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**Friedreich and dominant ataxias: quantitative differences in cerebellar dysfunction
measurements**

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Abstract

Background Sensitive outcome measures for clinical trials on cerebellar ataxias are lacking. Most cerebellar ataxias progress very slowly and quantitative measurements are required to evaluate cerebellar dysfunction.

Methods We evaluated two scales for rating cerebellar ataxias: the Composite Cerebellar Functional Severity (CCFS) and Assessment and Rating of Ataxia (SARA) scales, in

spinocerebellar ataxia patients and controls. We evaluated these scales for different diseases and investigated the factors governing the scores obtained. All patients were recruited prospectively.

Results There were 383 FRDA patients, 205 SCA patients and 168 controls. In FRDA, 31% of the variance of cerebellar signs with the CCFS and 41% of that with SARA were explained by disease duration, age at onset and the shorter abnormal repeat in the *FXN* gene. Increases in CCFS and SARA scores per year were lower for FRDA than for SCA (CCFS index: 0.123 ± 0.123 per year vs. 0.163 ± 0.179 , $p < 0.001$; SARA index: 1.5 ± 1.2 vs. 1.7 ± 1.7 , $p < 0.001$), indicating slower cerebellar dysfunction indexes for FRDA than for SCA. SCA2 patients had higher CCFS scores than SCA1 and SCA3 patients, but similar SARA scores.

Conclusions Cerebellar dysfunction, as measured with the CCFS and SARA scales, was more severe in FRDA than in SCA patients, but with lower progression indexes, within the limits of these types of indexes. Ceiling effects may occur at late stages, for both scales. The CCFS scale is rater-independent and could be used in a multicenter context, as it is simple, rapid, and fully automated.

Clinical trial registration number: NCT02069509

INTRODUCTION

There is clear need for scales for assessing cerebellar dysfunction for clinical trials on ataxia. It is crucial to capture small variations of cerebellar dysfunction for cerebellar diseases that progress slowly. The most frequent cerebellar diseases are Friedreich's ataxia (FRDA) and autosomal dominant spinocerebellar ataxias resulting from an expansion of CAG repeats in the SCA1,2, 3

and 7 genes[1]. FRDA is an autosomal recessive disease consisting of progressive cerebellar and sensory ataxia, beginning around puberty[2]. The European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) was created in framework European framework (as part of the FP7 program) and has assembled the necessary expertise for a fully translational research strategy on FRDA and its treatment. The European registry of FRDA patients is an essential component of clinical studies, including observational studies and clinical trials[3].

Several scales including clinical elements have been proposed for measuring FRDA severity and progression, including the International Cooperative Ataxia Rating Scale (ICARS)[4], the Friedreich Ataxia Rating Scale (FARS)[5] and the Scale for the Assessment and Rating of Ataxia (SARA)[6]. Performance-based scales have been successfully used in FRDA[7] and are less subject to inter-rater variability than clinical scales. This is a desirable feature given the multicenter context in which FRDA studies are performed. The Composite Cerebellar Functional Severity (CCFS) score is a quantitative performance-based scale validated for autosomal dominant spinocerebellar ataxia (SCA) in adults and children[8,9,10].

The objectives of this study were to compare severity of the disease of both FRDA and SCA, to assess clinical utility of the SARA and CCFS scales for studies, and to identify the factors governing the scores obtained for these scales. The results of this study will be important for the validation of these two scales for clinical trials.

METHODS

Within the EFACTS framework (www.e-facts.eu), FRDA patients were enrolled in a prospective, longitudinal study at 11 European centers[3].

Patients

Between October 2010 and June 2015, 605 adults and children over the age of six years were included in this study performed within the EFACTS network, including 383 patients (Aachen $n=27$, Bonn $n=14$, Brussel $n=27$, Innsbruck $n=35$, London $n=60$, Madrid $n=47$, Marburg $n=5$, Milan $n=80$, Munich $n=32$, Paris $n=42$ and Tübingen $n=14$) with both CCFS and SARA evaluations, together with information about age at onset (defined as age at the time of the first clinical symptoms) and disease duration (see online supplementary file Figure 1).

For an additional 199 FRDA patients (Aachen $n=2$, Bonn $n=2$, Innsbruck $n=6$, London $n=85$, Madrid $n=29$, Marburg $n=2$, Milan $n=53$, Munich $n=5$, Paris $n=7$ and Tübingen $n=8$) SARA scores and disease durations were available, but CCFS values were missing due a lack of availability of the device required for this test or the patient's limitations.

We also recruited 205 consecutive patients with dominant ataxias due to mutations of the SCA1, 2, 3, and 7 genes attending the Genetics Department and the National Reference Center for Rare Diseases of Pitié-Salpêtrière University Hospital in Paris. Age at onset, disease duration and SARA evaluation data were available for all these subjects.

Finally, 168 healthy control individuals (7 to 74 years of age) were also recruited in Milan and Paris.

For all individuals, information about the sex of the patient, age at examination, and center was available.

Ethical standards

Informed consent was obtained from patients or their authorized representatives (for patients under the age of 18 years or unable to confirm consent due to clinical impairment) before inclusion in the study, in accordance with the protocol for the EFACTS study or that for the SPATAX study (INSERM C10-41 and INSERM RBM 01-29). These studies were approved by the local ethic committees of each participating center, and are registered with ClinicalTrials.gov, number NCT02069509. This study was, therefore, performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments.

Genetics

Genetic testing (number of GAA-triplet-repeat expansions within the first intron of the frataxin gene or the existence of a point mutation) was performed for all FRDA patients as described by the Laboratory of Experimental Neurology at the Université Libre de Bruxelles (Brussels, Belgium)[11]. For EFACTS, inclusion required a confirmed genetic diagnosis of FRDA. Patients with point mutations were excluded ($n=15$). Genetic information for SCA subjects was taken from their medical records.

Clinical evaluation

SARA is a semi-quantitative scale developed for the assessment of functional impairments due to ataxia, with values from 0 (no ataxia) to 40 (most severe ataxia). It consists of eight items assessing stance, sitting, speech disturbance, finger chase, dysmetria, nose–finger test, tremor, fast alternating hand movements and heel–shin slide[6]. The CCFS is a quantitative assessment initially developed and validated for comparisons of SCA subjects with healthy controls. It includes two functional tests for the dominant hand: the nine-hole pegboard test (time required to place dowels in nine holes) and the click test (time required to perform 10 finger-pointing cycles)[8]. As performance is age-dependent, the times required to perform the two tests are adjusted for age by calculating Z-scores, which are then added together to give the CCFS score[10]. An electronic device is used to acquire test times automatically and to calculate the final score. CCFS score is a quantitative score, independent of age, with higher values indicative of more severe cerebellar impairment. Both tests were administered by a trained clinician or assistant, during the EFACTS visits for subjects with FRDA, and during routine annual follow-up visits for the other subjects.

Statistical analysis

Cerebellar dysfunction indexes were calculated by dividing the CCFS score (and the SARA score) by the disease duration to distinguish the impairment due to the disease itself from the impairment due to longer disease duration.

We compared population characteristics and severity scores between diagnoses, using the Pearson Chi-square test for qualitative variables or ANOVA for quantitative variables. Post-hoc pairwise *t*-tests were performed for each significant ANOVA, with *p*-values adjusted for multiple testing by Holm's method (p_c). Differences in characteristics between subjects with and without available CCFS data were assessed by ANOVA. For subjects without available CCFS data, we compared those unable to perform the test with those for whom the test could not be performed for technical reasons.

Correlation between CCFS score, SARA score, age at onset, disease duration and the number of repeats of the shorter allele were assessed and are reported with a 95% confidence interval and *p*-values.

We assessed the floor and ceiling effects of the SARA and CCFS scales, by analyzing the relationship between CCFS and SARA scores by linear regression, with the addition of a quadratic term to the regression model and with non-linear models (sigmoid models) for each diagnosis. In the sigmoid model, we used the Gauss-Newton algorithm, with estimation by least squares[12], and the most parsimonious model was retained. The relationship between the SARA dysfunction index and the CCFS dysfunction index was studied in a similar manner. Possible confounding factors were taken into account by multivariate linear regression analysis, including age at onset, disease duration and short allele length, in the FRDA population.

Structural equation modeling (SEM) was used to check the statistical plausibility of our hypotheses concerning the links between variables, based on recommended association of fit indices[13]: the standardized root mean square residual (SRMR), for which values below 0.08

were considered to indicate a good fit, and NFI (the normed fit index), for which values above 0.96 were considered to indicate a good fit.

No imputation was performed for missing data. Data are expressed as means \pm SD except for regression results, which are expressed as means \pm SE. Statistical analyses were carried out with R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 software for SEM. All tests were two-tailed and *p*-values below 0.05 were considered statistically significant.

RESULTS

Clinical characteristics (Table 1)

FRDA patients were significantly younger than SCA patients and older than controls (33.1 ± 14.6 years vs. 48.2 ± 13.9 and 21.4 ± 16.6 , respectively, $p_c < 0.001$ and $p_c < 0.001$). They were also significantly younger at disease onset (17.8 ± 11.3 years vs. 36.6 ± 12.9 , $p_c < 0.001$). Disease duration was significantly shorter for SCA patients than for FRDA patients (11.7 ± 8.5 years vs. 15.3 ± 9.0 , $p_c < 0.001$). The mean number of GAA repeats was 550 for the shorter allele (range: 60 – 1200) and 882 for the longer allele (range: 150 – 1334). The mean number of expanded CAG repeats was 46 for SCA1 (range: 39 – 57), 40 for SCA2 (range: 35 – 48), 72 for SCA3 (range: 56 – 78), and 48 for SCA7 (range: 42 – 62).

Table 1: Characteristics of subjects per diagnosis at visit

	FRDA (n=383)	SCA (n=205)	Controls (n=168)	P value ^a

Women, N (%)	216 (56%)	103 (50%)	103 (61%)	.0959
Age at examination, y, mean (SD) [minimum- maximum]	33.1 (14.6) [6-76]	48.2 (13.9) [15-83]	21.4 (16.6) [7-74]	<0.0001
Age at onset, y, mean (SD) [minimum- maximum]	17.8 (11.3) [1-65]	36.6 (12.9) [1-67]	-	<0.0001
Disease Duration, y, mean (SD) [minimum- maximum]	15.3 (9.0) [1-49]	11.7 (8.5) [0-56]	-	<0.0001

maximum]				
CCFS, mean (SD) [minimum-maximum]	1.225 (0.158) [0.883-1.756]	1.101 (0.175) [0.661-1.680]	0.843 (0.045) [0.706-0.981]	<0.0001
SARA (range, 0-40), mean (SD) [minimum- maximum]	18.3 (8.4) [1.5-38]	13.5 (7.1) [0-32]	0.8 (1.0) [0-1] (n=18)	<0.0001

Abbreviations: FRDA: Friedreich ataxia, SCA: dominant cerebellar ataxia; HSP: hereditary spastic paraplegia; CCFS: composite cerebellar functional severity; SARA: Scale for the Assessment and Rating of Ataxia.

^a P-value of the comparison between all disease groups (ANOVA test or Chi-square test)

Comparison of the severity scores between disease groups

Both CCFS and SARA scores differed between diseases, with these scores higher for FRDA patients than for SCA patients and controls (Table 1: CCFS: 1.225 ± 0.158 vs. 1.101 ± 0.175 and 0.843 ± 0.045 $p_c < 0.001$ and $p_c < 0.001$; SARA: 18.3 ± 8.4 vs. 13.5 ± 7.0 and 0.8 ± 1.0 , $p_c < 0.001$ and $p_c < 0.001$), indicating more severe disease. After adjustment for disease duration, we used these scales to evaluate the cerebellar dysfunction. The CCFS and SARA cerebellar dysfunction indexes were smaller in FRDA than in SCA patients (CCFS index: 0.123 ± 0.123 per year vs. 0.163 ± 0.179 , $p < 0.001$; SARA index: 1.5 ± 1.2 vs. 1.7 ± 1.7 , $p < 0.001$), indicating slower cerebellar dysfunction in FRDA than in SCA. Differences between genetic subtypes were detected in the SCA population: SCA2 patients had higher CCFS scores than SCA1 and SCA3 patients, but similar SARA scores (see online supplementary file Table 1).

Relationship between SARA score, CCFS score, and disease duration in FRDA and SCA patients (Figure 1)

Regression analyses showed that CCFS and SARA increased (worsening) with disease duration in FRDA (Figure 1A-1C), but a ceiling effect was observed only for SARA (negative quadratic term, $p = 0.0045$). This ceiling effect was weaker, but nevertheless present, in the subjects not undergoing CCFS testing included in the analysis (see online supplementary file Figure 2).

The scores on both scales increased in SCA patients (Figure 1B-1D) and a ceiling effect was observed for disease duration (negative quadratic term, $p = 0.0001$ and $p < 0.0001$, respectively).

Furthermore, for regressions of SARA score against CCFS score, the best model for the FRDA patients was a sigmoid model with both floor and ceiling effects (Figure 1E, $p < 0.0001$). The relationship between SARA and CCFS scores was not linear for SARA scores below 10 or above 24. For all SCA patients considered together, the best model was a sigmoid model (Figure 1F, $p < 0.0001$), also with thresholds of 10 and 24. The sigmoid relationship was also the best fit for SCA1, 2 and 3 considered separately (Figure 2A-B-C). For SCA7, the best relationship was linear, with 16 of the 18 SARA values lying between 6 and 24 (Figure 2D).

CCFS score and FRDA

CCFS score was more closely correlated with disease characteristics (disease duration, age at onset and number of repeats in the shorter allele ($r = 0.38$ [0.29;0.46] $p < 0.0001$, $r = -0.36$ [-0.44;-0.27] $p < 0.0001$ and $r = 0.30$ [0.20;0.38] $p < 0.0001$, respectively) than with demographic characteristics, such as age at examination ($r = -0.04$ [-0.14;0.06] $p < 0.0001$). As expected, age at onset was closely correlated with the number of repeats ($r = -0.65$ [-0.70;-0.59] $p < 0.001$). We determined whether the relationship between the number of repeats in the shorter allele and the scores for the two scales was due to a direct relationship or a confounding effect of age at onset and/or disease duration, taking into account the pattern of correlations between variables, by performing SEM with all these variables (Figure 3A-B). For both CCFS and SARA, scores were associated with the number of repeats in the shorter allele even after accounting for disease duration and age at onset. CCFS score, adjusted for the other covariates, increased by 0.28 ± 0.06 ($p < 0.0001$) for each additional repeat and by 0.46 ± 0.04 ($p < 0.0001$) for each additional year of

disease duration, whereas it decreased by 0.18 ± 0.06 for each additional year of age before onset ($p < 0.0001$). Similarly, SARA score increased by 0.34 ± 0.04 ($p < 0.0001$) for each additional repeat and by 0.60 ± 0.03 ($p < 0.0001$) for each additional year of disease duration, whereas it decreased by 0.10 ± 0.04 ($p = 0.017$) for each year of age before onset. The models explained 31% of the variance for CCFS and 42% of the variance for SARA.

Characteristics of the populations with and without available CCFS score data (see online supplementary file Table 2)

In total, 199 subjects underwent SARA testing, but not CCFS assessment. We found several differences between the patients who did and did not undergo CCFS testing. Patients who did not undergo CCFS testing had more severe disease: higher SARA scores (28.8 ± 7.8 vs. 18.3 ± 8.4 , $p < 0.0001$) and longer disease durations (23.4 ± 10.4 vs. 15.3 ± 9.0 , $p < 0.0001$) than patients who underwent CCFS testing. Those who were unable to perform the CCFS test had a longer disease duration (26.5 ± 9.5 vs. 19.6 ± 10.1 , $p < 0.0001$) and a higher SARA score (32.3 ± 5.0 vs. 24.4 ± 8.5 , $p < 0.0001$) than those for whom the test was not possible for technical reasons.

DISCUSSION

Cerebellar dysfunction, as assessed with the CCFS and SARA scales, was more severe in FRDA than in SCA patients. However, after adjustment for disease duration, cerebellar function was found to be less impaired in FRDA than in SCA patients, particularly for SCA1 and 2 patients, who are more prone to cerebellar dysfunction than patients with afferent ataxia. Thus the

differences observed at inclusion are more explained by the disease duration than by the severity of the patients. These results should be confirmed with longitudinal data. These adjustments on disease duration have well known limitations especially for shorter disease durations and the extremes of disability: patients with a lower score and a shorter disease duration will have the same indexes as patients with a higher score and a longer disease duration.

SARA scores followed a linear trend between 10 and 24, with a floor and a ceiling in both FRDA and SCA patients. There are several possible explanations for this. First, SARA is a clinical assessment and is, thus, bounded, whereas the CCFS is unbounded. Second, the most severely affected patients may not have performed CCFS, thereby introducing a bias, although 27% of the subjects undergoing CCFS testing had a SARA score above 24. The large number of missing CCFS data requires further investigation. Third, the CCFS is an objective scale whereas SARA is a clinical scale that is more subjective, despite being semi-quantitative and standardized. SARA score may be more variable in patients with more extensive neurological signs (pyramidal, extrapyramidal etc.). Finally, 21% of those with a CCFS score <10 were children. Only the CCFS was validated in children[10]. The CCFS and SARA scales may therefore assess dysfunction differently, and they may be complementary.

For disease duration, the ceiling effect of SARA[14] and of other clinical rating scales, including ICARS and FARS[15,16], has already been reported for patients with FRDA. The ceiling effect of SARA and CCFS observed in FRDA and SCA patients with long disease durations may

reflect an underperformance of these scales for the most severe disease stages, or a slowing of the biological progression of the disease[7,17]. If confirmed in longitudinal studies, this ceiling effect of both scales at late stages has implications for the follow-up of the most severely affected FRDA subjects, particularly in terms of the potential use of these scales in clinical trials[18,19]. And it adds a further bias to the indexes dividing the scores by the disease durations. There is no consensus method for determining progression of cerebellar dysfunction in patients with ataxia. There is a need for a powerful method to detect different rates of disease progression to assess the relationship between disability and disease duration and help guide treatment decisions.

The effect of the number of repeats on age at onset and on phenotypic severity has been reported elsewhere[20]. Our study confirmed these findings and showed that the two scales gave similar results, with independent effects of both age at onset and disease duration in addition to short allele length, even when the complex correlations between variables were taken into account with an adapted model. SEM findings depend on the hypothetical path, and, in this study, we confirmed the existence of a direct effect of age at onset and disease duration, and direct and indirect effects of short allele length on both scales. However, these factors accounted for only a moderate proportion of the variance for the scores on these scales.

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Competing interests

Audrey Tanguy Melac reports other from AbbVie, other from Lundbeck, outside the submitted work.

Dr Mariotti has nothing to disclose.

Dr Filipovic Pierucci has worked for the Health Economics and Health Policy Research Unit of Greater Paris University Hospitals.

Dr Giunti has nothing to disclose.

Dr. Arpa has nothing to disclose.

Dr. Boesch reports personal fees from Gruenenthal, personal fees from AbbVie, personal fees from Ipsen, personal fees from Allergan, outside the submitted work.

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Dr. Reetz has nothing to disclose.

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References

1. Pulst SM. Ataxia rating scales in the balance. *Nat Clin Pract Neurol* 2007;3:119.
2. Schulz JB, Boesch S, Bürk K, Dürr A, Giunti P, Mariotti C, et al. Diagnosis and treatment of Friedreich ataxia: a European perspective. *Nat Rev Neurol* 2009;5:222–234.

3. 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;14:174–182.
4. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. *J Neurol Sci* 1997;145:205–211.
5. Lynch DR, Farmer JM, Tsou AY, Perlman S, Subramony SH, Gomez CM, et al. Measuring Friedreich ataxia complementary features of examination and performance measures. *Neurology* 2006;66:1711–1716.
6. Schmitz-Hübsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia. Development of a new clinical scale. *Neurology* 2006;66:1717–1720.
7. Friedman LS, Farmer JM, Perlman S, Wilmot G, Gomez CM, Bushara KO, et al. Measuring the rate of progression in Friedreich ataxia: Implications for clinical trial design. *Mov Disord* 2010;25:426–432.
8. 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;131:1352–1361.
9. Tezenas du Montcel S, Charles P, Goizet C, Marelli C, Ribai P, Vincitorio C, et al. Factors influencing disease progression in autosomal dominant cerebellar ataxia and spastic paraplegia. *Arch Neurol* 2012;69:500–508.

10. Filipovic Pierucci A, Mariotti C, Panzeri M, Giunti P, Boesch S, Schulz JB, et al. Quantifiable evaluation of cerebellar signs in children. *Neurology* 2015;84:1225-1232.
11. Pandolfo M. Friedreich ataxia: detection of GAA repeat expansions and frataxin point mutations in congenital heart disease. *Methods Mol Med* 2006;126:197-216.
12. Bates DM, Watts DG, editors. *Nonlinear Regression Analysis and Its Applications*. New York, John Wiley & Sons 1998.
13. Hooper D, Coughlan J, editors. *Structural equation modelling: guidelines for determining model fit*. Dublin Institute of Technology, *Electronic Journal of Business Research Methods* 6 2008.
14. Marelli C, Figoni J, Charles P, Anheim M, Tchikviladze M, Vincitorio CM, et al. Annual change in Friedreich's ataxia evaluated by the Scale for the Assessment and Rating of Ataxia (SARA) is independent of disease severity. *Mov Disord* 2012;27:135–139.
15. Tai G, Corben LA, Gurrin L, Yiu EM, Churchyard A, Fahey M, et al. A study of up to 12 years of follow-up of Friedreich ataxia utilising four measurement tools. *J Neurol Neurosurg Psychiatry* 2015;86:660-666.
16. Ribai P, Pousset F, Tanguy ML, Rivaud-Pechoux S, Le Ber I, Gasparini F, et al. Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. *Arch Neurol* 2007;64:558–564.
17. Chan E, Charles P, Ribai P, Goizet C, Marelli C, Vincitorio CM, et al. Quantitative assessment of the evolution of cerebellar signs in spinocerebellar ataxias. *Mov Disord* 2011;26:534–538.

18. Jacobi H, du Montcel ST, Bauer P, Giunti P, Cook A, Labrum R, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: A longitudinal cohort study. *Lancet Neurology* 2015;14:1101-1108.
19. 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;15:1346-1354.
20. Dürr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996;335:1169–1175.

Figures

Figure 1 Relationship between CCFS score and disease duration (panel a, b), between SARA score and disease duration (panel c, d) and between SARA and CCFS scores (panel e, f), by diagnosis (FRDA or SCA)

The relationship between CCFS and disease duration is linear while the relationship between SARA and disease duration is quadratic in FRDA patients. In SCA patients, both relationships are quadratic. The relationship between CCFS and SARA is sigmoid in both FRDA and SCA patients with a not linear relationship below a threshold of 10 and above a threshold of 30 for FRDA patients, and below 6 and above 26 in SCA patients.

Figure 2 Relationship between CCFS and SARA scores, according to SCA subtype (panel a SCA1, b SCA2, c SCA3, d SCA7)

The relationship between SARA and CCFS scores is not linear below a threshold of 10 and above a threshold of 24 for SCA1 and SCA2, and below a threshold of 7 and above a threshold of 16 for SCA3.

Figure 3 Final model of the influence of short allele length, age at onset and disease duration on scores in FRDA patients

a CCFS score

The significant coefficients are indicated by asterisks. Value of fit indices: SRMR=0.045 and NFI=0.971.

b SARA score

The significant coefficients are indicated by asterisks. Values of fit indices: SRMR=0.048 and NFI=0.973.

Squares are representing the observed variables and arrows are representing the relationships between variables: single-headed arrows represent the impact of one variable on another and double-headed arrows represent correlations between pairs of variables. One-way arrows coming from outside are carrying the residual variance not explained by the model.

Tables

Table 1 Characteristics of the subjects by diagnosis

Supplementary files

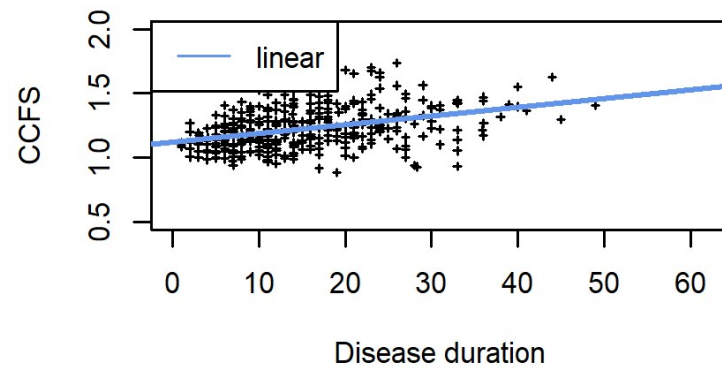
Table 1 Comparison of the characteristics of the main SCA subtypes

Table 2 Comparison of FRDA subjects with and without available CCFS score data

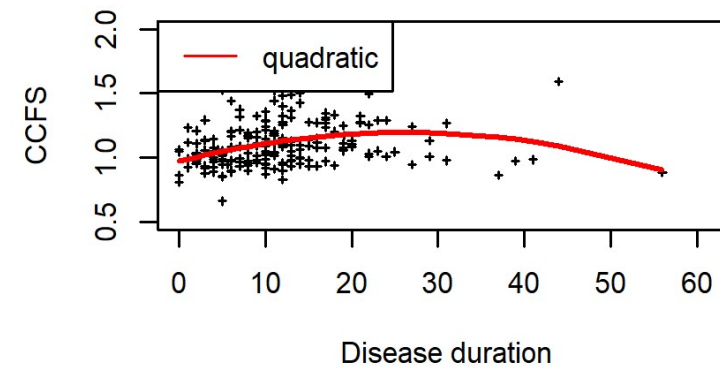
Figure 1 Flow chart, by diagnosis

Figure 2 Relationship between SARA score and disease duration for the subjects with an available CCFS score (blue curve) and for all subjects (red curve)

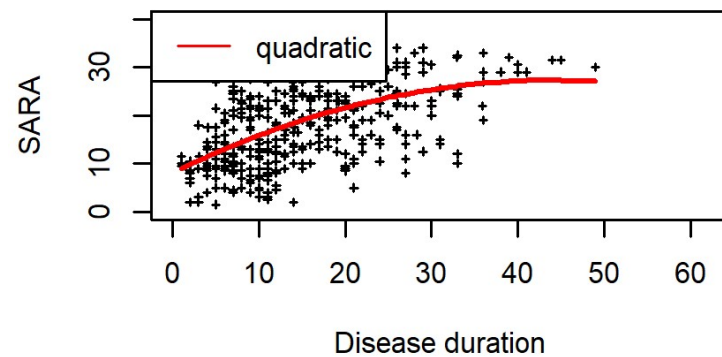
a Patients with FRDA



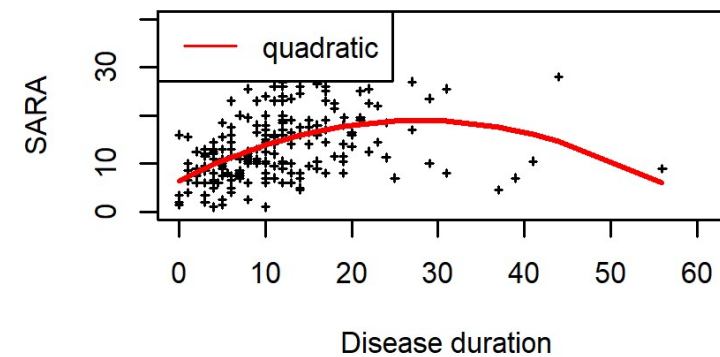
b Patients with SCA



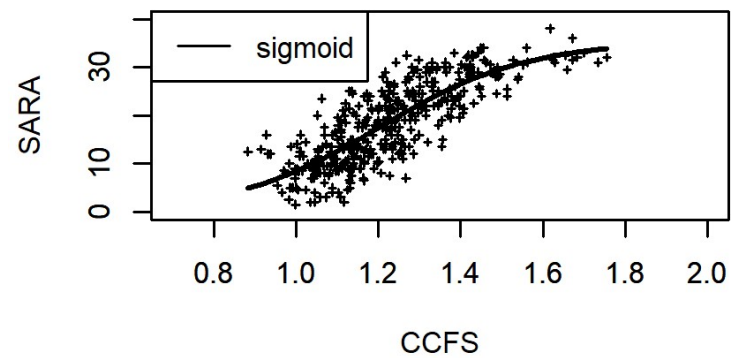
c Patients with FRDA



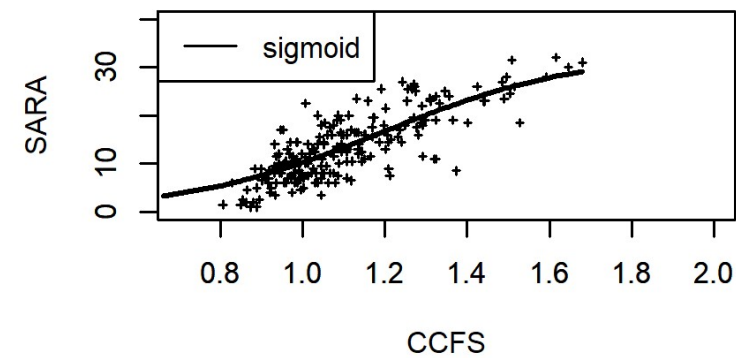
d Patients with SCA



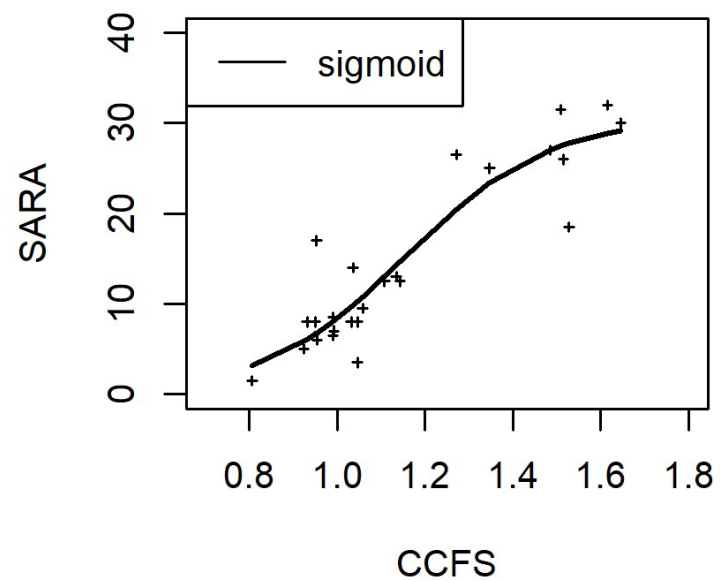
e Patients with FRDA



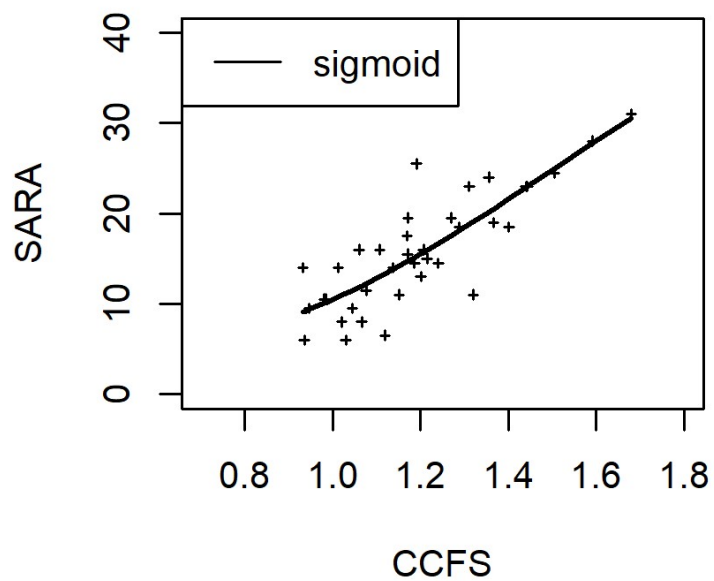
f Patients with SCA



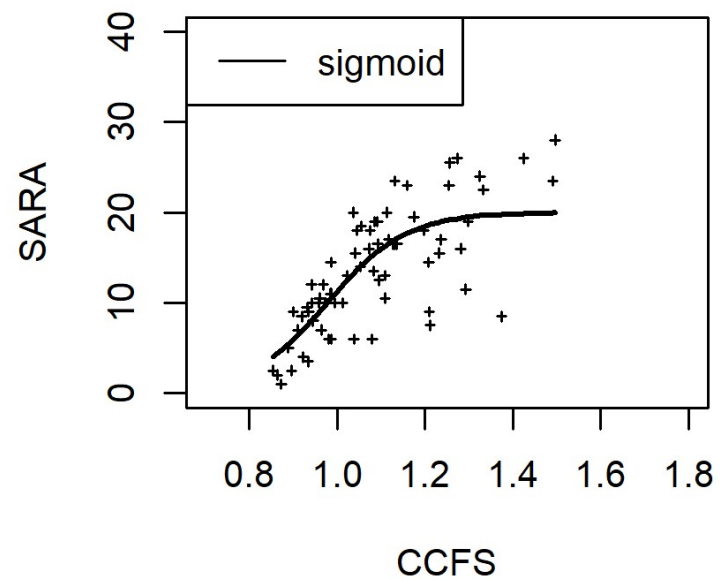
a Patients with SCA1



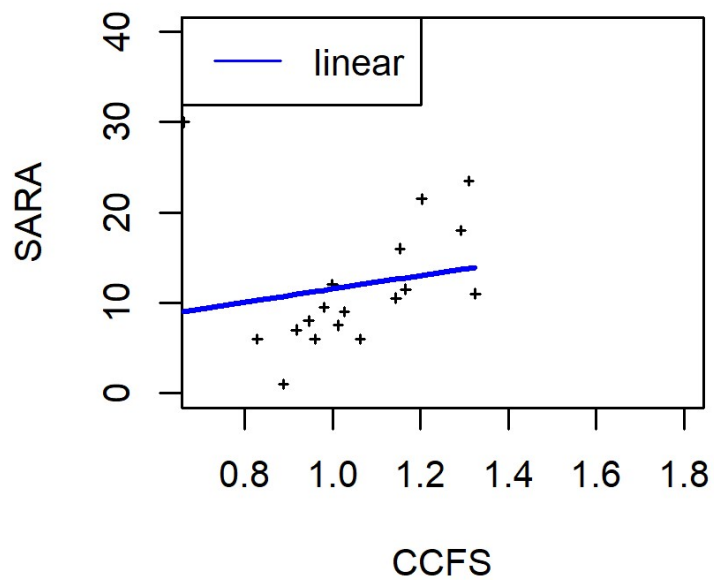
b Patients with SCA2



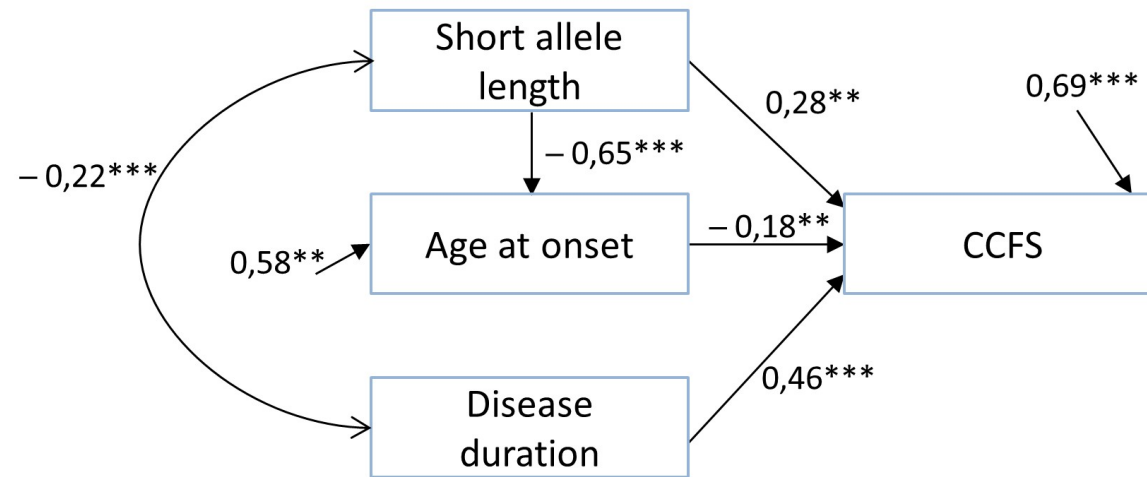
c Patients with SCA3



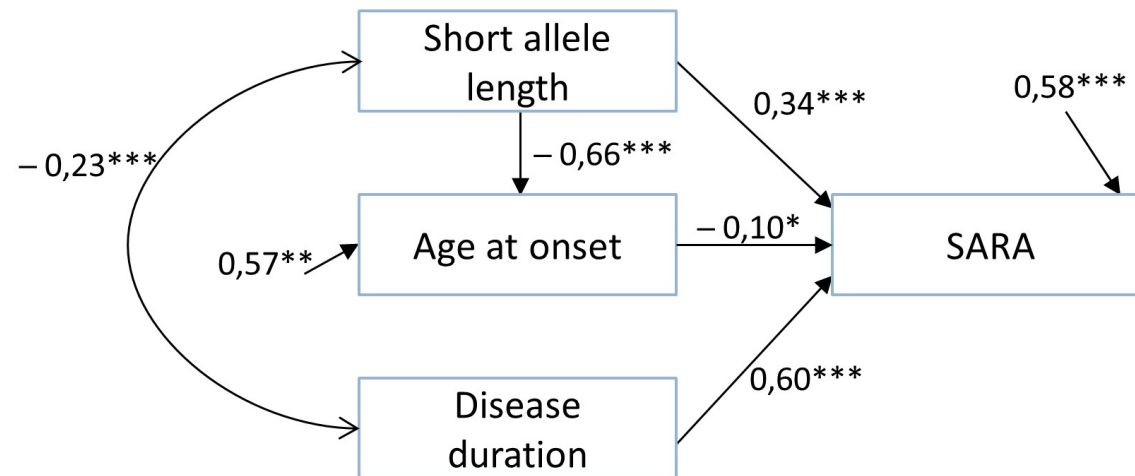
d Patients with SCA7



A



B



Supplemental data

Table e-1: Comparison of the main SCA subtypes characteristics and evolutions

	SCA 1 (n=21)	SCA 2 (n=30)	SCA 3 (n=53)	P value ^a
Age at baseline	47.0 ± 16.4	45.6 ± 12.5	47.9 ± 12.1	0.7493
Age at onset	40.2 ± 14.3	32.3 ± 12.6	37.7 ± 10.2	0.0456
Duration of disease	6.9 ± 5.8	13.3 ± 9.9	10.2 ± 6.0	0.0099
CCFS at baseline	1.140 ± 0.229	1.199 ± 0.189	1.084 ± 0.155	0.0238
CCFS delta per year	0.023 ± 0.091	0.051 ± 0.107	0.019 ± 0.067	0.2518
SARA at baseline	13.4 ± 8.9	15.5 ± 6.5	13.0 ± 6.8	0.2959
SARA delta per year	1.42 ± 3.05	1.35 ± 5.28	0.98 ± 2.68	0.8564

Abbreviations: CCFS: composite cerebellar functional severity; SARA: Scale for the Assessment and Rating of Ataxia.

Data are shown as mean \pm SD.

^aP-value of the comparison between SCA subtypes (ANOVA test)

Table e-2: Comparison of the FRDA patients with and without an available CCFS at visit

1

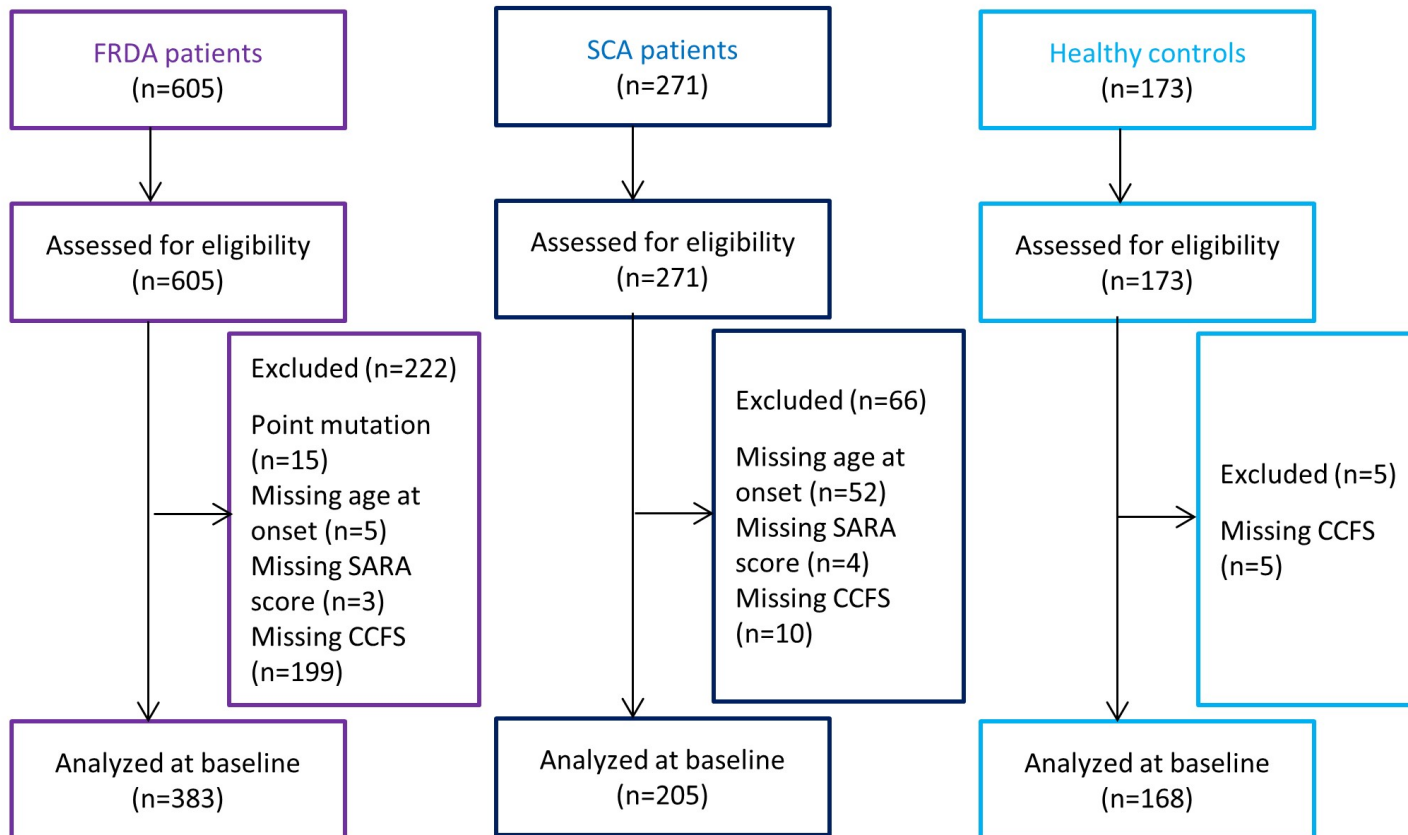
	Available CCFS (n=383)	No CCFS (n=199)	P value ^a
Age	33.1 ± 14.6	35.2 ± 12.6	0.0716
Age at onset	17.8 ± 11.3	11.8 ± 7.1	<0.0001
Duration of disease	15.3 ± 9.0	23.4 ± 10.4	<0.0001
SARA	18.3 ± 8.4	28.8 ± 7.8	<0.0001
SARA severity	1.6 ± 1.2	1.4 ± 0.6	0.0747
SARA delta per year	0.07 ± 0.37	0.06 ± 0.18	0.5434
SARA distribution			<0.0001
< 10	70 (18)	7 (4)	
10-24	208 (54)	35 (18)	
>24	105 (27)	157 (79)	

Children in patients among the patients with a SARA < 10	15 (21)	1 (1)	>0.9999
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Abbreviations: CCFS: composite cerebellar functional severity; SARA: Scale for the Assessment and Rating of Ataxia.

Data are shown as mean ± SD or number (percentages).

^a P-value of the comparison between the CCFS groups (Student t-test or chi-2 test)



FRDA patients

