinical scores only suggest weak relationships, but contrary modelling lift task measures from clinical data mainly leads to low RMSE values in cross-validation, suggesting reasonable model performance. Given the available model performance metrics, the lift task seems sensitive to details of motor function that cannot be covered with the administered clinical tools. As from the data presented here such a conclusion cannot be drawn, future research should aim to further sort out the relationship of the Q-Motor lift task to clinical measures and sensitivity to longitudinal change in FRDA.

For the pronate/supinate task, looking at the complexity of models, the number of required predictors for the best fit is lower than for the other two tasks and in many cases, it appears that the task response can be modelled well using SCAFI scores. Particularly, the nine-hole peg test shows a strong relationship to Q-Motor outcomes, especially from the pronate/supinate task, as for some Q-Motor outcomes, nine-hole peg test results are the sole predictor suggesting a linear relationship between both measures. However, the SCAFI in general is prominent across models. As the SCAFI is particularly difficult to administer in severely affected patients especially given that FRDA leads to patients becoming wheelchair-bound within 10–15 years of disease onset [14], the Q-Motor task might serve as an alternative here. Considering the structure of predictors across Q-Motor measures, the 8-m walk task, which patients are often not able to perform due to physical limitations, has less predictive quality than the other two SCAFI subtasks, which are less constrained in that regard. In fact, the present data set contains 9 cases in

Table 3 Generalised linear models in patients

Measure	Unit	Inter	Gend F	Age	AgeO	SARA	INAS	8 mW	9HPT	Pata	ADL
Lift task (manumotography), dominant hand											
Orientation-index	°/s	2.20			*− 0.03*		− 0.03	0.13	*− 0.81*	− 0.28	
Position-index	cm/s	0.90			*− 0.03*		− 0.03	− 0.11		*− 0.39*	
Grip force coeffvar	%	2.07			*− 0.03*		− 0.10	*0.48*	*− 0.63*	*− 0.70*	*0.09*
Grip force	*N*	1.61	*− 0.34*		*0.03*			− 0.11			
Lift task (manumotography), non-dominant hand											
Orientation-index	°/s	2.48	*0.50*		*− 0.04*			− 0.05		*− 0.64*	
Position-index	cm/s	0.93			*− 0.02*		− 0.04	− 0.13		*− 0.55*	
Grip force coeffvar	%	2.35			*− 0.03*			− 0.03		*− 0.55*	
Grip force	*N*	1.36			*0.03*	*0.08*	*− 0.16*	0.07			
Speeded finger tapping (digitomotography), dominant hand											
Inter-tap-interval	s	− 2.04	*0.15*		*0.01*	− 0.01	*0.04*		*− 0.35*	*− 0.11*	
Inter-tap-interval SD		− 3.82			− 0.02		0.08	10^{-3}			
Inter-peak-interval	s	− 1.46	*0.15*		*0.01*	− 0.01			*− 0.41*	*− 0.16*	*0.01*
Inter-peak-interval SD		− 3.84	0.29					0.03	*− 0.72*	− 0.12	
Inter-onset-interval	s	− 1.46	*0.16*		*0.01*	− 0.01			*− 0.41*	*− 0.16*	*0.01*
Inter-onset-interval SD		− 3.74						− 0.04	− 0.51	− 0.16	
Tap-duration	s	− 2.33	*0.18*		*0.01*				*− 0.36*	*− 0.13*	
Tap-duration SD		− 3.96						− 0.03	*− 0.36*	− 0.05	
Tap-force	%	3.38			0.01		-10^{-4}	*0.16*	− 0.20		
Frequency	Hz	1.46	*− 0.16*		*− 0.01*	0.01			*0.41*	*0.16*	*− 0.01*
Speeded finger tapping (digitomotography), non-dominant hand											
Inter-tap-interval	s	− 1.97	*0.21*		*0.01*		*0.03*		*− 0.25*	− 0.08	
Inter-tap-interval SD		− 3.76						0.02		− 0.32	
Inter-peak-interval	s	− 1.37	*0.20*		0.01		0.01		*− 0.24*	*− 0.15*	*0.01*
Inter-peak-interval SD		− 3.56					0.04	0.02		− 0.29	
Inter-onset-interval	s	− 1.38	*0.20*		*0.01*		0.01		*− 0.24*	*− 0.15*	*0.01*
Inter-onset-interval SD		− 3.45					− 0.02	− 0.04		− 0.39	
Tap-duration	s	− 1.99	*0.17*						*− 0.36*	*− 0.17*	
Tap-duration SD		− 3.63					− 0.04	− 0.03		− 0.36	
Tap-force	%	3.63	0.14				*− 0.05*			− 0.08	
Frequency	Hz	1.38	*− 0.20*		*− 0.01*		− 0.01		*0.24*	*0.15*	*− 0.01*
Pronate/supinate task (dysdiadochomotography), dominant hand											
Inter-tap-interval	s	− 1.04					0.02		*− 0.51*		*− 0.02*
Inter-tap-interval SD		− 2.23					*− 0.09*	0.04	*− 1.17*		
Inter-peak-interval	s	− 0.75							*− 0.56*		
Inter-peak-interval SD		− 2.27					− 0.06	− 0.11	*− 1.10*	*− 0.27*	
Inter-onset-interval	s	− 0.75							*− 0.56*		
Inter-onset-interval SD		− 2.17					*− 0.10*	− 0.18	*− 1.14*	*− 0.31*	
Tap-duration	s	− 1.92		*− 0.02*	*0.03*			0.01	*− 0.94*		
Tap-duration SD		− 3.17						− 0.10	*− 0.79*	− 0.26	
Tap-force	%	3.74				*0.03*	− 0.06	− 0.01			
Frequency	Hz	0.75							*0.55*		
Pronate/supinate task (dysdiadochomotography), non-dominant hand											
Inter-tap-interval	s	− 1.14					0.02	0.09	*− 0.70*	*0.19*	
Inter-tap-interval SD		− 2.42						− 0.01	*− 0.59*		
Inter-peak-interval	s	− 0.60				*− 0.02*			*− 0.73*		*0.02*
Inter-peak-interval SD		− 2.26						0.04	*− 0.80*		
Inter-onset-interval	s	− 0.60				*− 0.02*			*− 0.73*		*0.02*

Table 3 (continued)

Measure	Unit	Inter	Gend F	Age	AgeO	SARA	INAS	8 mW	9HPT	Pata	ADL
Inter-onset-interval SD		− 1.97					− 0.08	− 0.04	*− 0.95*		
Tap-duration	s	− 1.73	*0.20*						*− 0.63*		
Tap-duration SD		− 2.38	*0.34*					*− 0.60*		− 0.01	*− 0.09*
Tap-force	%	3.80	*− 0.14*		*− 0.01*	*0.01*					
Frequency	Hz	0.60				*0.02*			*0.72*		*− 0.02*

For each log-transformed Q-Motor measure, the estimates of each predictor are given. If a predictor was not included in the best fitting model, no value is given. Italic indicates $p \leq .05$. Abbreviations: *Inter*, intercept; *Gend F*, gender female; *AgeO*, age of onset; *Var*, variation. 8mW, 9HPT and Pata are the respective SCAFI subtasks

which patients that completed the Q-Motor examination were already wheelchair-bound, thus rendering the SCAFI 8 m walk test impossible to be administered. This also raises the question regarding further limitations of established clinical instruments, especially for severely affected patients. In theory, there are no practical limits for the Q-Motor, but even this task might become strenuous and difficult to administer in severely affected patients. More research is needed to explore those practical limits. With what is available now, the Q-Motor seems to be promising with patients that are wheelchair-bound but can still perform an upper limb motor assessment.

In previous works on Huntington's disease, it was reported that performance in a pronate/supinate task is directly related to cerebellar volume [44]. In FRDA, early neurodegeneration affects the spinal cord and especially the dorsal root ganglia [4, 45, 46] and in later stages the cerebellum [14, 47]. However, it has also been suggested that the neuronal loss in the spinal cord and dorsal root ganglia may reflect hypoplasia rather than progressive neurodegeneration with only later cerebellar volume loss reflecting true neurodegeneration [45]. Given the patterns of neuronal loss involved in FRDA, an objective and sensitive quantitative characterisation of this impairment would provide a useful clinical tool, as such a measure is not yet available outside of neuroimaging. Hence, the relationship between Q-Motor task measures and disease-specific neurodegeneration needs to be investigated systematically in future imaging studies. In Huntington's disease, associations between worse performance in Q-Motor and more pronounced neurodegeneration based on imaging data were detected in a large cohort study [32, 48, 49].

Longitudinally, we found only few effects. This was the case for grip force of the non-dominant hand in the lift task as well as for the following measures of the pronate/supinate task: inter-tap-interval of the non-dominant hand, inter-peak-interval of the dominant hand and inter-onset-interval of the dominant hand. As for changes in R^2 measures comparing models with and without a time-component, we found improvements in R^2 where there was a significant effect. This improvement ranged from marginal (R^2 about 0.02) to moderate (0.2). Generally, it seems reasonable to assume that some measures will be more sensitive to longitudinal change than others, but this needs to be addressed in future studies with a larger follow-up sample. A measure being able to capture more nuanced details of disease progression in FRDA would be desirable, but keeping in mind that FRDA progresses rather slowly compared to other neurodegenerative disorders and considering the small sample size in the present work, the absence of time effects for most measures is reasonable and not unexpected. While there were only few longitudinal effects in Q-Motor outcomes, no significant deterioration was observed in clinical scores. The observed improvement from baseline to follow-up for the SARA is unusual in contrast to previous research showing a decline by about 1 score per year [7] and likely reflects an artefact due to the small sample size, as there is one patient with an exceptionally large improvement between both timepoints (see above for details). We think that we can rule out methodological issues as the instrument was administered by the same set of trained professionals in both baseline and follow-up and care is taken for standardisation of data gathering and entry. Overall, research evaluating a longer time period and critically also including a larger sample should be able to shed further light on progression characteristics of Q-Motor tasks in FRDA. For comparison, in Huntington's disease, progression of Q-Motor changes was detectable after 1 year in symptomatic patients and observed over 3 years even in premanifest gene carriers without overt clinical symptoms [16, 50].

An important aspect to consider in clinical development for FRDA may be the recent observation that Q-Motor measures, which are rater-independent, may lack placebo effects in randomised placebo-controlled clinical trials and exhibit higher sensitivity when compared to clinical scales [17]. This was first seen in a small phase IIa study [51] and now confirmed in three large multicentre clinical trials in Huntington's disease, PRIDE-HD (EUDRAC-CT 2013-

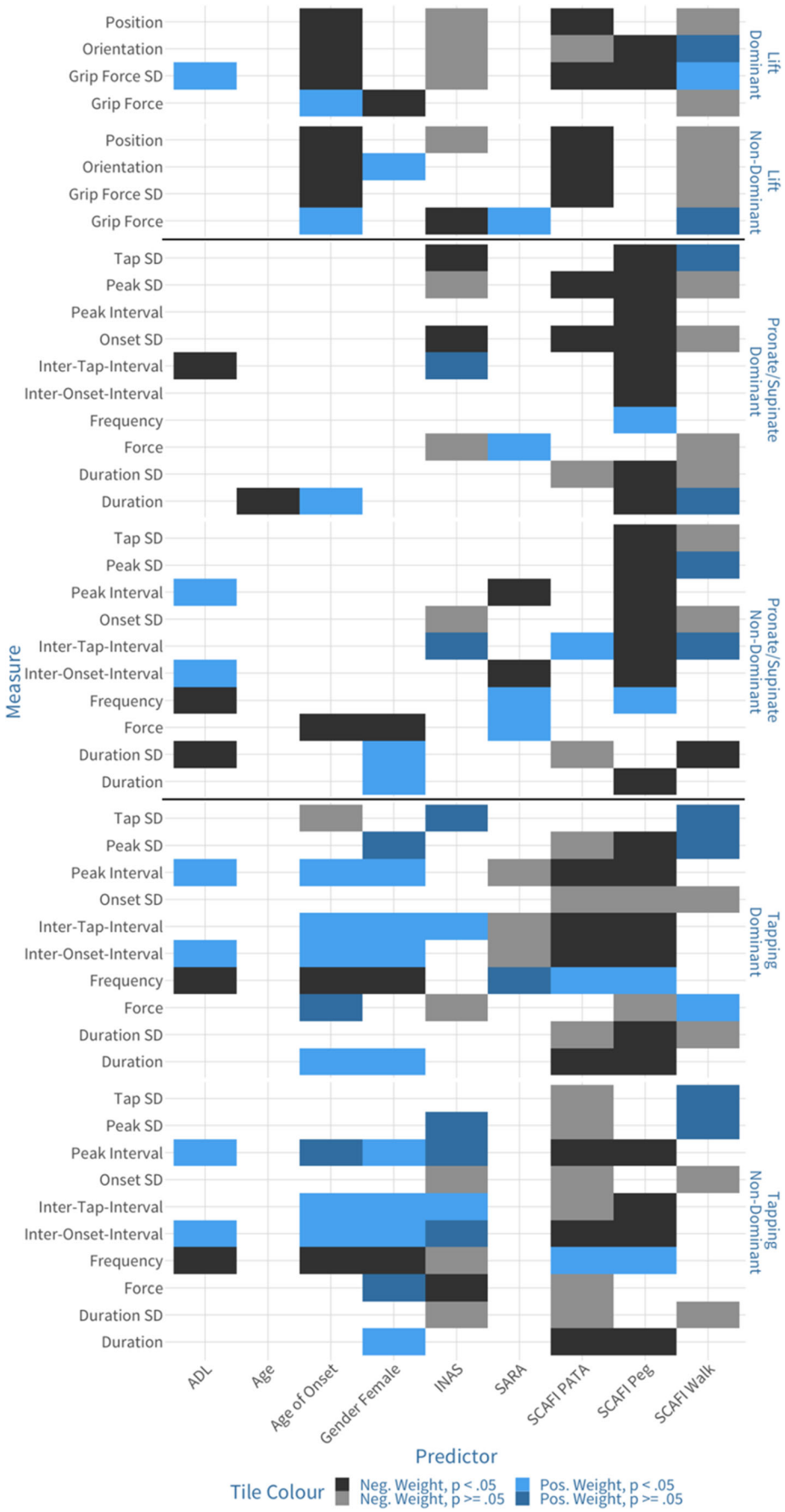

Fig. 3 Visualisation of the predictor structure of best fitting GLM. Blue tiles indicate positive weight, grey tiles indicate negative weight. Dark hues denote $p \leq .05$, light hues denote $p > .05$ and the absence of a tile shows that the specific predictor was not included in the best fitting model

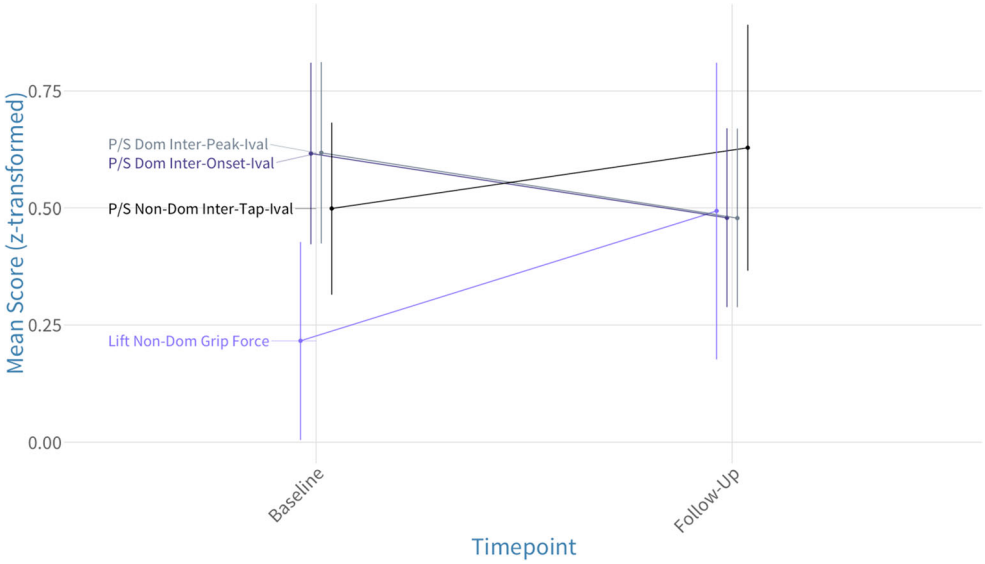

Fig. 4 Change from baseline to follow-up in Q-Motor measures in FRDA patients. Only measures with $p < .05$ for the time predictor are shown. Scores shown are z-transformed due to varying ranges of raw data. Error bars represent the standard error of the mean Abbreviations: P/S, pronate/supinate; Dom, dominant; Ival, interval

001888-23) [52], AMARYLLIS (EUDRAC-CT 2014-001291-56, Reilmann pers. Comm.) and LEGATO-HD (EUDRAC-CT 2014-000418-75, Reilmann pers. Comm).

As argued above, one major limitation of our study is the small sample of patients included, whereby it was not possible to split the data into training and validation samples for model building and testing, respectively. The even smaller amount of available data should also be taken into consideration when interpreting longitudinal modelling results and due to the small amount of controls in the follow-up, we did refrain entirely from longitudinal analysis within this group. For future Q-Motor examinations, the model equations provided here should be applied to a subject's data before the Q-Motor data analysis is done to verify their quality. Further, modelling omitted interactions entirely due to the danger of overfitting and the small set of input data available.

Conclusions

In summary, the present paper provides first insights into potential value of the Q-Motor assessment for clinical characterisation of FRDA. However, further properly powered studies are needed to explore the possible benefit of rater-independent quantitative measures compared to categorical rating scales, which may be influenced by examiner bias. Our Q-Motor results encourage such studies as quantitative tools may increase the sensitivity of subject characterisation in future FRDA studies.

Funding Information KR is funded by the German Federal Ministry of Education and Research (BMBF 01GQ1402). MS received support from the Else Kröner Fresenius Stiftung. ID was supported by the START-Program (08/16) of the Faculty of Medicine at the RWTH Aachen University.

Compliance with Ethical Standards

Conflict of Interest R Schubert is employee of the George-Huntington-Institute and is involved in analysis and development of Q-Motor measures. He received funding from the EU-FP7 consortium REPAIR-HD to develop Q-Motor-based quantitative cognitive assessments.

T Klockgether receives/has received research support from the Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF), the Bundesministerium für Gesundheit (BMG), the Robert Bosch Foundation, the European Union (EU) and the National Institutes of Health (NIH). He has received consulting fees from Biohaven and UBC. He has received a speaker honorarium from Novartis.

R Reilmann is founding director and owner of the George-Huntington-Institute, a private research institute focused on clinical and preclinical research in Huntington disease, and QuantiMedis, a clinical research organisation providing Q-Motor (quantitative motor) services in clinical trials and research. He holds appointments at the Dept. of Radiology of the University of Muenster and at the Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tuebingen. Dr. Reilmann serves as elected member of the Steering Committees of the European Huntington Disease Network (EHDN) and the Huntington Study Group (HSG), co-chair of the Task Force on Huntington's disease and member of the Task Force on Technology of the International Parkinson and Movement Disorder Society (IPMDS). He has provided consulting services, advisory board functions, clinical trial services, quantitative motor analyses and/or lectures for Actelion Pharmaceuticals, Amarin Neuroscience, AOP Orphan Pharmaceuticals, Cure Huntington Disease Initiative Foundation (CHDI), Desitin, Hoffmann-La Roche, IONIS Pharmaceuticals, Ipsen, Lundbeck, Link Medicine, MEDA Pharma, Medivation, Mitoconix, Neurosearch, Novartis AG, Omeros, Pfizer, Prana Biotechnology, Raptor Pharmaceuticals, Siena Biotech, Temmler Pharma, Teva Pharmaceuticals, uniQure, Vaccinex, Wave Life Sciences and Wyeth Pharmaceuticals. He has received grant support from the Bundesministerium für Bildung und Forschung (BMBF), the Cure Huntington Disease Initiative Foundation (CHDI), the Deutsche Forschungsgemeinschaft (DFG), the Deutsches Zentrum für Neurodegeneration und Entzündung (DZNE), the European Union 7th Framework Program (EU-FP7), the European Huntington Disease Network (EHDN), the High-Q-Foundation and the National Science Foundation (NSF).

All other authors declare that they have no conflict of interest.

Ethical Approval 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.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science (80-). 1996;271(5254):1423–7. Available from: https://doi.org/10.1126/science.271.5254.1423
2. Vankan P. Prevalence gradients of Friedreich's ataxia and R1b haplotype in Europe co-localize, suggesting a common Palaeolithic origin in the Franco-Cantabrian ice age refuge. J Neurochem. 2013;126(SUPPL.1):11–20.
3. Reetz K, Dogan I, Hohenfeld C, Didszun C, Giunti P, Mariotti C, et al. Nonataxia symptoms in Friedreich ataxia. Neurology. 2018 Aug 10; https://doi.org/10.1212/WNL.0000000000006121.
4. Bürk K. Friedreich ataxia: current status and future prospects. Cerebellum & Ataxias. 2017;4(1):4. Available from: https://doi.org/10.1186/s40673-017-0062-x
5. Delatycki MB, Corben LA. Clinical features of Friedreich ataxia. J Child Neurol 2012;27(9):1133–1137. Available from: https://doi.org/10.1177/0883073812448230
6. Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 2015;14(2):174–82.
7. Reetz K, Dogan I, Hilgers RD, Giunti P, Mariotti C, Durr A, et al. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. Lancet Neurol. 2016;15(13):1346–54.
8. Schmitz-Hübsch T, Du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia. Neurol Int. 2006;66(1):1717–20.
9. Schmitz-Hubsch T, Giunti P, Stephenson DA, Globas C, Baliko L, Sacca F, Mariotti C, Rakowicz M, Szymanski S, Infante J, van de Warrenburg BPC, Timmann D, Fancellu R, Rola R, Depondt C, Schols L, Zdzienicka E, Kang J S, Dohlinger S, Kremer B, Melegh B, Filla A, Klockgether T SCA Functional Index: a useful compound performance measure for spinocerebellar ataxia. Neurol Int 2008 Aug 12;71(7):486–492. Available from: https://doi.org/10.1212/01.wnl.0000324863.76290.19
10. Jacobi H, Rakowicz M, Rola R, Fancellu R, Mariotti C, Charles P, et al. Inventory of non-ataxia signs (INAS): validation of a new clinical assessment instrument. Cerebellum. 2013;12(3):418–28.
11. Du Montcel ST, Charles P, Ribai P, Goizet C, Le Bayon A, Labauge P, et al. Composite cerebellar functional severity score: validation of a quantitative score of cerebellar impairment. Brain. 2008;131(5):1352–61.
12. Tanguy Melac A, Mariotti C, Filipovic Pierucci A, Giunti P, Arpa J, Boesch S, et al. Friedreich and dominant ataxias: quantitative differences in cerebellar dysfunction measurements. J Neurol Neurosurg Psychiatry. 2017;jnnp-2017-316964. Available from: https://doi.org/10.1136/jnnp-2017-316964%0A
13. Corben LA, Tai G, Wilson C, Collins V, Churchyard AJ, Delatycki MB. A comparison of three measures of upper limb function in Friedreich ataxia. J Neurol 2010 Apr 13;257(4):518–523. Available from: https://doi.org/10.1007/s00415-009-5352-7
14. Pandolfo M. Friedreich ataxia: the clinical picture. J Neurol. 2009;256(SUPPL. 1):3–8.
15. Gordon A M, Quinn L, Reilmann R, Marder K. Coordination of prehensile forces during precision grip in Huntington's disease. Exp Neurol. 2000;163(1):136–48.
16. Reilmann R, Kirsten F, Quinn L, Henningsen H, Marder K, Gordon AM. Objective assessment of progression in Huntington's disease: a 3-year follow-up study. Neurol Int 2001 Sep 11;57(5):920–924. Available from: https://doi.org/10.1212/WNL.57.5.920
17. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. In: Handbook of Clinical Neurology. 1st ed. Elsevier B.V.; 2017. p. 209–25. Available from: https://doi.org/10.1016/B978-0-12-801893-4.00018-3
18. Reilmann R, Holtbernd F, Bachmann R, Mohammadi S, Ringelstein EB, Deppe M. Grasping multiple sclerosis: do quantitative motor assessments provide a link between structure and function? J Neurol. 2013;260(2):407–14.
19. Holtbernd F, Deppe M, Bachmann R, Mohammadi S, Ringelstein EB, Reilmann R. Deficits in tongue motor control are linked to microstructural brain damage in multiple sclerosis: a pilot study. BMC Neurol. 2015 Dec 8;15(1):190. Available from: https://doi.org/10.1186/s12883-015-0451-9
20. Maetzler W, Ellerbrock M, Heger T, Sass C, Berg D, Reilmann R. Digitomotography in Parkinson's disease: a cross-sectional and longitudinal study. Siegel A, editor. PLoS One. 2015 Apr 22;10(4):e0123914. Available from: https://doi.org/10.1371/journal.pone.0123914
21. Schaeffer E, Maetzler W, Liepelt-Scarfone I, Sass C, Reilmann R, Berg D. Quantitative motor assessment of dyskinesias in Parkinson's disease. J Neural Transm 2015;122(9):1271–1278. Available from: https://doi.org/10.1007/s00702-015-1383-7
22. Hoffmann S, Siedler J, Brandt AU, Piper SK, Kohler S, Sass C, et al. Quantitative motor assessment of muscular weakness in myasthenia gravis: a pilot study. BMC Neurol. 2015;1–7. Available from: https://doi.org/10.1186/s12883-015-0517-8
23. Jeppesen Kragh F, Bruun N, Budtz-Jørgensen E, Hjermind LE, Schubert R, Reilmann R, et al. Quantitative measurements of motor function in Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies: a proof-of-concept study. Dement Geriatr Cogn Disord. 2018;46:168–79.
24. Hashimoto Y, Honda T, Matsumura K, Nakao M, Soga K, Katano K, et al. Quantitative evaluation of human cerebellum-dependent motor learning through prism adaptation of hand-reaching movement. PLoS One. 2015;10(3):1–19.
25. Lee J, Kagamihara Y, Kakei S. A new method for functional evaluation of motor commands in patients with cerebellar ataxia. PLoS One. 2015;10(7):1–22.
26. Menegoni F, Milano E, Trotti C, Galli M, Bigoni M, Baudo S, et al. Quantitative evaluation of functional limitation of upper limb movements in subjects affected by ataxia. Eur J Neurol. 2009;16(2):232–9.
27. Sanguineti V, Morasso PG, Baratto L, Brichetto G, Mancardi GL, Solaro C. Cerebellar ataxia: quantitative assessment and cybernetic interpretation. Hum Mov Sci. 2003;22(2):189–205.
28. Klein A, Sacrey LAR, Dunnett SB, Whishaw IQ, Nikkhah G. Proximal movements compensate for distal forelimb movement impairments in a reach-to-eat task in Huntington's disease: new insights into motor impairments in a real-world skill. Neurobiol Dis 2011;41(2):560–569. Available from: https://doi.org/10.1016/j.nbd.2010.11.002
29. Giancardo L, Sánchez-Ferro A, Arroyo-Gallego T, Butterworth I, Mendoza CS, Montero P, Matarazzo M, Obeso JA, Gray ML, Estépar RSJ Computer keyboard interaction as an indicator of early

Parkinson's disease. Sci Rep 2016;6:1–10. Available from: https://doi.org/10.1038/srep34468
30. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971 Mar [cited 2015 Apr 20];9(1):97–113.
31. World Medical Association. World Medical Association Declaration of Helsinki. JAMA. 2013 Nov 27;310(20):2191. Available from: https://doi.org/10.1001/jama.2013.281053
32. Bechtel N, Scahill RI, Rosas HD, Acharya T, van den Bogaard SJA, Jauffret C, Say MJ, Sturrock A, Johnson H, Onorato CE, Salat DH, Durr A, Leavitt BR, Roos RAC, Landwehrmeyer GB, Langbehn DR, Stout JC, Tabrizi SJ, Reilmann R Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurol Int 2010 Dec 14;75(24):2150–2160. Available from: https://doi.org/10.1212/WNL.0b013e3182020123
33. Reilmann R, Bohlen S, Klopstock T, Bender A, Weindl A, Saemann P, Auer DP, Ringelstein EB, Lange HW Grasping premanifest Huntington's disease—shaping new endpoints for new trials. Mov Disord 2010 Dec 15;25(16):2858–2862. Available from: https://doi.org/10.1002/mds.23300
34. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
35. Hurvich CM, Tsai C-L. Regression and time series model selection in small samples. Biometrika. 1989 Jun;76(2):297.
36. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr. 1974;19(6):716–23.
37. Calcagno V, Mazancourt C De. glmulti: an R package for easy automated model selection with (generalized) linear models. J Stat Softw 2010;34(12):1–29.
38. Kohavi R. A study of cross-validation and bootstrap for accuracy estimation and model selection 2 methods for accuracy estimation. Proc of IJCAI'95. 1995;1137–45.
39. Satterthwaite FE. An approximate distribution of estimates of variance components. Biometrics Bull. 1946 Dec;2(6):110. Available from: https://doi.org/10.1002/9780470057339.vai016
40. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015 Jun 23;67(1):883–5.
41. Nakagawa S, Johnson PCD, Schielzeth H. The coefficient of determination R 2 and intra-class correlation coefficient from generalized linear mixed-effects models revisited and expanded. J R Soc Interface. 2017 Sep;14(134):20170213. Available from: https://doi.org/10.1098/rsif.2017.0213%0A.
42. Germanotta M, Vasco G, Petrarca M, Rossi S, Carniel S, Bertini E, et al. Robotic and clinical evaluation of upper limb motor performance in patients with Friedreich's ataxia: an observational study. J Neuroeng Rehabil. 2015;12(1).
43. Krishnan V, de Freitas PB, Jaric S. Impaired object manipulation in mildly involved individuals with multiple sclerosis. Motor Control 2008;12(1):3–20. Available from: https://doi.org/10.1123/mcj.12.1.3
44. Rees EM, Farmer R, Cole JH, Haider S, Durr A, Landwehrmeyer B, et al. Cerebellar abnormalities in Huntington's disease: a role in motor and psychiatric impairment? Mov Disord. 2014;29(13):1648–54.
45. Koeppen AH, Becker AB, Qian J, Feustel PJ. Friedreich ataxia: hypoplasia of spinal cord and dorsal root ganglia. J Neuropathol Exp Neurol. 2017 12;76(2):nlw111. Available from: https://doi.org/10.1093/jnen/nlw111
46. Dogan I, Romanzetti S, Didszun C, Mirzazade S, Timmann D, Saft C, et al. Structural characteristics of the central nervous system in Friedreich ataxia: an in vivo spinal cord and brain MRI study. J Neurol Neurosurg Psychiatry. 2018 26;jnnp-2018-318422. Available from: https://doi.org/10.1136/jnnp-2018-318422
47. Gomes CM, Santos R. Neurodegeneration in Friedreich's ataxia: from defective frataxin to oxidative stress. Oxid Med Cell Longev. 2013;2013:1–10.
48. Dumas EM, van den Bogaard SJA, Ruber ME, Reilmann R, Stout JC, Craufurd D, Hicks SL, Kennard C, Tabrizi SJ, van Buchem MA, van der Grond J, Roos RAC Early changes in white matter pathways of the sensorimotor cortex in premanifest Huntington's disease. Hum Brain Mapp 2012 Jan;33(1):203–212. Available from: https://doi.org/10.1002/hbm.21205
49. Scahill RI, Hobbs NZ, Say MJ, Bechtel N, Henley SMD, Hyare H, et al. Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. Hum Brain Mapp. 2013;34(3):519–29.
50. Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, Borowsky B, Landwehrmeyer B, Frost C, Johnson H, Craufurd D, Reilmann R, Stout JC, Langbehn DR Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12(7):637–649. Available from: https://doi.org/10.1016/S1474-4422(13)70088-7
51. Reilmann R, Rouzade-Dominguez M-L, Saft C, Süssmuth SD, Priller J, Rosser A, Rickards H, Schöls L, Pezous N, Gasparini F, Johns D, Landwehrmeyer GB, Gomez-Mancilla B A randomized, placebo-controlled trial of AFQ056 for the treatment of chorea in Huntington's disease. Mov Disord. 2015 Mar;30(3):427–431. Available from: https://doi.org/10.1002/mds.26174
52. Reilmann R, McGarry A, Landwehrmeyer G, Kieburtz K, Grachev I, Eyal E, et al. Efficacy, safety, and tolerability of pridopidine in Huntington disease (HD): results from the phase II dose-ranging study. Pride-HD Mov Disord. 2017;32(S2):S189.