BRAIN
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Predictive models for ataxia progression and conversion in spinocerebellar ataxia type 1 and 3

Emilien Petit,[1] Giulia Coarelli,[1] David Morgan,[2] Paulina Cunha,[1] Hortense Hurmic,[1] Jennifer Faber,[3,4,5] Marcus Grobe-Einsler,[3] Thiago Rezende,[6] Sheng-Han Kuo,[7] George R. Wilmot,[8] Liana S. Rosenthal,[9] Jeremy D. Schmahmann,[10] Talene A. Yacoubian,[11] Susan L. Perlman,[12] Michael D. Geschwind,[13] Christopher M. Gomez,[14] Trevor Hawkins,[15] S. H. Subramony,[16] Vikram G. Shakkottai,[17] Khalaf O. Bushara,[18] Theresa A. Zesiewicz,[19] Stefan M. Pulst,[20] Young Woo Park,[21] Christophe Lenglet,[21] Thomas Klockgether,[5] Henry L. Paulson,[22] Alexandra Durr,[1] Gülin Öz,[21] Tetsuo Ashizawa,[23] and Sophie Tezenas du Montcel[1] for the READISCA consortium

The READISCA study aims to prepare for clinical trials in spinocerebellar ataxia types 1 and 3 (SCA1 and SCA3). Hence, we searched for predictive variables of ataxia onset (phenoconversion) and progression.

Individuals with SCA1 or SCA3 and controls were enrolled from 2018 to 2021 in the USA and Europe. Clinical scores, MRI measures and neurofilament light chain (NfL) levels were assessed annually for 5 years. In the pre-ataxic group at baseline, we compared phenoconverters with non-converters. A Bayesian mixed model was used to model the longitudinal progression of clinical scores and NfL levels. The impact of data-driven selected baseline variables (demographic, clinical and MRI) on the expected Scale for Assessment and Rating of Ataxia progression was tested.

Forty-three controls, 55 SCA1 carriers and 124 SCA3 carriers were included; a subset of the cohort ($n = 109$) had MRI data. Converters from pre-ataxic to ataxic stages represented 5/22 (22%) and 12/38 (32%) for SCA1 and SCA3, respectively. Converters were more depressed (Patient Health Questionnaire 9: 3.9 ± 2.9 versus 2.3 ± 2.6, $P = 0.04$), had higher plasma NfL levels (17.6 ± 5.7 versus 11.1 ± 5.9 pg/ml, $P < 0.0001$), more cerebellar white matter atrophy ($1.44\% \pm 0.12\%$ of total intracranial volume versus $1.54\% \pm 0.16\%$, $P = 0.032$) and more Inventory of Non-Ataxia Signs signs (1.8 ± 1.3 versus 0.7 ± 0.8, $P = 0.002$). All clinical scores except Cerebellar Cognitive Affective Syndrome significantly worsened during the study. NfL levels significantly increased in non-converters and ataxic SCA3 (1.06 ± 0.33 pg/ml/year, $P = 0.002$ and 0.57 ± 0.21 pg/ml/year, $P = 0.01$, respectively) but not in controls and ataxic SCA1 (0.31 ± 0.26 pg/ml/year, $P = 0.24$ and 0.26 ± 0.42 pg/ml/year, $P = 0.55$, respectively). In the best predictive model of Scale for Assessment and Rating of Ataxia progression after 1 year ($R^2 = 0.54$), factors linked with faster progression were higher functional stage ($P < 0.001$), higher Composite Cerebellar Functional Score ($P = 0.002$) and higher total creatine in cerebellar white matter ($P = 0.026$).

Factors significantly linked to conversion, namely NfL levels, depression and lower motor neuron involvement, differ from those driving disease progression. The NfL levels and lower motor neuron signs could be used as predictors of phenoconversion and MRI variables as ataxia progression predictors. Psychological care should be provided in the pre-ataxic phase of the disease.

1 Sorbonne Université, Institut du Cerveau-Paris Brain Institute-ICM, CNRS, Inria, Inserm, AP-HP, Groupe Hospitalier Sorbonne Université, Paris 75013, France

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2 Department Translational Neuroscience, Michigan State University, Grand Rapids, MI 49503, USA
3 Center for Neurology, Department of Parkinson's Disease, Sleep and Movement Disorders, University Hospital of Bonn, Bonn 53127, Germany
4 Department of Neuroradiology, University Hospital of Bonn, Bonn 53127, Germany
5 German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany
6 Department of Neurology, University of Campinas, Campinas 13083-887, Brazil
7 Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA
8 Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322, USA
9 Department of Neurology, Johns Hopkins University, Baltimore, MD 21287, USA
10 Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
11 Department of Neurology, University of Alabama at Birmingham, Birmingham, AL 35233, USA
12 Department of Neurology, University of California, Los Angeles, Los Angeles, CA 90095, USA
13 Department of Neurology, University of California, San Francisco, CA 94143, USA
14 Department of Neurology, University of Chicago, Chicago, IL 60637, USA
15 Department of Neurology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO 80045, USA
16 Department of Neurology, University of Florida, Gainesville, FL 32611, USA
17 Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
18 Department of Neurology, University of Minnesota, Minneapolis, MN 55455, USA
19 Department of Neurology, University of South Florida, Tampa, FL 33612, USA
20 Department of Neurology, University of Utah, Salt Lake City, UT 84132, USA
21 Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota, Minneapolis, MN 55455, USA
22 Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA
23 Stanley H. Appel Department of Neurology Houston Methodist Hospital, Houston, TX 77030, USA

Correspondence to: Emilien Petit
Paris Brain Institute, Sorbonne Université UM75 Inserm U1127 CNRS UMR 7225
CRMR Neurogénétique, 47, Boulevard de l'Hôpital, Paris 75013, France
E-mail: Emilien.petit@icm-institute.org

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Introduction

Spinocerebellar ataxias of types 1 and 3 (SCA1 and SCA3, respectively) are neurodegenerative diseases caused by (CAG)*n* repeat expansions in the *ATXN1* and *ATXN3* genes, respectively, resulting in the expansion of a polyglutamine tract in the corresponding proteins.[1,2] These expansions are pathological when they exceed a threshold, 39 for SCA1 and 60 for SCA3, and the longer the expansion, the earlier the age of onset,[3] and the faster the disease progression in SCA1.[4] The main symptom of SCAs is cerebellar ataxia, widely assessed by the Scale for Assessment and Rating of Ataxia (SARA),[5] but many other clinical signs develop during the disease progression and are assessed by the Inventory of Non-Ataxia Signs (INAS).[6] Additionally, SCA carriers are more prone to depression and fatigue, but it remains unclear whether these are caused by the clinical symptoms or are a direct consequence of neurodegeneration.

To date, no effective treatments are available, because most of the clinical trials in SCAs have failed, which could be the result of both the inefficiency of the treatments proposed until now and the poor design of the trials. Several obstacles make trials in SCAs difficult. First, the disease progresses relatively slowly, with participants' SARA increasing by 1–2 points every year.[7] Second, the measurement of symptoms depends on the condition of the participant at the time of the examination,[8] in addition to the rater, even if the rater is properly trained, leading to noisy measures. One option to improve the statistical power of future studies is to identify sensitive predictors of disease progression in order to use power enhancement in trials.[9]

To address these questions, we used the READISCA[10] study, which collected longitudinal clinical, imaging and blood biomarker data from early SCA participants in the USA and Europe over a period of 5 years. We report here the longitudinal results of clinical and blood biomarkers to identify the variables sensitive to change, in addition to those with the strongest predictive power for conversion and disease progression over a specified time period.

Materials and methods

Participants

Participants were enrolled in the READISCA cohort between 2018 and 2021, with the last follow-up visit occurring in June 2023. Individuals with SCA1 or SCA3 and relatives were recruited from 18 US and two European ataxia referral centres. Relatives were grouped in the control or pre-ataxic group depending on their genotyping results. All enrolment procedures were described in the READISCA baseline report.[11] The visits were scheduled to occur annually for 4 years, plus an optional visit at 6 months, but some were postponed owing to the coronavirus disease 2019 pandemic. The study was then extended by an additional 6 months. At each visit except the 6 month one, clinical outcomes and blood samples were collected, in addition to MRI for half of the participants. The baseline MRI data were published previously[12] (Fig. 1).

The study was approved by the ethics committees of the participating centres in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants at the time of enrolment. The trial protocol is available online. The

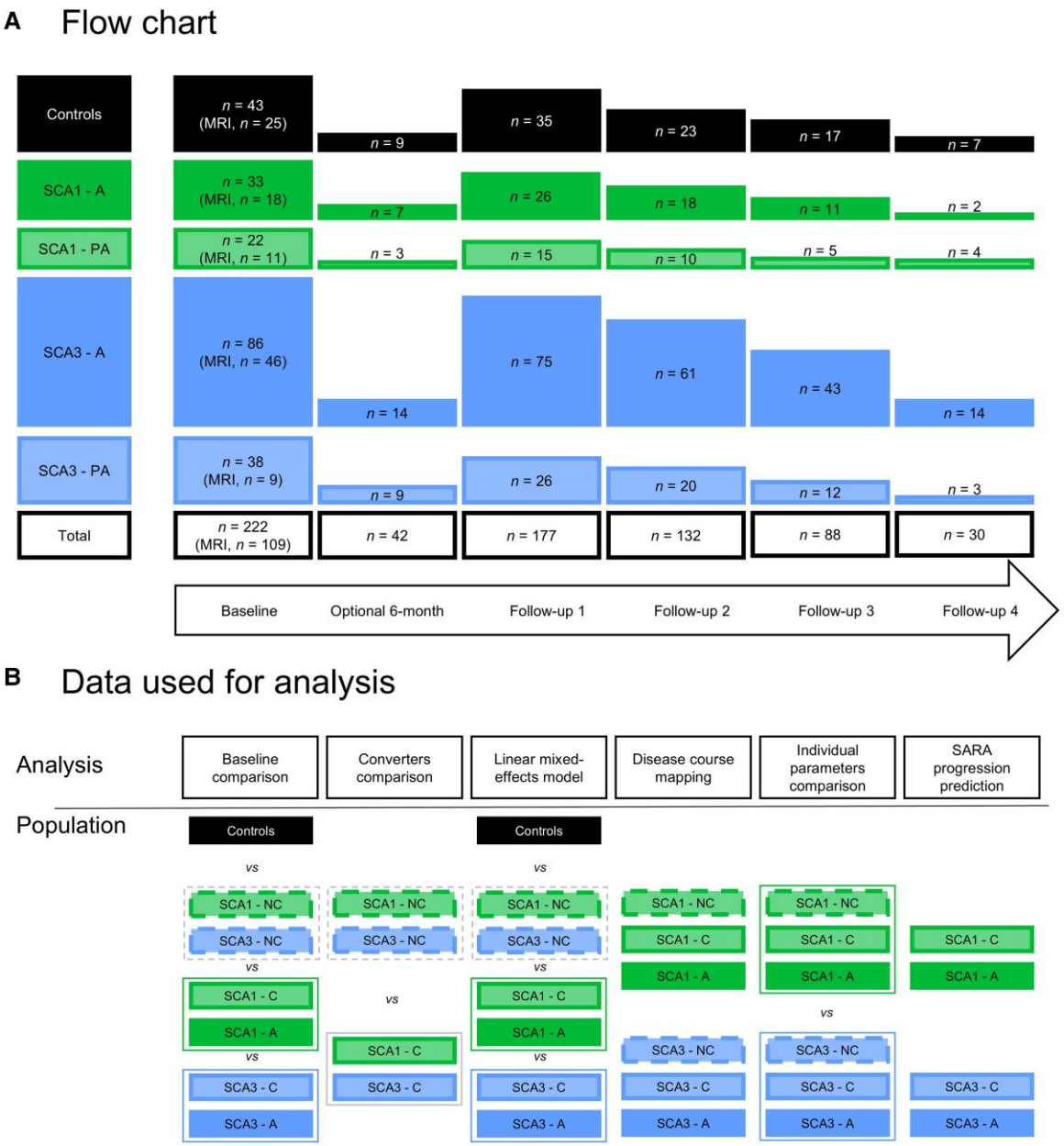

Figure 1 Flow chart and population used in each analysis. (**A**) Flow chart. Controls are displayed in black, SCA1 in green and SCA3 in blue, and pre-ataxic participants are shown with transparency. The height of each block is proportional to the number of participants. Participants who were pre-ataxic at baseline moved from the pre-ataxic to ataxic category if they phenoconverted during the study. Only baseline MRI data were used; these were available for approximately half of the cohort. At the optional 6-month visit, only SARA was measured. (**B**) Data used for each analysis. A = individuals with ataxia at baseline; C = converters; NC = non-converters; SARA = Scale for Assessment and Rating of Ataxia; SCA = spinocerebellar ataxia.

authors have received informed consent forms from all study participants and have them on file. The trial has been registered on Clinicaltrials.gov (NCT03487367).

Clinical assessments

We used the SARA scale to assess the presence and severity of cerebellar ataxia.[5] Participants were considered converters if they were pre-ataxic at baseline and had a visit with SARA ≥ 3 later in the study (even if they drop below three in later visits). We conducted a sensitivity analysis using a stricter definition of converters, including only pre-ataxic participants at baseline who had a SARA ≥ 3 at their final visit. Axial SARA was computed as the sum of the items gait, stance, speech and sitting, whereas appendicular SARA was computed as the sum of items finger-nose, finger-chase, heel-shin slide and fast alternating hand movements. We used INAS to assess additional cerebellar signs during a neurological examination, and INAS count was used as a quantitative score. We analysed anatomical functional systems that had shown differences between pre-ataxic and control groups in the baseline analysis[11]: (i) upper motor neuron involvement, defined by the presence of either hyper-reflexia, extensor plantar reflex or spasticity; and (ii) lower motor neuron, defined by the presence of distal paresis, muscle atrophy or fasciculations. The Composite Cerebellar Function Score (CCFS) was measured.[13] We assessed cognitive impairment with the Cerebellar Cognitive Affective

Syndrome (CCAS[14]) scale, fatigue with the Fatigue Severity Scale (FSS[15]), and activities of daily living with the Friedreich's Ataxia Activities of Daily Living (FARS-ADL[16]) scale. Depressive symptoms were assessed with the Patient Health Questionnaire 9 (PHQ-9[17]), and we computed the EuroQol 5D index (EQ-5D[18]) from the EQ-5D set to measure health-related quality of life.

Estimated time to onset was computed as the difference between age at baseline visit and age at onset, estimated with the formula from Tezenas *et al.*[3] for SCA1 and Peng *et al.*[19] for SCA3 (positive if the participant is older than the estimated age at onset).

All investigators were experienced in the use of the scales used. Web-based certification was required for the SARA score.

Neurofilament light chain measurements

Plasma samples were collected on EDTA tube anticoagulants, frozen at −80°C, and stored in the local biobank (EU) or BioSEND (https://biosend.org/) repository (USA). Plasma neurofilament light chain (NfL) levels were measured in duplicate using an ultra-sensitive single molecule array on the Simoa HD-1 analyser (Quanterix), as previously established.[20] Plasma NfL levels were measured initially at baseline visits, then at all follow-up visits. In the USA and France, reference samples were measured at both baseline and follow-up visits to ensure bridging between sites. A correction term was applied to the follow-up measurement because the ratio of measurement of bridging samples was not close enough to 1.

MRI measurements

MRI measurements included volumetric measures obtained from T1-weighted structural scans, microstructural measures obtained from diffusion MRI, and neurochemical concentrations obtained by magnetic resonance spectroscopy at 3 T using a harmonized protocol. Details of the acquisition protocol and analytical pipelines are described by Chandrasekaran *et al.*[12] MR measures that showed the highest sensitivity to pre-ataxic and early ataxic differences[12] and short-term progression[21] in SCA1 and SCA3 were evaluated in the predictive analyses. These included pons, cerebellar white matter (CBWM) and superior cerebellar peduncle (SCP) volumes for both SCA1 and SCA3. For SCA1, we focused on magnetic resonance spectroscopy metrics: total creatine, *N*-acetyl aspartate (NAA) and glutamate concentrations, and total NAA over myo-inositol and total NAA over total creatine ratios in both the pons and CBWM. For SCA3, we focused on diffusion MRI metrics: fractional anisotropy (FA) and mean diffusivity (MD) in the inferior cerebellar peduncle (ICP), SCP, and right and left and middle cerebellar peduncle (MCP).

Grouping of participants

To distinguish participants who showed disease progression from those who did not, individuals who converted during the study were grouped together with those who were already ataxic at baseline. This resulted in four groups: controls, non-converters, SCA1 ataxic (including both participants who were ataxic at baseline and those who converted during the study) and SCA3 ataxic (similarly including both baseline ataxic individuals and converters) (Fig. 1B).

Statistical analysis

Baseline characteristics were described as the mean ± standard deviation (SD) for quantitative variables and frequency (percentage) for qualitative variables. For quantitative variables, comparisons between four groups (controls, non-converters, SCA1 and SCA3) were performed using ANOVA with Tukey's *post hoc* comparison and between two groups (converters versus non-converters) using unpaired Student's *t*-test. For qualitative variables, χ^2 tests were used. For quantitative variables that showed a significant difference between converters and non-converters, we used logistic regression and receiver operating characteristic curve with Youden's procedure to determine the optimal threshold between groups.

We first modelled longitudinal progression of clinical scores using linear mixed-effects models, with the time since inclusion as the time variable. The models included the time, the group and their interaction as fixed effects, and an intercept and a slope as random effects for each participant. For each clinical score and NfL levels, we examined the slope differences across groups and effect sizes for a 1-year progression using Cohen's *d*.[22]

To describe the joint progression of clinical scores and NfL levels, we used a disease course mapping model[23,24] based on a Bayesian mixed model (Supplementary material). We fitted this model with all significantly worsening variables simultaneously with data from SCA carriers only.[25] This model enables the description of the trajectory of each participant using individual parameters we can interpret as onset age and progression rate (slope). These parameters can be used to calculate a 'disease course age', which maps participants along the time line of disease progression. Additionally, variable-specific onset allows us to model earlier or later onset of progression for each variable (Supplementary Fig. 1). These individual parameters were compared between ataxic participants to assess genotype differences. Pearson correlations between variable-specific onsets were calculated to determine groups of variables with correlated progression.

To determine which variable was prognostic of a SARA change, we predicted the SARA value at baseline and at 1 year with the Bayesian model and calculated the estimated 1-year SARA change. We used the estimated SARA change and not the observed SARA change to avoid the bias of misestimation of SARA at baseline. We searched for the baseline clinical outcomes or biomarkers (NfL and MRI) significantly associated with this progression.

In the sub-cohort with available baseline MRI data, we looked for univariable linear regression between baseline variables and estimated SARA change, and we described the estimate and variance explained by each predictor. For variables that showed significant effect in the separated SCA analysis, we conducted a pooled analysis with SCA1 and SCA3 after verifying that there was no significant interaction between the variable and genotype to explain the estimated SARA change. We performed a bi-directional stepwise Akaike information criterion regression to select the most predictive variables in a multivariable model, and a sensitivity analysis of this variable selection with bootstrapping over 100 runs to ensure stability of the results.

Statistical tests were performed at the conventional two-tailed type 1 error of 0.05. A disease course mapping model was performed using Leaspy v.1.4, in Python v.3.4. Data were analysed using R v.4.4.2 (R Core Team, 2024).

Results

Baseline comparison between controls, SCA1 and SCA3

A total of 222 participants were recruited, including 43 controls, 55 SCA1 and 124 SCA3 participants (Table 1). Controls and non-

Table 1 Baseline characteristics of the SCA1 and SCA3 participants and controls

Variable	Controls ($n = 43$)	Non-converters (SCA1 $n = 17$, SCA3 $n = 26$)	SCA1 ($n = 38$)	SCA3 ($n = 98$)	P-value
Sex (female)	21 (48.8%)	27 (62.8%)	21 (55.3%)	52 (53.1%)	0.6065
Age (years)	38.7 ± 9.5[c,d]	36.5 ± 7.9[c,d]	46.4 ± 8.9[a,b]	46.3 ± 10.3[a,b]	<0.0001
Normal allele length (CAG repeat number)	–	–	29.1 ± 2.3 $n = 36$	21.9 ± 5.3 $n = 92$	–
Pathological allele length (CAG repeat number)	–	–	45.5 ± 3.7 $n = 37$	70.8 ± 4.1 $n = 96$	–
Estimated time to onset (years)	–	−5.1 ± 9.0[c,d]	6.2 ± 6.2[b] $n = 36$	8.0 ± 8.1[b] $n = 96$	<0.0001
Follow-up duration (years)	2.5 ± 1.6	2.3 ± 1.4	1.8 ± 1.4	2.4 ± 1.5	0.1242
Number of visits	3.1 ± 1.5	3.2 ± 1.6	2.8 ± 1.4	3.2 ± 1.5	0.5486
NfL	4.6 ± 2.3[b,c,d] $n = 38$	11.1 ± 5.9[a,c,d] $n = 34$	21.1 ± 10.1[a,b] $n = 33$	21.6 ± 6.7[a,b] $n = 79$	<0.0001
SARA	0.7 ± 1.1[c,d]	0.8 ± 0.9[c,d]	7.9 ± 3.8[a,b]	6.9 ± 3.7[a,b]	<0.0001
Axial SARA	0.2 ± 0.5[c,d]	0.3 ± 0.7[c,d]	4.3 ± 2.3 [a,b]	3.9 ± 2.6 [a,b]	<0.0001
Appendicular SARA	0.5 ± 0.8[c,d]	0.5 ± 0.7[c,d]	3.6 ± 1.8[a,b,d]	3.0 ± 1.5[a,b,c]	<0.0001
CCFS	0.883 ± 0.061[c,d] $n = 39$	0.880 ± 0.087[c,d] $n = 38$	0.963 ± 0.095[a,b] $n = 30$	0.952 ± 0.089[a,b] $n = 87$	<0.0001
CCAS	104.1 ± 8.5[c,d]	99.5 ± 11.8[c,d] $n = 40$	89.6 ± 13.1[a,b] $n = 36$	93.5 ± 12.9[a,b] $n = 94$	<0.0001
CCAS fail	1.00 ± 1.21[c,d]	1.16 ± 1.31[c,d] $n = 38$	2.36 ± 1.6[a,b] $n = 33$	1.87 ± 1.73[a,b] $n = 95$	0.0002
PHQ9	2.8 ± 4.1[c,d]	2.3 ± 2.6[c,d]	4.9 ± 4.7	5.6 ± 5.9[a,b] $n = 97$	0.0003
FSS	19.7 ± 9.8[c,d]	21.6 ± 9.6[c,d]	26.3 ± 14.8	31.0 ± 14.3[a,b]	<0.0001
FARS-ADL	0.4 ± 0.6[c,d]	0.6 ± 1.3[c,d]	5.6 ± 4[a,b]	5.6 ± 4.4 [a,b] $n = 97$	<0.0001
Functional stage	0.09 ± 0.29[c,d]	0.31 ± 0.48[c,d]	1.92 ± 0.8 [a,b]	1.8 ± 0.92 [a,b]	<0.0001
INAS count	0.33 ± 0.52[c,d]	0.74 ± 0.82[c,d]	2.13 ± 1.42 [a,b,d]	2.86 ± 1.82[a,b,c] $n = 96$	<0.0001
EQ5D	0.94 ± 0.1[c,d]	0.95 ± 0.08[c,d]	0.79 ± 0.15[a,b] $n = 37$	0.82 ± 0.17[a,b] $n = 96$	<0.0001

Data are expressed as the mean ± standard deviation. The P-values are the ANOVA P-values when comparing all four groups, and t-test P-values when comparing SCA1 and SCA3. CCAS = Cerebellar Cognitive Affective Syndrome total score; CCAS fail = Cerebellar Cognitive Affective Syndrome number of failed items; CCFS = Composite Cerebellar Functional Score; EQ-5D = EuroQol 5D; FARS-ADL = Friedreich's Ataxia Activities of Daily Living; FSS = Fatigue Severity Score; INAS = Inventory of Non-Ataxia Signs; NfL = plasma neurofilament light chain concentration (in picograms per millilitre); PHQ9 = Patient Health Questionnaire 9; SARA = Scale for Assessment and Rating of Ataxia.
[a]Significant Tukey's difference to controls.
[b]Significant Tukey's difference to non-converters.
[c]Significant Tukey's difference to SCA1.
[d]Significant Tukey's difference to SCA3.

converters were younger than SCA ataxic participants (38.7 ± 9.5 years versus 44.0 ± 10.3, $P = 0.002$). As expected, non-converters had a mean negative expected time to onset, significantly lower in comparison to ataxic (−5.1 ± 9.0 versus 7.5 ± 7.6 years, $P < 0.0001$). Individuals pre-ataxic at baseline (non-converters and converters) represented 40% (22/55) in SCA1 and 31% (38/124), $P = 0.29$ in SCA3. All clinical scores were significantly worse in SCA ataxic participants compared with controls, and no clinical score was significantly impaired in non-converters. The NfL levels (expressed in pg/ml)were already increased in non-converters compared with controls, but lower than ataxic SCA1 and SCA3 (controls, 4.6 ± 2.3; non-converters, 11.1 ± 5.9; SCA1, 21.1 ± 10.1; SCA3, 21.6 ± 6.7; all $P < 0.001$, except the SCA1–SCA3 comparison; Table 1). The mean follow-up was 2.3 ± 1.5 years and was shorter for SCA1 (1.9 ± 1.4 years) compared with controls (2.4 ± 1.6 years) and SCA3 (2.4 ± 1.4 years), but this difference was not significant ($P = 0.12$). Seven controls (16%), 13 SCA1 (24%) and 18 SCA3 (15%) participants had only one baseline visit (Fig. 1). Participants had a median (IQR) of 3 (2;3) clinical visits.

Predictive variables of conversion

During the study, 17 pre-ataxic participants at baseline phenoconverted (5 SCA1 and 12 SCA3). Among them, three had a SARA < 3 at their last visit. Converters had higher estimated time to onset (i.e. were closer to estimated conversion) at baseline. They were older, had higher SARA scores on both axial and appendicular items and higher INAS counts (Supplementary Table 1). Lower motor neuron involvement was more frequent in converters than in non-converters [23% (4/17) versus 2% (1/43), $P = 0.031$], specifically in SCA3 [33% (4/12) versus 0% (0/26), $P = 0.010$]. In addition, converters were more depressed at baseline (PHQ9: 3.9 ± 2.9 versus 2.3 ± 2.6, $P = 0.039$), had higher plasma NfL levels (17.6 ± 5.7 versus 11.1 ± 5.9 pg/ml, $P < 0.001$) than non-converters and more CBWM atrophy (1.44% ± 0.12% of total intracranial volume versus 1.54% ± 0.16%, $P = 0.032$). Owing to the small sample size, only univariate logistic models were considered. The best predictor of conversion was plasma NfL at baseline [area under the curve = 0.80 (0.67;0.92)], with the threshold being 13.2 pg/ml, with specificity = 0.70 and sensitivity = 0.80. When using the stricter definition of converters, the differences in PHQ9 and CBWM did not remain significant (for PHQ9: from 3.9 ± 2.9 versus 2.3 ± 2.6 to 3.6 ± 3.1 versus 2.4 ± 2.7; for CBWM: from 1.44 ± 0.12 versus 1.54 ± 0.16 to 1.45 ± 0.13 versus 1.53 ± 0.16).

Independent modelling of clinical scores and NfL progression

No significant progression in any of the scores was observed in controls (Table 2). SCA3 ataxic participants showed significant progression in all clinical scores except for CCAS. SCA1 ataxic participants showed significant progression in SARA, CCFS and FARS-ADL (Table 2). SARA progression was not significantly different between SCA1 and SCA3 (1.21 ± 0.19 versus 1.15 ± 0.10 per year, $P = 0.77$). In both SCAs, the SARA was the variable most sensitive to change,

Table 2 Linear longitudinal progression of clinical outcomes and neurofilament light chain

Variable	Control slope	Control ES	NC slope	pNC	NC ES	SCA1 slope	pSCA1	SCA1 ES	SCA3 slope	pSCA3	SCA3 ES
SARA	−0.018 ± 0.151	−0.014	−0.011 ± 0.155	0.9741	−0.009	1.214 ± 0.192*	<0.0001	**0.946**	1.15 ± 0.102*	<0.0001	**0.896**
Axial SARA	−0.009 ± 0.101	−0.009	−0.064 ± 0.104	0.7031	−0.067	0.83 ± 0.131*	<0.0001	0.874	0.688 ± 0.068*	<0.0001	0.725
Appendicular SARA	−0.013 ± 0.082	−0.016	0.03 ± 0.085	0.7153	0.037	0.357 ± 0.108*	0.0069	0.435	0.409 ± 0.055*	<0.0001	0.498
CCFS	−0.002 ± 0.004	−0.035	−0.002 ± 0.005	0.9564	−0.042	0.022 ± 0.006*	0.001	0.478	0.011 ± 0.003*	0.0169	0.231
CCAS	0.511 ± 0.464	0.097	1.447 ± 0.511*	0.1779	0.275	0.749 ± 0.653	0.7676	0.142	0.425 ± 0.324	0.8793	0.081
CCAS fail	−0.107 ± 0.067	−0.113	−0.108 ± 0.078	0.9997	−0.113	−0.085 ± 0.1	0.8507	−0.089	0.046 ± 0.048	0.0657	0.048
PHQ9	−0.163 ± 0.222	−0.068	−0.128 ± 0.236	0.9144	−0.053	0.372 ± 0.288	0.1435	0.155	0.384 ± 0.153*	0.0447	0.16
FSS	−0.032 ± 0.646	−0.004	−0.111 ± 0.689	0.9331	−0.016	0.939 ± 0.851	0.3651	0.132	1.066 ± 0.442*	0.1636	0.15
FARS-ADL	−0.009 ± 0.175	−0.006	0.09 ± 0.181	0.694	0.059	0.77 ± 0.228*	0.0074	0.509	0.914 ± 0.118*	<0.0001	0.604
Functional stage	−0.01 ± 0.043	−0.023	0.023 ± 0.045	0.5908	0.053	0.076 ± 0.057	0.2269	0.173	0.171 ± 0.029*	0.0007	0.389
INAS	−0.03 ± 0.077	−0.031	−0.017 ± 0.083	0.9055	−0.017	0.166 ± 0.106	0.1361	0.17	0.209 ± 0.052*	0.0121	0.213
EQ5D	0.001 ± 0.007	0.011	0 ± 0.008	0.9511	0.003	−0.01 ± 0.01	0.379	−0.117	−0.021 ± 0.005*	0.0138	−0.254
NfL	0.314 ± 0.264	0.097	1.06 ± 0.33*	0.0818	**0.329**	0.256 ± 0.424	0.908	0.079	0.573 ± 0.215*	0.4496	0.178

Control, NC, SCA1 and SCA3 are the estimates (ES) and standard error (SE) of the linear annual progression of each outcome. For these columns, significant increases are highlighted by an asterisk. pNC, pSCA1 and pSCA3 are the *P*-values of the comparison on progression speed between controls and NC, SCA1 and SCA3, respectively. Control, NC, SCA1 and SCA3 ES are the effect sizes of the progression; in bold are the best effect sizes for NC, SCA1 and SCA3. *Significant ($P < 0.05$) increase. CCAS = Cerebellar Cognitive Affective Syndrome total score; CCAS fail = Cerebellar Cognitive Affective Syndrome number of failed item; CCFS = Composite Cerebellar Functional Score; EQ-5D = EuroQol 5D; FARS-ADL = Friedreich's Ataxia Activities of Daily Living; FSS = Fatigue Severity Score; INAS = Inventory of Non-Ataxia Signs; NC = non-converters; NfL = plasma neurofilament light chain concentration; PHQ9 = Patient Health Questionnaire 9; SARA = Scale for Assessment and Rating of Ataxia.

with a strong effect size for the variation at 1 year (0.946 for SCA1 and 0.896 for SCA3). Axial SARA had slightly lower effect sizes, with 0.874 for SCA1 and 0.725 for SCA3. Plasma NfL concentrations increased significantly in non-converters and SCA3 ataxic participants (1.06 ± 0.33 pg/ml/year, $P = 0.002$ and 0.57 ± 0.2133 pg/ml/year, $P = 0.010$, respectively), but not in controls and SCA1 ataxic participants (0.31 ± 0.2633 pg/ml/year, $P = 0.24$ and 0.26 ± 0.4233 pg/ml/year, $P = 0.55$, respectively), showing that NfL increased faster at pre-ataxic stages. Additionally, NfL was the variable most sensitive to change in non-converters (effect size = 0.329). Nevertheless, NfL increase was not significantly faster in SCA3 compared with controls ($P = 0.45$). The CCAS score improved significantly in non-converters (1.45 ± 0.51, $P = 0.0053$), demonstrating a potential training effect for this scale.

Joint modelling of clinical score and NfL progression using disease course mapping model

Slope and general onset analysis

We included all scores except the CCAS in the disease course mapping model because they all showed a longitudinal worsening (Fig. 2A) (separated curves are available in Supplementary Fig. 2). This worsening was not significant for all scores in SCA1 (only SARA and FARS-ADL were significantly worsening), probably owing to the small sample size, because the mean progression was similar to SCA3. Only data from SCA carriers were used for this analysis. The disease course age clearly separated the non-converters, converters and ataxic-at-baseline groups with values of 31.7 ± 6.1, 40.5 ± 3.9 and 49.6 ± 4.3 years ($P < 0.0001$) (Fig. 2B). There were no significant differences in slope and onset between SCAs ($P = 0.92$ and $P = 0.44$) (Supplementary Table 2), and these two parameters were significantly negatively correlated in SCA3 ($R = -0.32$, $P = 0.006$) but not in SCA1 ($R = 0.015$, $P = 0.94$). Thus, SCA3 participants progressed faster if they had an earlier age at onset. No significant differences of individual parameters were found between countries ($P = 0.15$ and $P = 0.87$). As expected, CAG repeat length was strongly correlated with modelled onset ($R = -0.89$, $P < 0.0001$ and $R = -0.7$, $P < 0.0001$ for SCA1 and SCA3, respectively) (Supplementary Fig. 3), and correlated with slope only in SCA3 ($R = 0.27$, $P = 0.014$).

Variable-specific onset correlations

We found two groups of variables that showed positive correlations of variable-specific onset, i.e. groups of variables with an onset shifted in the same direction. The first group was composed of variables related to clinical manifestations of the disease and biomarkers: SARA, functional stage, INAS count and NfL, with the highest (Supplementary Fig. 4) correlation between SARA and functional stage ($R = 0.73$, $P < 0.0001$). The second group was more associated with activities of daily living and quality of life variables: PHQ9, FSS, CCFS, FARS-ADL and EQ5D, with a very strong correlation between FSS and PHQ9 ($R = 0.96$, $P < 0.0001$). This shows that the onset of ataxia and the first impact of the disease on ADL are separated in the course of the disease. Nevertheless, we could not identify clusters of participants with earlier clinical onset and later ADL onset and vice versa.

The only significant differences in variable-specific onset between SCAs were that SCA3 participants showed a later increase in CCFS and SARA compared with SCA1 (CCFS: 1.8 ± 5.5 years in SCA3 versus −1.1 ± 5.3 years in SCA1, $P = 0.007$, and SARA: 0.41 ± 2.55 years in SCA3 versus −0.58 ± 2.33 years in SCA1, $P = 0.046$)

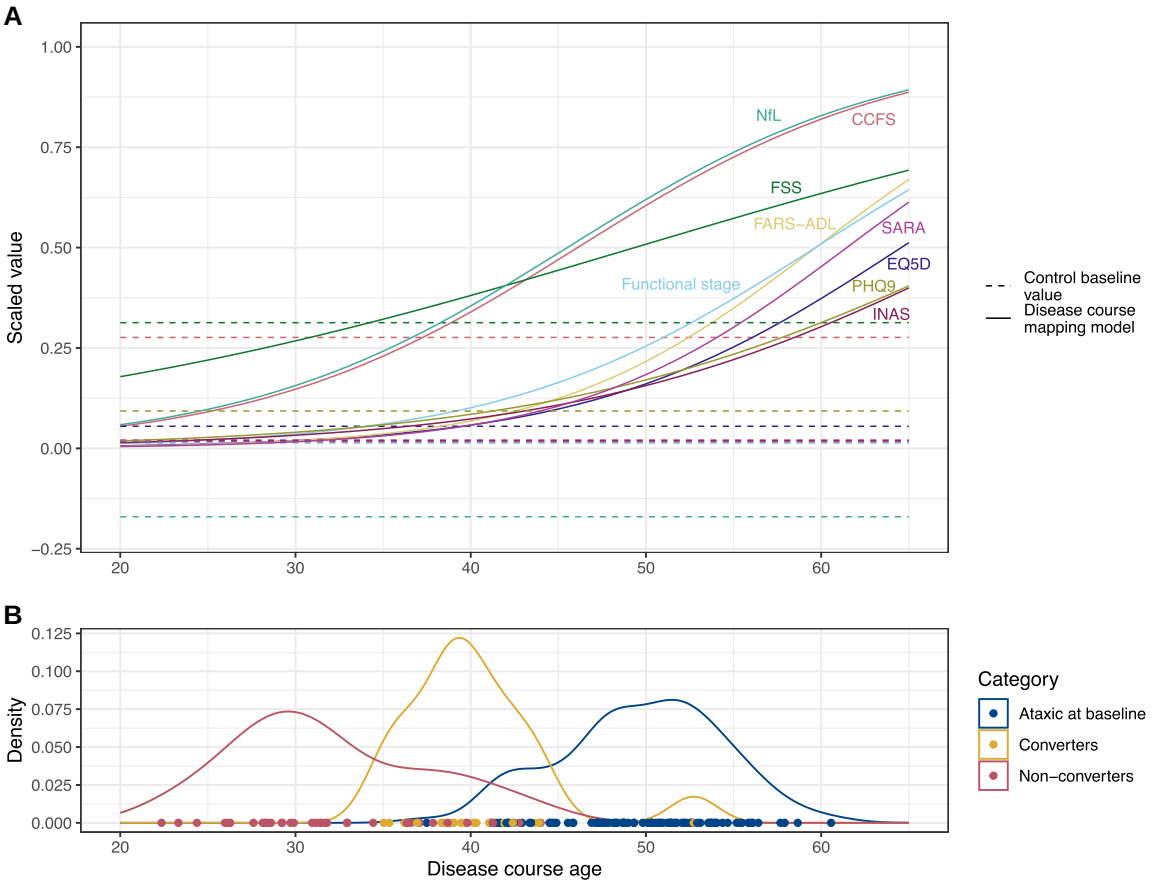

Figure 2 Disease course mapping. (**A**) The disease course mapping model, using all SCA carriers. Each curve represents the progression of a clinical or biological marker along the disease time line (disease course age). Values were rescaled between 0 and 1. For bounded variables (FARS-ADL, FSS, Functional stage, INAS, PHQ9 and SARA), 0 corresponds to 0 on the scale and 1 to the maximum score on the scale. For unbounded variables (CCFS, NfL), 0 and 1 correspond to the 10% and 90% percentile of observed data for SCA participants, respectively. EQ5D is bounded between 0 and 1, but it was inverted (i.e. 0 corresponds to 1 and vice versa) to ensure that the score increases. Individual graphs by variable can be found in Supplementary Fig. 2. (**B**) The distribution of the disease course age of non-converters, converters and ataxic participants at baseline. The model successfully maps the participants on the disease course time line. CCAS = Cerebellar Cognitive Affective Syndrome total score; CCFS = Composite Cerebellar Functional Score; EQ-5D = EuroQol 5D; FARS-ADL = Friedreich's Ataxia Activities of Daily Living; FSS = Fatigue Severity Score; INAS = Inventory of Non-Ataxia Signs; NfL = plasma neurofilament light chain concentration; PHQ9 = Patient Health Questionnaire 9; SARA = Scale for Assessment and Rating of Ataxia.

(Supplementary Table 2). This indicates that upper limb ataxia is more rapidly impacted in SCA1.

Predictive variables of SARA progression

Only ataxic participants with at least two visits and baseline brain MRI data were included in this analysis ($n = 62$). The correlation between the 1-year change estimated by the model and the annualized SARA progression between baseline and the first follow-up visit was 0.49, $P < 0.0001$.

The best baseline predictors of 12-month SARA progression were clinical. In SCA1, higher CCFS, FARS-ADL was the most linked variable to SARA progression with estimates of 0.63 ± 0.13 for a 0.1-point increase in CCFS ($R^2 = 0.58$) and 0.11 ± 0.03 for FARS-ADL ($R^2 = 0.53$) (Fig. 3). The best predictive biomarkers were NfL (0.25 ± 0.11 per SD, i.e. for a 1 SD increase, $R^2 = 0.29$), and total creatine in CBWM (0.31 ± 0.12 per SD, $R^2 = 0.29$). In SCA3, functional stage and CCFS models had estimates of 0.52 ± 0.10 ($R^2 = 0.40$) and 0.44 ± 0.10 ($R^2 = 0.31$). The best predictive biomarkers were SCP volume (-0.30 ± 0.09 per SD, $R^2 = 0.21$) and R-SCP-FA (-0.28 ± 0.09 per SD, $R^2 = 0.17$). There were no significant differences between SCA in the impact of any variable on the SARA progression. In the pooled SCA1 and SCA3 group, functional stage and CCFS had estimates of 0.51 ± 0.08 ($R^2 = 0.42$) and 0.48 ± 0.08 ($R^2 = 0.38$), with the best biomarkers being SCP volume (-0.30 ± 0.07 per SD, $R^2 = 0.23$), R-SCP-FA (-0.27 ± 0.07 per SD, $R^2 = 0.19$) and total creatine in CBWM (0.28 ± 0.08 per SD, $R^2 = 0.17$).

In the stepwise selection model, higher CCFS, functional stage and total creatine in CBWM were linked to faster SARA progression (total $R^2 = 0.54$). The sensitivity analysis showed that the three covariates had a consistent effect on SARA progression (Supplementary Table 3).

Discussion

The READISCA project provides critical data on the clinical and biomarker progression of pre-ataxic and early ataxic SCA1 and SCA3 carriers. The study included 222 participants (43 controls, 55 SCA1 and 124 SCA3), followed for ≤5 years. We showed that clinical scales, except CCAS, worsened significantly during the study. Additionally, biomarker changes could be observed before ataxia

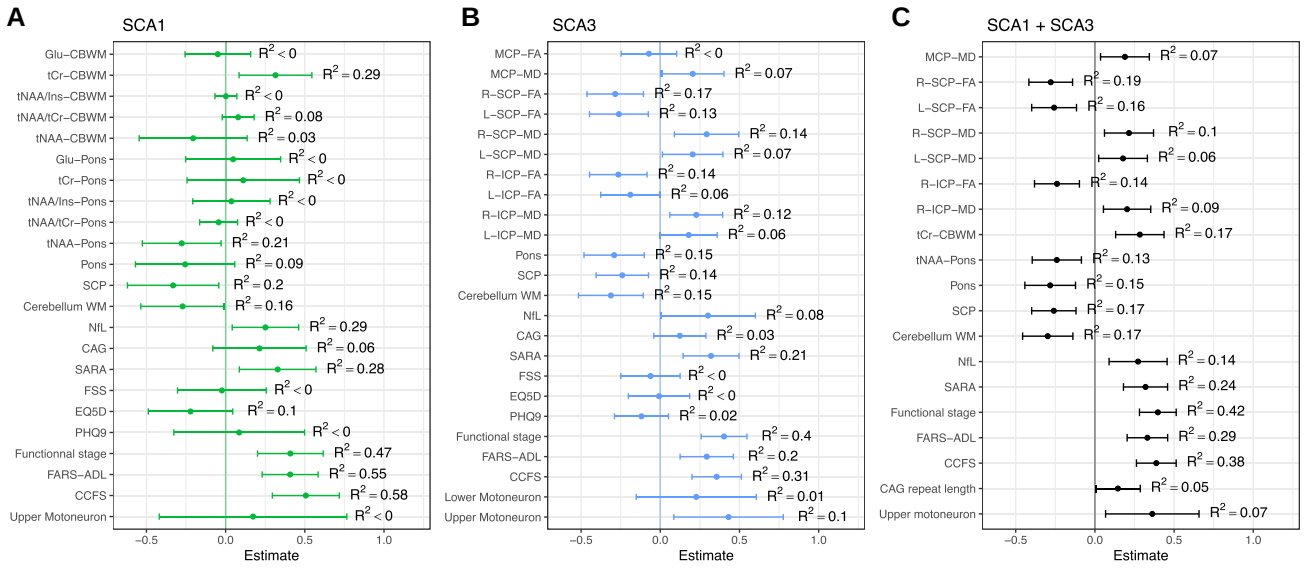

Figure 3 Clinical and MRI predictive power of SARA progression for SCA1 and SCA3 participants. (**A**) SCA1. (**B**) SCA3. (**C**) SCA1 and SCA3 individuals combined. All continuous variables were standardized to be comparable. Univariable models with the standardized variable were computed to explain the predicted SARA progression at 1 year. Estimates are shown with 95% confidence interval. For example, the top data-point (MCP-RD) in **C** means that for SCA1 and SCA3 combined, an increase of 1 standard deviation of MCP-RD concentration leads to a predicted increased SARA progression of +0.19 (0.11;0.27), and the adjusted R^2 is 0.07. CBWM = cerebellar white matter; CCFS = Composite Cerebellar Functional Scale; EQ5D = EuroQol 5D Index; FA = fractional anisotropy; FARS-ADL = Friedreich Ataxia Rating Scale-Activities of Daily Living; FSS = Fatigue Severity Score; Glu = glutamate; ICP = inferior cerebellar peduncle; Ins = myo-inositol, L = left; MCP = middle cerebellar peduncle; MD = mean diffusivity; NfL = neurofilament light chain, PHQ9 = Patient-Health Questionnaire-9; R = Right; SCP = superior cerebellar peduncle; tCr = total creatine; tNAA = total *N*-acetyl aspartate.

onset. We used a disease course mapping model to create a comprehensive model of the disease in its early stages and identified clinical and biological predictors of progression.

From baseline data, we showed that pre-ataxic participants with SCA1 and SCA3 had significantly higher numbers of non-ataxia signs, higher plasma NfL levels and abnormalities in brain MRI markers.[11,12] Analysing the longitudinal data, which included 17 phenoconversions, we found that NfL levels, depression, CBWM atrophy and lower motor neuron involvement were associated with conversion. Given that NfL levels are related to the rate of neurodegeneration,[26] this suggests an acceleration of neurodegeneration during the conversion time window. However, the relatively short follow-up period compared with the slow progression of the disease does not allow this acceleration to be observed clearly at the individual level. Converters also had a shorter estimated time to onset estimated by CAG, supporting the value of onset prediction models. In contrast, MRI markers of converters, such as pons or SCP volume, were not significantly different from non-converters, although they differed from controls.[12]

The progression of SARA score, FARS-ADL or INAS has already been described extensively in many studies.[4,7,27] However, the progression of common impairments in SCA, such as depression, has been described in a European cohort[28] but not replicated in an American SCA cohort.[29] In our study, we found significant progression of both depression (measured by PHQ9, 0.38 ± 0.15 points/year) and fatigue (measured by FSS, 1.07 ± 0.44 points/year) in ataxic SCA3 participants. On the contrary, the CCAS scale showed an overall improvement (significant in non-converters), highlighting a probable training effect (observed in a wider cohort, unpublished data), that makes this score unsuitable for longitudinal assessment. SARA score showed the best sensitivity to change across all clinical variables, with strong effect sizes (>0.8) in ataxic participants. Taking only axial SARA slightly decreased the effect size, highlighting the importance of appendicular items, at least in early stages. Finally, NfL levels increased faster in pre-ataxic than in ataxic subjects, confirming the sensitivity of this biomarker in pre-ataxic stages,[30] but with relatively low effect size (0.33) owing to high variability. Contrary to SCA1, NfL levels in SCA3 continued to increase significantly after conversion, which is consistent with the overall higher levels observed in SCA3,[30] potentially attributable to the characteristic neuropathy/ganglionopathy associated with the disease, in opposition to the slower increase in controls attributable to ageing. However, we still lack data from earlier stages to determine the time frame of the first biomarker changes linked to SCAs.

Although it is reasonable to model the progression of clinical scores and biomarkers with linear slopes over a relatively short period of time given the slow disease progression, this approach seems inadequate for a global model aiming to represent progression accurately, owing to non-linear patterns in the early stage of disease.[31] To address this issue, we used a disease course mapping model that can simultaneously model the progression of multiple outcomes with a logistic increase. This model, which aims to place all observed individuals on a common time line for each outcome, allows us to describe the progression of each participant with individual parameters. The clear differences in disease course age between non-converters, converters and ataxic participants at baseline confirm the ability of the model to map participants along the disease course. The individual parameter analysis captured the strong correlation between CAG repeat length and age of onset. In contrast to previous results from EUROSCA data,[14] no association between CAG and progression speed was found for SCA1, but a weak association was observed for SCA3. This lack of correlation might be attributed to the relatively small sample size in the SCA1 group, or to the slower progression of SARA in the very early stages, which could result in lower variability in SARA progression. Variable-specific onset showed a very strong correlation of the

onset of fatigue and depression, which were inversely correlated with the onset of SARA and functional stage. This suggests that these impairments might not be directly related to ataxia symptoms but might represent a distinct aspect of the disease. Nevertheless, depressive mood is accessible to psychological support and treatment, and very early management should be provided. Having a robust progression model and MRI data at baseline allowed us to focus on the predictive power of baseline covariates on the SARA progression. The model-estimated 1-year SARA progression was correlated with the observed annualized SARA change between baseline and first annual follow-up. We found that baseline predictors of SARA change were mainly clinical (functional stage, CCFS), but total creatine level in CBWM was also retained in the model. The results on predictive power of baseline measures need to be replicated, but having a decent R^2 of 0.54, such models could drastically reduce the sample size of future clinical trials using prediction-powered inference methods.[9]

Limitations

Despite being a multicentre study, this study was limited by the relatively small sample size, especially for the converters analysis, with only 17 converters. This limited our analysis to univariate models, reaffirming the need for sharing multimodal data on pre-ataxic SCAs to build more robust models of conversion. Moreover, we considered a participant ataxic if a SARA of ≥3 was measured at one visit, but this definition lacks robustness because participants might have SARA of <3 at the next visit. Additionally, the longitudinal MRI data are not yet available, making our progression model incomplete and missing a key point for understanding the temporal dynamics in SCAs. Finally, the final SARA prediction models were trained on small sample sizes on a pooled SCA1 and SCA3 group, and their use is limited to early stages of ataxia, and the generalizability was assessed only through cross-validation and needs a validation cohort for external validation.

Conclusion

With the gathering of these large pre-ataxic and early ataxic SCA participants, we highlighted the relevance of NfL dosage both for the prediction of conversion and for the monitoring of disease progression in the pre-ataxic stage. We showed a significant progression of all ataxia-related clinical scales (SARA, CCFS, functional stage INAS), in addition to depression and fatigue, with the last two having a very strong temporal correlation. Finally, we showed that baseline severity of clinical and MRI markers could be predictors of the 1-year SARA progression.

Data availability

All data have been uploaded to the NIMH Data Archive (https://nda.nih.gov/, Collection C3155).

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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