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Authors

Petit, Emilien
Schmitz-Hübsch, Tanja
Coarelli, Giulia
et al.

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SARA captures disparate progression and responsiveness in spinocerebellar ataxias

Emilien Petit[1], **Tanja Schmitz-Hübsch**[4], **Giulia Coarelli**[1], **Heike Jacobi**[3], **Anna Heinzmann**[1], **Karla P Figueroa**[6], **Susan L Perlman**[7], **Christopher M Gomez**[8], **George R Wilmot**[9], **Jeremy D Schmahmann**[10], **Sarah H Ying**[11], **Theresa A Zesiewicz**[12], **Henry L Paulson**[13], **Vikram G Shakkottai**[13], **Khalaf O Bushara**[14], **Sheng-Han Kuo**[15], **Michael D Geschwind**[16], **Guangbin Xia**[17], **Stefan M Pulst**[6], **SH Subramony**[17], **Claire Ewenczyk**[1], **Alexis Brice**[1], **Alexandra Durr**[1], **Thomas Klockgether**[2], **Tetsuo Ashizawa**[5], **Sophie Tezenas du Montcel**[1]

[1]Sorbonne Université, Paris Brain Institute - ICM, Inserm, CNRS, Inria, AP-HP, Paris, France

[2]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[3]Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany

[4]Experimental and Clinical Research Center, a cooperation of Max-Delbrueck Center of Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany.

[5]Weill Cornell Medicine at Houston Methodist Hospital, Houston, Texas, USA

[6]Department of Neurology, University of Utah, Salt Lake City, UT 84132, USA.

[7]Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA.

[8]Department of Neurology, University of Chicago, Chicago, IL, USA.

[9]Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA.

[10]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[11]Department of Neurology, Johns Hopkins University, Baltimore, MD, USA.

[12]Department of Neurology, University of South Florida, Tampa, FL, USA.

[13]Department of Neurology, University of Michigan, Ann Arbor, MI, USA.

[14]Department of Neurology, University of Minnesota, Minneapolis, MN, USA.

[15]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA.

[16]Department of Neurology, University of California, San Francisco, CA, USA.

[17]Department of Neurology and McKnight Brain Institute, University of Florida, Gainesville, FL, USA.

Abstract

Corresponding author : Sophie Tezenas du Montcel. sophie.tezenas@aphp.fr.

Background and objectives: The Scale for Assessment and Rating of Ataxia (SARA) is a widely used clinical scale to assess cerebellar ataxia but faces some criticisms about the relevancy of all its items. To prepare for future clinical trials, we analyzed the progression of SARA and its items in several polyQ spinocerebellar ataxias (SCA) from various cohorts and describe the sensitivity to change.

Methods: We included data from patients with SCA1, SCA2, SCA3, and SCA6 from four cohorts (EUROSCA, RISCA, CRC-SCA, and SPATAX) for a total of 850 carriers and 3431 observations. Longitudinal progression of the SARA and the items since inclusion was measured with a mixed model. Cohort and genetic effects were assessed. In addition, we looked at the respective contribution of each item to the full scale. Sensitivity to change of the scale and the impact of item removal was evaluated by calculating sample sizes needed in various scenarios.

Results: Longitudinal progression was linear in all cohorts but with different slopes for SCA1, SCA2 and SCA3 participants (respectively 2.0±0.1, 1.3±0.7, and 1.6±0.7 annual SARA increase), the EUROSCA cohort having the fastest progression. SARA at baseline had no effect on progression, while SCA1 and SCA2 participants with longer CAG repeat expansion had faster progression. Items were not contributing equally to the full scale through ataxia severity: *gait*, *stance*, *hand-movement*, and *heel-shin* contributed the most in the early stage, and *finger-chase, nose-finger*, and *sitting* in the later stage. Sample sizes needed to detect a reduction in SARA progression of 50% over 2 years were highly dependent on the cohort analyzed, with 173 patients considering EUROSCA versus 854 considering CRC-SCA data. Few items drove the sensitivity to change of SARA, but changes in the scale structure could not improve its sensitivity in all populations.

Discussion and Conclusion: SARA progression pace and its variability showed high heterogeneity across cohorts and SCAs. However, no combinations of items improved the sensitivity in all SCAs or populations taken separately. Therefore, SARA remains the best current tool to assess ataxia severity and inclusion criteria based on stage should be considered for future trials.

INTRODUCTION

Autosomal dominant cerebellar ataxias of type 1, 2, 3, and 6, also known as spinocerebellar ataxias (SCA1, 2, 3, and 6), are clinically heterogeneous neurodegenerative diseases. They are caused by (CAG)n repeat expansions in the *ATXN1*, *ATXN2*, *ATXN3*, and *CACNA1A* genes respectively, which leads to the expansion of a polyglutamine tract in the corresponding proteins (Coarelli et al., 2023; Durr, 2010). SCAs are rare diseases, with a global prevalence of 0.0 to 5.6 per 100,000 (Ruano et al., 2014). The number of CAG repeats determines disease carrier status, the threshold between what is considered a pathological or a normal size varies for each SCA and the longer the repeats in the expansion the earlier the age at onset (Tezenas du Montcel et al., 2014), and the faster the disease in SCA1 and SCA2 (Jacobi et al., 2011).In the context of readiness for clinical trials in SCAs, there is a need to understand the natural progression of the disease over the individual course of disease to refine inclusion criteria for potential treatments. Cerebellar ataxia (encompassing signs and symptoms) is clinically progressive over the disease course and considered to reflect progression of the underlying pathology of SCA and it can be

assessed using the Scale for Assessment and Rating of Ataxia (SARA)(Schmitz-Hubsch et al., 2006). A previous meta-analysis already studied the progression of the SARA for these 4 SCA subtypes in different cohorts to estimate the annual progression of the SARA score (Diallo et al., 2020). Additionally, the sensitivity to change of SARA has already been studied in several ataxias (Traschütz et al., 2023) where some modifications of the scale by removing items seemed to increase its overall sensitivity. Nevertheless, the progression of individual items and their contribution to the full scale in terms of sensitivity to change was not studied in SCA1, 2, 3 and 6.

In this study, we aim to (1) assess the progression of the full score and of each item and their differences between cohorts and SCAs, (2) describe the contribution of each item to the full scale over all SARA ranges, (3) analyze the sensitivity to change of the full scale by sample size estimations, and find potential better combinations of items to create a more sensitive scale. For the purposes of our study, we pooled data of SCA1, 2, 3, and 6 patients from four cohorts (EUROSCA, CRC-SCA, SPATAX, and RISCA cohorts). The first three are composed of ataxic patients and RISCA only included pre-ataxic ones, allowing us to have patients at all stages of the disease.

MATERIAL AND METHODS

Study population

The data from the four cohorts of SCA carriers were pooled together. Three cohorts included affected subjects with 2 Europeans ones : EUROSCA (Jacobi et al., 2015) and SPATAX (Monin et al., 2015)) and one from the US : CRC-SCA (Ashizawa et al., 2013). The last cohort included European presymptomatic expansion carriers RISCA (Jacobi et al., 2020).From these cohorts, which included participants with different SCA types, we have selected the subjects with a positive genetic test for *ATXN1*, *ATXN2*, *ATXN3* or *CANCA1A* gene.. Only patients with at least 2 visits with available information on SARA and SARA items were kept for analysis. The characteristics of the four cohorts are given below and in Table 1.

EUROSCA: the study was performed at 17 European centers. Patients were eligible when they had progressive, otherwise unexplained ataxia and a positive molecular genetic test for SCA1, SCA2, SCA3, or SCA6. Patients were consecutively recruited within a predetermined period between July 2005 and August 2006.Patients were seen at a baseline visit, followed by annual visits for 3 years. After the initial 3 years observation period, study participants entered an extension phase in which study assessments were done in connection with routine visits resulting in irregular intervals between visits.

CRC-SCA: the study was performed at 12 US centers. Patients were eligible if they had a positive molecular gene test for SCA1, SCA2, SCA3, and SCA6 and if they were at least 6 years old. Subjects with concomitant disorders that affect SARA and other ataxia measures used in the study were excluded. The study started in April 2010. The clinical evaluation was performed at the baseline visit and every six months thereafter until two years from the baseline visit or until the end of August 2012. The study continued after August 2012, but we only had data from the first 2 years.

RISCA:

Between Sept 13, 2008, and Dec 1, 2011, offspring or siblings of patients with SCA1, SCA2, SCA3, or SCA6 were enrolled in a prospective, longitudinal observational study at 14 European centers. To be eligible for inclusion in this study, individuals had to have no ataxia and be aged 18–50 years if directly related to individuals with SCA1, SCA2, or SCA3, or 35–70 years if directly related to individuals with SCA6. Non-converters, namely patients not having a visit with a SARA > 3 were removed from the database. These patients undergo irregular visits but some of them are seen by the clinician on a yearly basis.

SPATAX:

Since 2005 (first visit with SARA assessed), all individuals with spinocerebellar degenerations were referred to the (French) National reference center for neurogenetic diseases and were entered in the SPATAX database (created in 2000, using the REDCap electronic data capture tools to collect and manage data, which was hosted and insured by the Paris Brain Institute (Institut du Cerveau, ICM). We included participants with SCA 1, 2, 3 and 6. We removed the overlapping individuals from EUROSCA and RISCA since SPATAX participated in those studies.

Outcomes

To evaluate the cerebellar ataxia, we used the SARA score (Schmitz-Hubsch et al., 2006). In addition, we analyzed the SARA items, grouped as follows: the four axial SARA items (*gait* (0–8), *stance* (0–6), *sitting* (0–4) and *speech disturbance* (0–6)) and the four appendicular SARA items (*finger-chase* (0–4), *nose-finger* (0–4), *fast-alternating hand movements* (0–4), and *heel-shin slide* (0–4)). Appendicular items are calculated as the average of both sides, leading to half-point values.

Participants were stratified into three groups following their SARA at baseline: Early-stage patients (<10), mild stage (10–25), and advanced stage (>25). These thresholds are arbitrary but were chosen to detect the expected floor and ceiling effects of the scale.

Age of onset is defined as the time reported by the patient for the onset of the disease. For RISCA participants who converted during the study, no age of onset was reported and it was then set asthe age at the first visit with a SARA over 3. The estimated age at onset was calculated with the CAG repeats as proposed in for SCA1, 2, and 6 (Tezenas du Montcel et al., 2014) and for SCA3(Peng et al., 2021). The Time to Onset (TTO) is defined as the time to the estimated age at onset at a visit time.

Statistical analysis

Descriptive statistics—Data at baseline are described, with frequencies and percentages for qualitative data and means and standard deviations (SD) for quantitative variables. For the comparison between the sample selected for analysis (at least two visits) with those not selected for analysis (no follow-up) and the comparison of the characteristics of the patients in each cohort we used a chi-squared test for qualitative variables and ANOVA for quantitative ones.

Modeling of the SARA score progression—We modeled the SARA and SARA items change from baseline. Linear progression was first tested against other types of progression (splines and beta), with the lcmm R package. In all SCAs, the best model was a linear progression since baseline, so we used linear mixed models (fitted with Restricted Maximum Likelihood, with the lmer R package (Bates et al., 2015)) for all our models. As we were investigating the change from baseline, no fixed intercepts were included in the model, only fixed slopes. The random effect included individual intercept and slope.

The effect of the cohort, SARA group at baseline, and standardized expanded CAG repeat length was assessed by adding interaction with the slope of these covariables. The significance of these interactions was determined using a likelihood ratio test. CAG repeat length was standardized within all SCAs and the effect of CAG on slopes was expressed as annual point of SARA per standard deviation of CAG repeat length.

Transversal Item contribution to the full scale—Each SARA item was divided by its maximum score, normalizing them between 0 and 1 to make them comparable. For this analysis, the SARA scores were grouped with increments of 5 between 0 and 40 and (0–5, 5–10, etc..), within each group, the mean and the 95% CI interval for each item were computed, allowing us to compare the relative contribution of each item to the full scale. The mean value was also compared to the bissector that represents how an equal contribution to the scale of the item would look like.

Sample size calculation—Sample size estimation was done using the *longpower* R package (Iddi and C Donohue, 2022) for a 2-year trial with five visits, assuming a 50% reduction of SARA progression in the treated group (50% reduction of the slope), using the parameters from the linear mixed models of items progression since inclusion (mean slope, variance of the slope and residual variance). For each subset by SCA or by cohort, we iteratively added items that were most decreasing (or less increasing) the needed sample size to build a *stepwise-optimized SARA* (SO-SARA), inspired from (Traschütz et al., 2023). For each of these SO-SARAs we calculated the required sample size, mean progression, random slope variance, and residual variance.

Statistical tests were performed at the conventional two-tailed type I error of 0.05. Data were analyzed using R version 4.2.0 (R Core Team, 2018).

RESULTS

Data description

Patients with only 1 visit, not included in the further analysis, had higher SARA at baseline and longer disease duration (Supplementary Table 1) suggesting a lower probability of follow-up when being more advanced in the disease. We included a total of 850 mutation carriers for analysis: 186 SCA1 (107 EUROSCA, 37 in CRC-SCA, 16 in SPATAX, and 26 in RISCA), 248 SCA2 (146 EUROSCA, 51 CRC-SCA, 29 SPATAX, and 22 RISCA), 272 SCA3(120 EUROSCA, 91 CRC-SCA, 50 SPATAX, and 11 RISCA) and 144 SCA6(86 EUROSCA, 52 CRC-SCA, 4 SPATAX, and 2 RISCA), summing up to 3431 observations. The median number of visits per patient was 4 (IQR: 3;5) and the mean time between two

visits was 14.1±8.7 months. These numbers were heterogeneous among cohorts: SPATAX participants had the lowest mean number of visits (2.9±1.1) and EUROSCA ones the highest (4.8±1.7). CRC-SCA had the shortest time between two visits (6.6±1.6 months) and RISCA had the longest (25.8±8.5 months).

The cohorts differed by the following characteristics (Supplementary Table 2, 3, 4, and 5). RISCA subjects were younger than the three other cohorts because of their inclusion criteria (SARA <3 at the baseline visit). In SCA1 and SCA3, there were significant differences in CAG repeat length between cohorts. In SCA1, CRC-SCA participants had significantly fewer CAG repeats than SPATAX and EUROSCA ones (46.0±3.6 vs 47.7±5.7 and 50.3±6.8, p=0.021 and p=0.028 respectively) and later age of onset. In SCA3, CRC-SCA participants had longer CAG repeat lengths than EUROSCA ones (70.4±3.6 vs 68.8±4.2, p=0.0037), but this was not associated with difference in ages of onset.

Among the cohorts with ataxic patients at baseline, CRC-SCA participants had lower SARA at baseline than SPATAX participants in SCA2 and SCA3 (p=0.017 and p=0.038 respectively).

Modeling of the SARA score progression from baseline

Modeling conformed linear progression of SARA in all genotypes. Mean annual changes from baseline of SARA scores were 1.8 ± 0.09, 1.2 ± 0.06, 1.3 ± 0.07, and 0.9 ± 0.10 for SCA1, 2, 3, and 6 respectively.

The cohort interaction with slope was significant for SCA1 (p=0.039), SCA2 (p=0.045), and SCA3 (p<0.0001) (Table 2). EUROSCA participants always had the higher annual change with 2.0±0.1, 1.3±0.7, and 1.6±0.7 respectively in SCA1, SCA2, and SCA3. RISCA participants had the slowest progression in SCA1 (1.2±0.2), SPATAX participants in SCA2 (0.7±0.2), and CRC ones in SCA3 (0.7±0.2). The CAG repeat length effect on slope was significant for SCA1 (0.38±0.08, p <0.0001) and SCA2 (0.19±0.06, p = 0.026), after adjustment by cohort. There was no effect of SARA at baseline on slope of SARA progression.

Items contribution to the full scale

Throughout the progression of the total SARA, the contribution of the items was variable depending on the disease stages and the SCA (Figure 1). The item *sitting* had a low contribution in the early and middle stages in every SCA as its mean normalized value was lower than every other item for every group with SARA < 20. In SCA1 and SCA2, items *gait*, *stance*, *hand-movement*, and *heel-shin* had higher mean normalized values than *finger-chase* and *nose-finger* for groups of SARA between 15 and 30. In SCA2 specifically, *heel-shin* had a significantly higher value than every other item in the 0–5 SARA visit group. In SCA3, the differences in dynamics between items were larger: *gait* was the highest item for SARA from 15 to 30.

Modeling of the item progression from baseline

The progression of each SARA item is displayed in Figure 2. The item progression was significantly positive for every item and every SCA in the pooled cohort, except for the finger-nose item in SCA6. Items *gait* and *stance* progressed the fastest in all SCAs, *finger-chase* and *nose-finger* the slowest.

Baseline SARA interaction with slope was not significant for any of the SCAs and items. Cohort differences were found at the item level: In SCA1 for item *sitting* (p=0.04), SPATAX participants had the fastest progression (0.29) and RISCA ones were nearly constant (0.03). In SCA3 for item *stance* (p=0.03), EUROSCA participants had the fastest progression (0.32) and SPATAX ones the slowest (0.09), and for item *heel-shin slide* (p=0.002), RISCA participants had the fastest (0.23) and CRC ones decreasing (−0.08). CAG repeat length effect on items progression was only found in SCA1 for item *gait* and *nose-finger* (0.09±0.02, p=0.012 and 0.05±0.01, p=0.038 respectively) (Supplementary Table 6).

Stepwise Optimized SARA by cohort

All SCAs were pooled in this cohort comparison. The sample size needed to assess a 50% reduction in total SARA progression over 2 years was the highest in CRC-SCA (n=854) and the lowest for EUROSCA (n=173) and RISCA (n=179) (Figure 3A). This was mainly due to the high slope variance in CRC-SCA, probably because of a shorter time of follow-up. The most sensitive items were heterogeneous between cohorts, but *gait* was the most sensitive one in all cohorts but SPATAX (ranked 2nd), where the best item was *sitting*. For RISCA participants, the second-best item was *heel-shin*, suggesting that this item is of interest in the early stage of the disease.

Stepwise Optimized-SARA by SCA

The sample size needed to assess a 50% reduction in SARA progression over 2 years in the pooled cohort was the lowest in SCA1 (n=114) due to faster progression. SCA2 and SCA3 had close sensitivity with respectively 208 and 232 patients needed. Because the slope variance and model error were similar between SCAs (Figure 3B), the estimated sample size was mainly driven by the progression speed of the SARA, as a larger progression leads to a smaller sample size. Full SARA was never the most sensitive scale in any SCA. In SCA1 and SCA2, the best sensitivity was reached at 6 items (n=113 and n=201) reducing the sample size by 1(1%) and 7(3%).In SCA3 the best sensitivity was reached with 4 items (n=185), reducing by 47(20%) the needed sample size. In SCA6, the best sensitivity was reached with only 3 items (*gait, speech* and *finger-chase*, 374 patients needed) and SARA was the worst combination of item, leading to 526 patients needed (29% increase). In all SCAs, *gait* was the first and best item, followed by *stance* in SCA2 and *speech* in the other SCAs. In the total dataset, namely with all SCAs pooled, the best sensitivity was reached at 6 items (*heel-shin* and *nose-finger* not included), but only reducing sample size by 9 (4%) patients compared to the full scale.

DISCUSSION

In this retrospective multi-cohort analysis, we showed that there were high discrepancies in SARA progression between cohorts and SCAs at both the full scale and the item level. The analysis of sensitivity to change of various combination of items highlighted that no item removal can reliably increase the sensitivity of the scale in every SCAs or population.

The ataxia progression of a total of 850 carriers of pathological repeats in ATXN1, ATXN2, ATXN3, and CACNA1A was analyzed, along 3431 visits for a mean follow-up duration of XX years. At baseline, apart from the obvious differences of RISCA participants compared to the ataxic cohorts, there were only slight differences in CAG repeat length in SCA1 and SCA3 cohorts, with CRC-SCA patients having smaller repeats than EUROSCA ones. The ataxia progression was assessed from inclusion, as the change from baseline of the SARA score. Although a recent publication suggested a non-linear progression of the SARA on similar data (pooled EUROSCA and RISCA cohorts), when taking the disease duration as time variable (Jacobi et al., 2023), we found a linear progression since inclusion. This suggests that the SARA progression pace along the disease is not varying fast enough to be detectable on few years of follow-up. In addition, we found no significant differences in SARA progression speed between early, mild and advanced stage participants. In ataxic patients and converters, the SARA progression's pace since inclusion was consistent with precedent findings with 1.8 ± 0.09, 1.2 ± 0.06, 1.3 ± 0.07, and 0.9 ± 0.10 for SCA1, 2, 3 and 6 respectively (Jacobi et al., 2011, p. 6). Wide differences were highlighted in the SARA progression's pace between cohorts in for SCA1, SCA2, and SCA3 patients, with EUROSCA participants progressing nearly twice as fast as the slowest cohort for each SCA. These differences were also present at the item level and cannot be explained by geographical or ethnical reasons as SPATAX participants (French cohort) had progression more similar to CRC-SCA ones (US cohort) than EUROSCA ones (European cohort). These differences cannot be explained by disease stages or genetic factors either, as they were similar between cohorts. One bias could be that SPATAX contributed to EUROSCA and RISCA, and so the remaining SCA patients in SPATAX have a different profile than the inclusion criteria of EUROSCA/RISCA. Moreover, the follow-up duration was shorter for the SPATAX or CRC-SCA cohort than EUROSCA cohort, which can lead to higher misestimation of the SARA progression. The differences between cohorts highlight that sample size estimations are highly dependent on the data used and that their absolute value must be taken cautiously.

In the analysis of the contribution of each item to the SARA scale, the item contribution to the full scale throughout disease progression was heterogeneous, with *gait*, *stance*, and *heel-shin* having higher contribution in the early stage and *sitting*, *finger-chase*, and *nose-finger* in the later stage. In addition, the progression of the items was heterogeneous; *gait* and *stance* (respectively ranging from 0–8 and 0–6) items were progressing faster, as would be expected with their wider range. The *speech* item had a moderate progression despite ranging from 0–6. We did not observe an impact of the baseline SARA on the longitudinal progression as we expected ceiling and floor effects, respectively in very advanced participants and in the converters in the RISCA cohort. Similar to prior report (Jacobi et al., 2011), the expanded

CAG repeat length was associated with faster SARA progression in SCA1 and SCA2, and even at the item level in SCA1 for *gait* and *nose-finger*.

In the context of a clinical trial using SARA as the primary endpoint, SCA1 patients would require a smaller sample size due to faster progression, with 114 patients needed for a 2-year trial with a 50% efficacy of the intervention tested. The SO-SARA analysis showed that a few items mainly drive the sensitivity to change of SARA, and the addition of less sensitive items leads to a very small decrease (or even increase) of the sample size. Nevertheless, even if the axial items were often the most sensitive ones, the sensitivity ranking of items was heterogeneous among SCAs and cohorts. This shows that even if total SARA was never the best combination of items in terms of sensitivity, there is no combination of items that would improve the sensitivity in all SCAs or populations taken separately. Especially, the follow-up duration seems to be an important factor in sample size estimation, as in CRC-SCA, a short period of follow-up (less than 2 years) leads to high slope variance in the mixed effect model and therefore high estimated sample size.

The estimated sample sizes remain very large for such a rare disease as our estimations are based on a 2-year trial with 5 visits, which is long for a clinical trial, and with a 50% reduction on the slope, namely a relatively strong treatment effect. Moreover, one limitation in our analysis is that we did not consider any placebo effect, assuming that the placebo arm would progress similarly to natural history, which is unlikely (Choi et al., 2022; Coarelli et al., 2022). Because of its linear property, and the usefulness of all items throughout all the disease stages, SARA remains a good tool to assess the ataxia progression in SCAs. However, the relatively slow progression of the disease constrains the relevance of using a clinical scale to show moderate treatment effects in short-term clinical trials. Clinical trials should focus on detecting modification of biomarkers levels, specifically at the pre-ataxic stage which has been shown to be a relevant time window to treat patients. Modification of biomarkers modifications (NFLs (Faber et al., 2023; Tezenas Du Montcel et al., 2023), IRM (Chandrasekaran et al., 2022)) already occurs in this stage while the SARA stays at very low levels. The READISCA project (for which longitudinal will be available soon), which includes both pre-ataxic and ataxic SCA1 and SCA3 participants in a multi-continental study, will help to clarify these early modifications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

EUROSCA and RISCA data are available on the Critical-Path Institute website, and CRC-SCA data will be uploaded as well in 2024. SPATAX data can be provided by the corresponding author.

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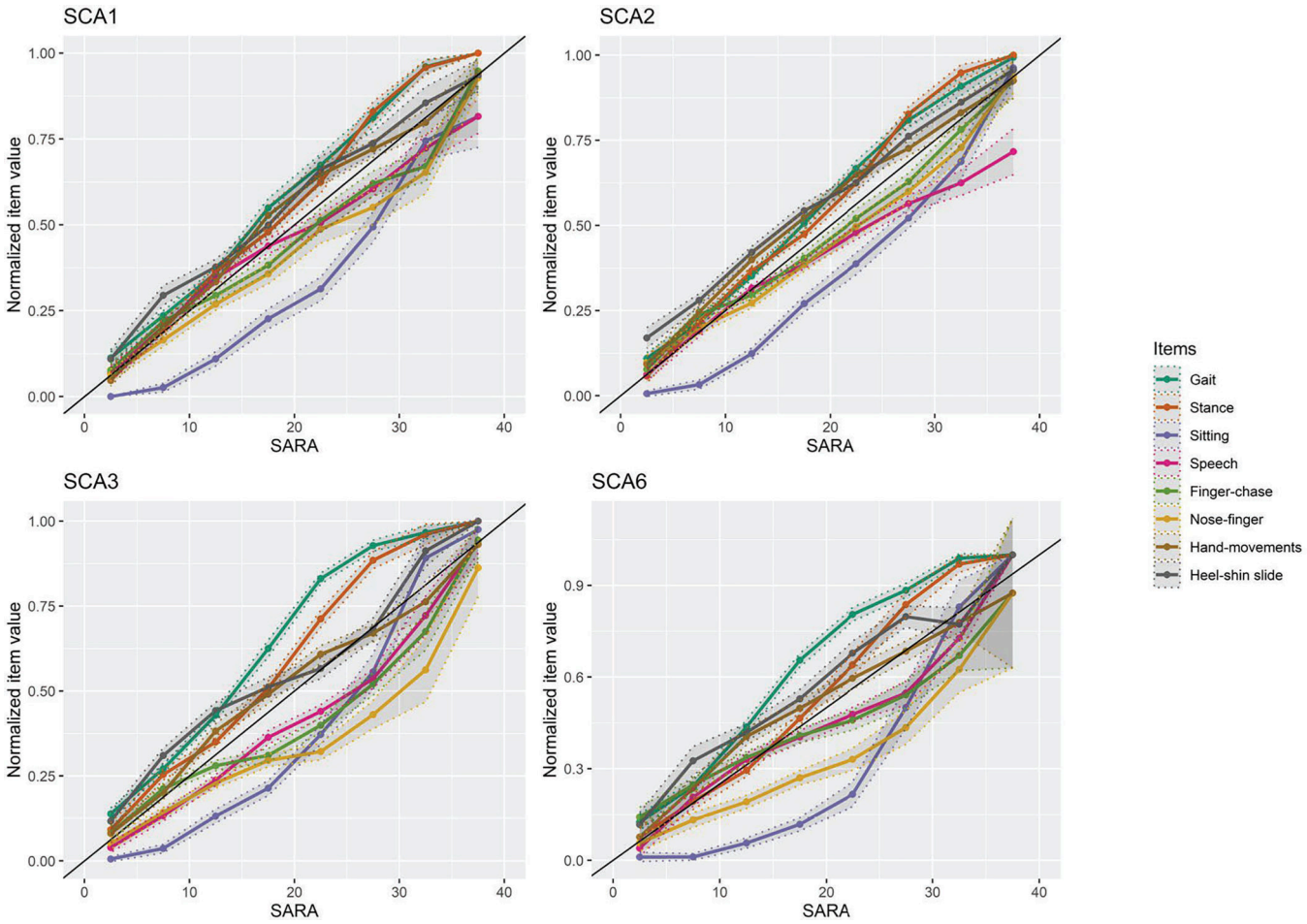

Figure 1: Contribution to the SARA scale of each individual item of the scale

Each point represents the mean (with 95% CI) of a normalized item score for SARA values grouped in increments of 5 points. Thus on the x-axis, the point is displayed in the middle of the group: for instance, the point referring to the 0–5 SARA group is displayed at SARA = 2.5. Non-overlapping CI are considered significant differences. The black line is the bisector and represents how the curve would be if all items were contributing equally throughout the disease. Values above the bisector correspond to items that contribute more than the average to the SARA score while values below the bisector correspond to items that contribute less than the average to the SARA score

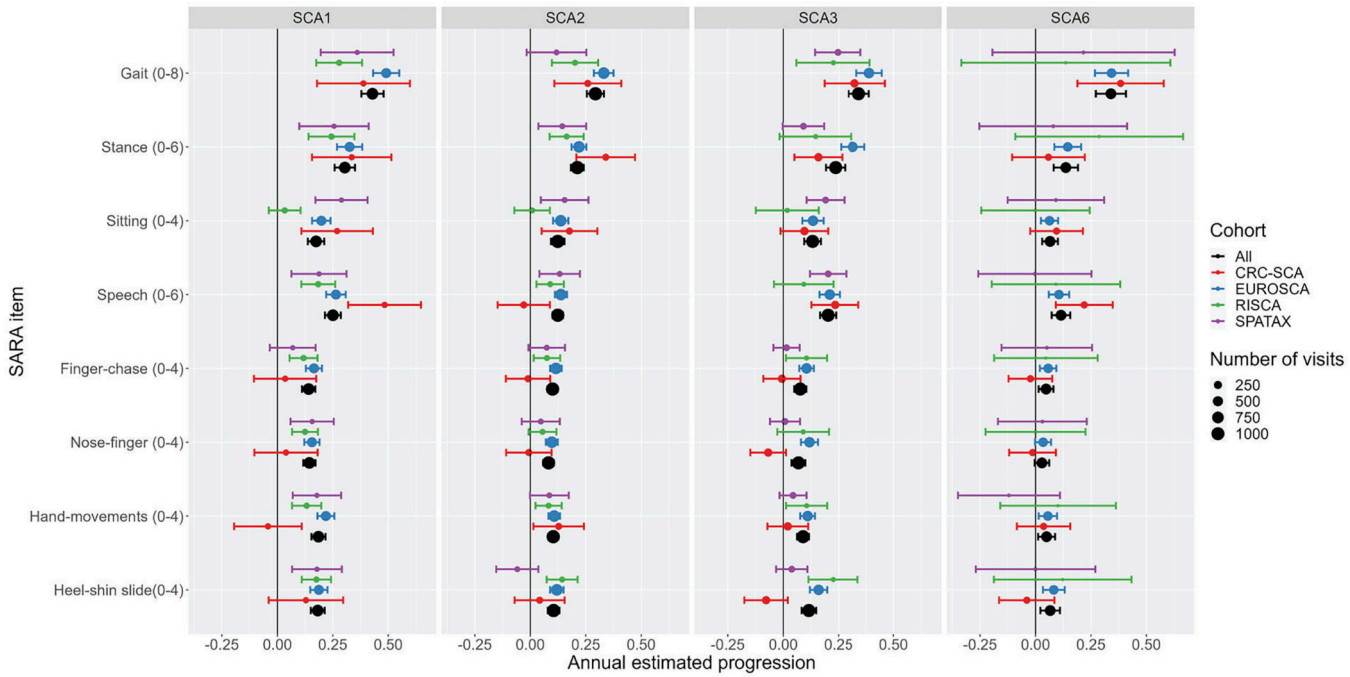

Figure 2: Items mean annual progression per genotype and cohort

In color are displayed the estimation (with 95% CI) of the cohort interaction with fixed slope in the linear mixed effect model. In black is the estimation of the linear mixed effect model on the pooled cohort.

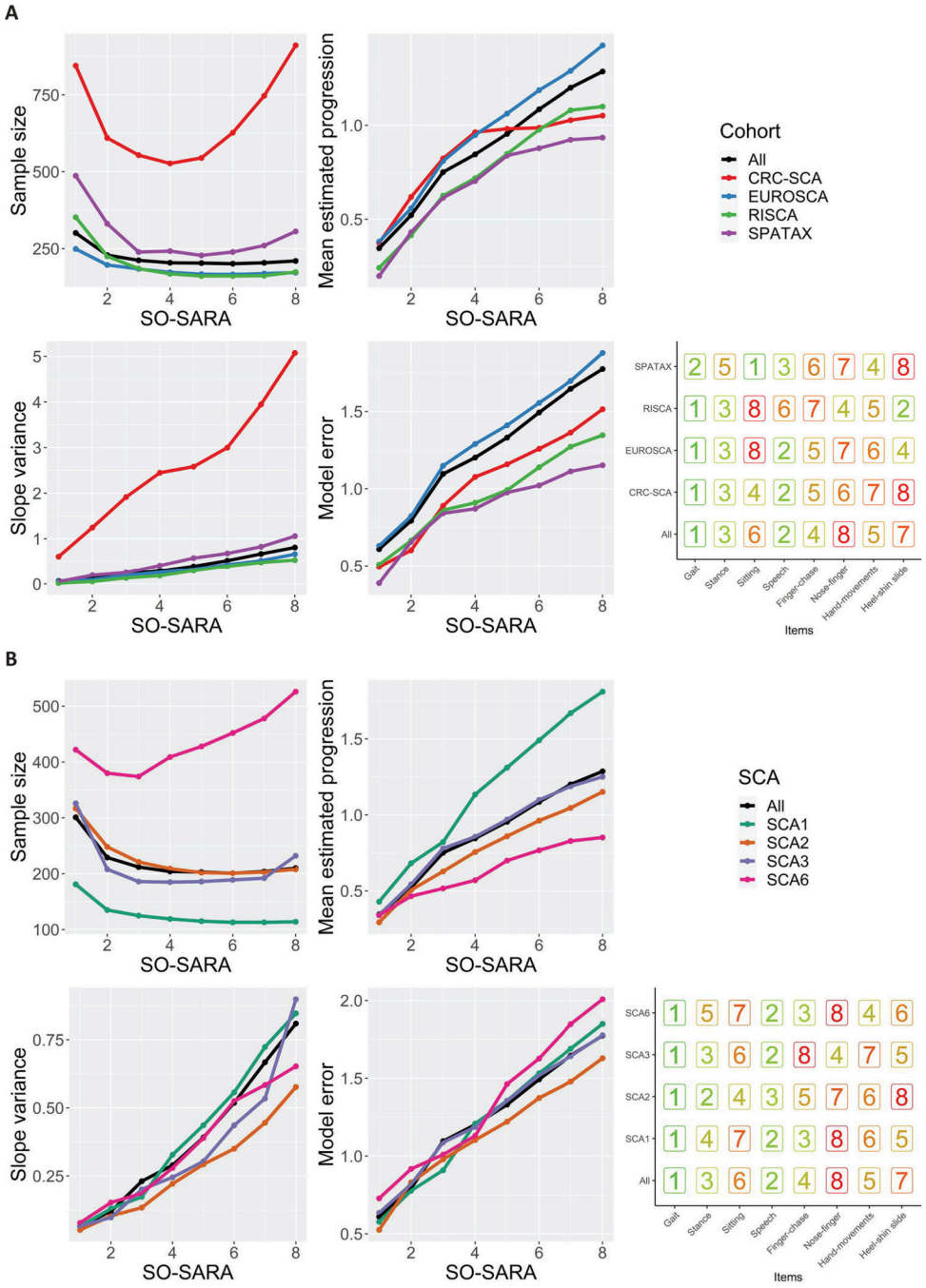

Figure 3: Stepwise-optimized SARA par Cohort (panel A) and per genotype (panel B)

Table 1:

Cohort's Inclusion criteria and follow-up characteristics

	CRC-SCA	**EUROSCA**	**RISCA**	**SPATAX**
Study Population	Patients with SCA 1, 2, 3 and 6 of all races/ethnicities and both genders	Patients with SCA 1, 2, 3 and 6	Unaffected adults' individuals that descend from SCA1, SCA2, SCA3 and SCA6 patients	Patients with SCA 1, 2, 3 and 6
Inclusion Criteria				
Ataxia	Presence of symptomatic ataxic disease	Progressive, otherwise unexplained ataxia	Absence of ataxia (SARA < 3)	
Molecular diagnosis	Pathogenic expansions in ATXN1, 2, 3 and CACNA1A either in the subject or another affected family member	Pathogenic expansions in ATXN1, 2, 3 and CACNA1A	Offspring and sibs of an individual with a Pathogenic expansions in ATXN1, 2, 3 and CACNA1A	Pathogenic expansions in ATXN1, 2, 3 and CACNA1A
Age	6 years and above.	-	− 18 – 50 years for descendants of SCA1, SCA2 or SC3 patients − 35 – 70 years for descendants of SCA6 patients	>18 years
Consent	Willingness to participate in the study and ability to give informed consent	Written informed consent by the patient or his legal agent	Written, informed consent	Written, informed consent
Number of visits	3.0±1.2	4.8±1.7	4.0±1.0	2.9±1.1
Time between 2 visits (months)	6.6± 1.6	14.3 ± 6.8	25.9 ± 8.5	19.5 ± 15.4
Follow-up time (years)	1.1±0.5	4.5±2.4	6.5±2.0	3.1±2.0
Pre-ataxic subjects at baseline	2/231 (1%)	7/459 (2%)	61/61 (100%)	4/99 (4%)

Table 2:

Annual SARA progression rate by SCA genotype and cohort

	SCA1			SCA2			SCA3			SCA6		
Predictors	**Estimates**	**95% CI**	**p-value**	**Estimates**	**95% CI**	**p-value**	**Estimates**	**95% CI**	**p-value**	**Estimates**	**95% CI**	**p-value**
Overall Cohort effect			**0.039**			**0.045**			**<0.001**			
[CRC] * TIME	1.75	1.07 – 2.44	**<0.001**	0.89	0.42 – 1.36	**<0.001**	0.71	0.36 – 1.05	**<0.001**			
[EUROSCA] * TIME	2.01	1.82 – 2.20	**<0.001**	1.29	1.14 – 1.43	**<0.001**	1.55	1.38 – 1.72	**<0.001**			
[RISCA] * TIME	1.19	0.86 – 1.53	**<0.001**	0.87	0.53 – 1.21	**<0.001**	1.09	0.56 – 1.62	**<0.001**			
[SPATAX] * TIME	1.53	0.96 – 2.10	**<0.001**	0.66	0.23 – 1.09	**0.002**	0.84	0.53 – 1.14	**<0.001**			
Expanded CAG repeat length (standardized) * TIME	0.38	0.22 – 0.53	**<0.001**	0.19	0.07 – 0.31	**0.003**						
TIME										0.85	0.66 – 1.04	**<0.001**

Models were selected by starting with the full model followed by a backward selection removing CAG repeats length first and then the cohort (Likelihood Ratio Tests). The p-value of the cohort effect is the overall effect of the cohort variable. The best model for SCA1 and SCA2 included both the cohort and the CAG repeat length, for SCA3 the cohort, and for SCA6 none of these two variables.