RESEARCH ARTICLE

Digital Gait Measures Capture 1-Year Progression in Early-Stage Spinocerebellar Ataxia Type 2

Jens Seemann, MSc,[1,2] Lina Daghsen, MSc,[3] Matthieu Cazier, MSc,[3] Jean-Charles Lamy, PhD,[3] Marie-Laure Welter, MD, PhD,[3] Martin A. Giese, PhD,[1,2] Matthis Synofzik, MD,[4,5] Alexandra Durr, MD, PhD,[3] Winfried Ilg, PhD,[1,2*] and Giulia Coarelli, MD, PhD[3*]

[1]*Section Computational Sensomotorics, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany*
[2]*Centre for Integrative Neuroscience (CIN), Tübingen, Germany*
[3]*Sorbonne Université, Paris Brain Institute—ICM, Inserm, CNRS, AP-HP, Paris, France*
[4]*Division Translational Genomics of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany*
[5]*German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany*

ABSTRACT: Background: With disease-modifying drugs in reach for cerebellar ataxias, fine-grained digital health measures are highly warranted to complement clinical and patient-reported outcome measures in upcoming treatment trials and treatment monitoring. These measures need to demonstrate sensitivity to capture change, in particular in the early stages of the disease.
Objective: Our aim is to unravel gait measures sensitive to longitudinal change in the—particularly trial-relevant—early stage of spinocerebellar ataxia type 2 (SCA2).
Methods: We performed a multicenter longitudinal study with combined cross-sectional and 1-year interval longitudinal analysis in early-stage SCA2 participants ($n = 23$, including nine pre-ataxic expansion carriers; median, *ATXN2* CAG repeat expansion 38 ± 2; median, Scale for the Assessment and Rating of Ataxia [SARA] score 4.8 ± 4.3). Gait was assessed using three wearable motion sensors during a 2-minute walk, with analyses focused on gait measures of spatio-temporal variability that have shown sensitivity to ataxia severity (eg, lateral step deviation).
Results: We found significant changes for gait measures between baseline and 1-year follow-up with large effect sizes (lateral step deviation $P = 0.0001$, effect size $r_{prb} = 0.78$), whereas the SARA score showed no change ($P = 0.67$). Sample size estimation indicates a required cohort size of $n = 43$ to detect a 50% reduction in natural progression. Test–retest reliability and minimal detectable change analysis confirm the accuracy of detecting 50% of the identified 1-year change.
Conclusions: Gait measures assessed by wearable sensors can capture natural progression in early-stage SCA2 within just 1 year—in contrast to a clinical ataxia outcome. Lateral step deviation represents a promising outcome measure for upcoming multicenter interventional trials, particularly in the early stages of cerebellar ataxia.

Key Words: gait; spinocerebellar ataxia; SCA2; motor performance measure; longitudinal analysis

***Correspondence to:** Dr. W. Ilg, Section Computational Sensomotorics, Hertie Institute for Clinical Brain Research, University of Tübingen, Otfried-Müller-Straße 25, 72076, Tübingen, Germany; E-mail: winfried.ilg@uni-tuebingen.de Dr. G. Coarelli, Institut du Cerveau/Paris Brain Institute—ICM, Hôpital de la Pitié-Salpêtrière, CRMR Neurogénétique, Sorbonne Université UM75– Inserm U 1127—CNRS UMR 7225, 47 Boulevard de l'Hôpital, CS21414, 75646, Paris, France; E-mail: giulia.coarelli@icm-institute.org

There exists a pre-publication of this manuscript on medRxiv: doi 10.1101/2023.10.08.23296692.

Relevant conflicts of interest/financial disclosures: J.S., L.D., M.C., J.L., M.L.W., A.G., and G.C. report no disclosures. A.D. serves as an advisor to Critical Path Ataxia Therapeutics Consortium; her institution (Paris Brain institute) receives her consulting fees from Pfizer, Huntix, UCB, Reata, PTC Therapeutics as well as research grants from the National Institutes of Health, Biogen, Servier, and the National Clinical Research Program; and she holds partly a Patent B 06291873.5 on "Anaplerotic Therapy of Huntington's disease and other polyglutamine diseases" (2006). M.S. has received consultancy honoraria from Ionis, UCB, Prevail, Orphazyme, Servier, Reata, GenOrph, AviadoBio, Biohaven, Zevra, and Lilly, all unrelated to the present manuscript. W.I. received consultancy honoraria by Ionis Pharmaceuticals, unrelated to the present work.
Funding agencies: BIOGEN and IONIS funded and INSERM sponsored the NCT04288128 study (to A.D.).

Received: 12 October 2023; **Revised:** 29 January 2024; **Accepted:** 2 February 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29757

Introduction

With disease-modifying drugs on the horizon for degenerative ataxias,[1-4] sensitive performance measures are highly warranted. Gait disturbance often presents as a first sign of cerebellar ataxia[5-7] and is one of the most patient-reported disabling features throughout the disease course;[8-10] therefore, suggesting a high potential for gait performance measures as both progression and response markers in upcoming treatment trials.[3]

To date, gait measures, including step variability, have demonstrated their sensitivity to ataxia severity mostly in cross-sectional studies of degenerative cerebellar diseases (see reviews in Ilg et al, Milne et al, and Buckley et al),[6,11-13] including also specifically spinocerebellar ataxia type 2 (SCA2).[14,15] However, correlations with clinical scores could be strongly influenced by the range of disease severity.[16] In cohorts spanning a wide range of disease stages, many gait measures—including non-specific ones such as speed—show correlations with disease severity that are often predominantly driven by subjects at both ends of the disease severity spectrum.[16] Notably, in interventional trials, the aim of assessing motor performance measures is qualitatively different: namely to quantify individual change over short trial-like time frames (eg, 1 year)—and here, often only in a rather specific disease severity stratum.

Therefore, to serve as valid outcome measure for capturing change—whether natural history or treatment response change—gait measures need to demonstrate their sensitivity to individual longitudinal change over those time frames and in those disease severity strata that are relevant for interventional trials.[3,17] Here, we present longitudinal gait data from a multicenter SCA2 cohort collected using wearable sensors in a trial-relevant time frame and disease severity stratum. Specifically, we show that digital measures of motor performance allow to capture longitudinal changes within 1-year in an early-stage SCA2 population where clinical ataxia scores failed to show sensitivity to change.

Methods

Patients

SCA2 individuals were recruited from the French National Reference Center for Rare Diseases "Neurogenetics" in Paris, Pitié-Salpêtrière Hospital (n = 15, assessed 2020–2022) and from the Ataxia Clinic of the University Hospital Tübingen (n = 8, assessed 2020–2022). Individuals were included based on the following inclusion criteria: (1) presence of a CAG repeat in the *AXTN2* gene ≥32; (2) age: 18 to 75 years; (3) Scale for the Assessment and Rating of Ataxia (SARA) score ≤15; and (4) able to walk without walking aids. The exclusion criteria were: severe visual or hearing impairment, cognitive impairment (assessed as per clinician global impression as standard part of the Inventory of Non-Ataxia Signs [INAS], in particular with respect to limiting the understanding of instructions or execution of the gait task),[18] or orthopedic limitations (eg, severe arthrosis, severe lumbar sciatica, or previous lower limb fractures or hip/knee replacements) that functionally affect gait, especially in the longitudinal analysis.

The study population comprised of 14 participants at the ataxic stage as defined by a SARA[19] score of ≥3 (subgroup $SCA2_{ATX}$), and nine subjects in the pre-ataxic stage (SARA score <3)[19] (subgroup $SCA2_{PRE}$). Subject descriptions are given in Table 1.

Estimated time from onset was defined as the difference between current age and estimated age at onset,[20] with estimated disease onset calculated based on the individual's CAG repeats, as described in Tezenas du Montcel et al.[21] Negative values denote estimated disease onset in the future, positive values denote estimated disease onset in the past. Neurological signs other than ataxia were assessed by the INAS.[18]

Healthy controls (HC) (n = 33) consisted of expansion-negative first-degree relatives of SCA2 carriers and unrelated healthy individuals, all without signs of neurodegenerative disease on clinical examination. SARA assessments were performed by expert neurologists (Paris, G.C.; Tübingen, M.S.).

The study was approved by the local institutional review boards of both participating centers (NCT042 88128, IRCB 2018-A02563-52, CPP 19081-60311 for Paris and 598/2011BO1 for Tübingen). Written informed consent was obtained from all study participants before enrolment.

Gait Assessment

Participants performed a 2-minute walk test on quiet, non-public indoor floors in institutional settings by walking back and forth across lines on the floor that were 20 m apart. Participants were instructed to walk at a comfortable and natural pace. Three Opal inertial sensors (APDM, Portland, OR) were attached to both feet, and the posterior trunk at the level of L5 using elastic Velcro straps. Inertial sensor data were collected and wirelessly streamed to a laptop for automatic generation of gait and balance metrics using Mobility Lab software (APDM). Stride events, as well as spatiotemporal gait parameters from the motion sensors, were extracted using APDM's Mobility Lab software (Version 2),[22] which has been shown to provide good-to-excellent accuracy and repeatability.[23,24] For each detected stride, the following features were extracted:

TABLE 1 *Subject characteristics*

	Subjects	Age	Gender	SARA	$SARA_{p\&g}$	CAG	T2EDO
$SCA2_{PRE}$	PRE 1	x	f	2	1	x	3
	PRE 2	x	f	0.5	0	x	−15
	PRE 3	x	f	1.5	0	x	−18.6
	PRE 4	x	m	0	0	x	−5.8
	PRE 5	x	f	1.5	1	x	0.3
	PRE 6	x	m	0	0	x	−18.1
	PRE 7	x	m	1	1	x	17.7
	PRE 8	x	m	0	0	x	−15.3
	PRE 9	x	m	1	0	x	−8.2
$SCA2_{ATX}$							
	ATX 1	35	m	5	1	38	−4
	ATX 2	39	m	7	1	38	0
	ATX 3	59	f	13	5	37	15.4
	ATX 4	28	m	13.5	6	42	3
	ATX 5	64	m	5.5	1	35	10.4
	ATX 6	39	f	7.5	2	39	3.7
	ATX 7	43	m	12	2	38	3.8
	ATX 8	37	f	3.5	1	39	1.7
	ATX 9	41	m	10	2	39	5.7
	ATX 10	44	m	9.5	1	39	8.7
	ATX 11	44	m	4	1	37	0.5
	ATX 12	37	f	4	1	39	1.7
	ATX 13	54	m	5.5	1	38	14.9
	ATX 14	48	m	3.5	1	38	8.88
Baseline assessment	Group						
	HC	42 ± 12.4	15f/18 m	0.15 ± 0.48	0 ± 0	–	–
	$SCA2_{PRE}$	37.9 ± 14.7	4f/5 m	0.83 ± 0.75	0. 3 ± 0.5	36.2 ± 2.2	−6.6 ± 12
	$SCA2_{ATX}$	43.7 ± 9.8	4f/10 m	7.4 ± 3.6	1.85 ± 1.6	38.3 ± 1.5	5.3 ± 5.6
	SCA2	41.4 ± 12	8f/15 m	4.8 ± 4.3	1.26 ± 1.48	37.5 ± 2.0	0.6 ± 10.4

Note: Clinical ataxia severity was determined by the SARA.[19] The $SARA_{p\&g}$ subscore is defined by the first three items of the SARA score, which capture gait, standing and sitting.[64] Positive T2EDO values denotes that estimated onset has already happened in the past. Negative T2EDO values describe estimated onsets in the future. At the bottom of the table, the average values for the different groups in the baseline assessment are provided. For pre-ataxic subjects we provided no individual age and CAG-repeats (x), because this would facilitate an individual identification of pre-ataxic mutation carriers.

Abbreviations: $SCA2_{PRE}$, pre-ataxic subjects; SARA, Scale for the Assessment and Rating of Ataxia; $SARA_{p\&g}$, $SARA_{posture\&gait}$; CAG, number of CAG repeat expansions for SCA2 subjects; PRE, pre-ataxia; T2EDO, genetically estimated timespan to disease onset for SCA2 subjects (in years, calculated according to Tezenas du Montcel et al);[21] f, female; m, male; $SCA2_{ATX}$, ataxia subjects; ATX, ataxia; HC, healthy controls; SCA2, comprising pre-ataxic and ataxic subjects.

stride length, stride time, lateral step deviation, and foot angles at initial contact. Turning movements and one stride before and after the turns were excluded from the analysis.

From the rich source of possible gait measures, we adopted a hypothesis-driven approach here, selecting only those measures that were considered promising candidate features based on previous studies.

Stride Length and Stride Time Variability

Measures of spatiotemporal gait variability, such as step length/stride length and step time/stride time variability, have been shown in several cross-sectional studies[15,25-29] and a longitudinal study in SCA3[30] to be sensitive to ataxia-related gait changes and to be associated with an increased risk of falls.[31] Variability

measures were calculated using the coefficient of variation (CV) = σ/μ, with the standard deviation normalized to the mean.[32] On this basis, stride length CV ($StrideL_{CV}$) and stride time CV ($StrideT_{CV}$) were determined.

Lateral Step Deviation

In a previous cross-sectional study examining ataxic gait characteristics in laboratory as well as in real-life assessments,[33] we identified lateral step deviation (LatStepDev) and a composite measure of spatial step variability (SPcmp) (combining $StrideL_{CV}$ and LatStepDev), as most sensitive to ataxia severity.[33,34] In addition, LatStepDev has recently been shown to be sensitive to short-term therapy-induced improvements in SCA27B.[35] LatStepDev was determined based on three consecutive steps by calculating the absolute perpendicular deviation of the midfoot position from the line connecting the first and the third step[33,34] (see Supplementary Fig. S3-1 in Supplement S3). A two-strides sliding window was used over all strides to be analyzed and all absolute values are averaged over both legs.

Toe-out Angle Variability

Motivated by Shah et al,[15] we examined an additional feature of variability, namely toe-out $angle_{SD}$. The variability (standard deviation) of Toe-out angle was determined as the lateral angle of the foot during the stance phase, relative to the forward motion of the gait cycle.[34] Increased toe-out angle has been shown to be associated with increased stride width, and variability in stride width is associated with dynamic postural instability.[15] We also included gait speed as a general indicator of functional mobility.

Statistics

Differences between groups were determined using the non-parametric Kruskal-Wallis test, with post-hoc analysis using the Mann-Whitney *U* test. Effect sizes were determined using Cliff's δ.[36] For longitudinal analyses, repeated measures analyses were performed using the non-parametric Friedman test to determine within-group differences between assessments, with post-hoc analysis using a Wilcoxon signed-rank test for pairwise comparisons. Effect sizes for repeated measures were determined by matched-pairs rank biserial correlation.[37] We report three levels of significance: (1) uncorrected $*P < 0.05$; (2) Bonferroni-corrected for multiple comparisons $**P < 0.05/n$ with n = 6: number of gait features analyzed; and (3) $***P < 0.001$. Spearman's ρ was used to examine the correlation between gait measures and SARA scores. Statistical analysis was performed using MATLAB (version R2020B, The MathWorks, Natick, MA). Based on the effect size of longitudinal change, a sample size estimation was performed using G*power 3.1[38] to determine the required cohort size for different levels of reduction of natural progression by a hypothetical intervention. Test–retest reliability of gait measures was calculated using intraclass correlation coefficient (ICC) (2, 1)[39,40] and calculating the split-half reliability (dividing the walking task into two 1 minute segments). ICC values <0.5, between 0.5 and 0.75, between 0.75 and 0.9, and >0.90 were considered as poor, moderate, good, and excellent reliability, respectively.[39] The ICC is used to determine the minimal detectable change (MDC), which is critical in determining whether a treatment-related slowing of disease progression can be reliably detected or is lost in the measurement noise.[41,42]

$$MDC_{90} = 1.65 \times SD_{baseline} \times \left(\sqrt{2}[1 - ICC]\right)$$

With 1.65 is the z-score of 90% level of confidence.

Results

The mean age at baseline assessment was 41.4 ± 12 years [21–66] ($SCA2_{ATX}$: 43.7 ± 9.8 years [28–66]), the mean SARA score was 4.8 ± 6.75 [0–13.5] ($SCA2_{ATX}$: 7.4 ± 3.6 [3.5–13.5]) (Tables 2 and 3). In addition, the entire SCA2 population present a mean CAG repeat size of 37.5 ± 2 [32–42], ($SCA2_{ATX}$: 38.3 ± 1.5 [35–42]) and a mean estimated time from onset of 0.6 ± 10 years ($SCA2_{ATX}$: 5.3 ± 5.6 years). SARA score was correlated with CAG repeat size ($r = 0.53$, $P = 0.0088*$) and estimated time from onset ($r = 0.61$, $P = 0.0019**$) (Tables 2 and 3). Results of the INAS score for all individual SCA2 subjects at baseline and follow-up can be found in Supplement S1 (Table S1-2, S1-3).

Cross-Sectional Analysis of Gait Measures Capturing Ataxia Severity

Cross-sectional analysis revealed group differences between SCA2 versus HC in all gait measures examined except gait speed (eg, LatStepDev: $P = 0.01*$, $\delta = 0.4$; SPcmp: $P = 0.02*$, $\delta = 0.35$; $StrideT_{CV}$: $P = 0.008**$, $\delta = 0.42$) (Table 2). As expected, effect sizes of the group differences became larger for the subpopulation $SCA2_{ATX}$ versus HC when the pre-ataxic SCA2 mutation carriers were excluded (LatStepDev: $\delta = 0.67$; SPcmp: $\delta = 0.61$; $StrideT_{CV}$: $\delta = 0.67$; see Table 3). No group differences were found between pre-ataxic SCA2 mutation carriers ($SCA2_{PRE}$) and HC for any of the gait parameters ($P > 0.35$).

Concurrent validity was confirmed for all the ataxia-specific gait measures showing highly significant correlations with the SARA score (eg, LatStepDev: $P < 0.0001***$, $r = 0.74$; SPcmp: $P = 0.00011***$, $r = 0.72$; $StrideT_{CV}$: $P < 0.0001***$, $r = 0.82$) (Fig. 1 and Table 2). For these analyses, the effect sizes of the

correlations became smaller (but still remained significant) for the subpopulation $SCA2_{ATX}$, because of the smaller range of ataxia severity (Table 3). In addition, gait measures showed correlations to CAG repeat size (LatStepDev: $r = 0.44$, $P = 0.035$*; $StrideT_{CV}$: $r = 0.65$, $P = 0.0007$**) and estimated time from onset (LatStepDev: $r = 0.44$, $P = 0.037$*; $StrideT_{CV}$: $r = 0.58$, $P = 0.0041$**).

Sensitivity of Gait Measures to Longitudinal Change at 1 Year

We next analyzed the ability of gait measures to detect longitudinal changes at a 1-year follow-up assessment (time interval: 373 ± 22 days; follow-up data available for all 23 SCA2 participants). Although ataxia measured by SARA failed to detect longitudinal change ($P = 0.67$, effect size $r_{prb} = 0.05$) (Table 2), paired statistics revealed differences between baseline and follow-up for the gait measures LatStepDev ($P = 0.001$**, $r_{prb} = 0.78$) and SPcmp ($P = 0.03$*, $r_{prb} = 0.5$) (Table 2, Fig. 2A). Descriptive statistics for the subgroup $SCA2_{PRE}$ (n = 9) can be found in Supplementary S2.

Given the largest effect size, LatStepDev was selected for sample size calculation. To detect a 50% reduction in natural progression with a hypothetical intervention (80% power and two-sided 5% type I error), n = 43 subjects would be required using the LatStepDev as the primary outcome measure (Fig. 2B). Subgroup analyses revealed a comparable effect size on the longitudinal change for the ataxic subgroup $SCA2_{ATX}$ (LatStepDev, $r_{prb} = 0.771$) (Table 3), resulting in a reduced estimated sample size of n = 37 because of slightly better test–retest reliability (Fig. 2B). Test–retest reliability and MDC analysis confirm the accuracy of detecting a 50% reduction in identified 1-year change (Table 2).

In contrast, it was not possible to calculate a sample size estimate for the SARA score because it did not show a 1-year change. For comparison, we have included in Fig. 2B the estimated sample sizes based on the SARA of recent studies (n = 97, red cross; Diallo et al[43]) and (n = 98, black cross; Moulaire et al[44]), which were reported for SCA2 populations with more advanced disease stages (eg, median, 10.5 SARA points in Moulaire et al[44]) (Fig. 2).

Discussion

Gait disturbance often presents as the first sign of cerebellar ataxia[5,6] and is one of the most disabling patient-relevant feature throughout the disease course,[8-10] suggesting a high potential as a marker for capturing change—whether related to disease

TABLE 2 *Results of cross-sectional and longitudinal analyses for the SCA2 population*

SCA2	Baseline m ± sd	HC vs SCA2		Corr SARA		ICC	MDC_{90}	1-year follow-up		
		P	δ	r	*P*			m ± sd	*P*	r_{prb}
Age at examination	41.4 ± 12	0.98	0.005	0.26	0.24	–	–	–	–	–
Estimated time from onset	0.6 ± 10.4	–	–	0.61	0.0019**	–	–	–	–	–
SARA	4.8 ± 4.3	<0.001**	0.82	–	–	–	–	4.85 ± 4.63	0.67	0.05
$SARA_{p\&g}$	1.26 ± 1.48	<0.001**	0.69	–	–	–	–	1.43 ± 1.8	0.35	0.22
Speed	1.33 ± 0.15	0.57	0.09	0.07	0.73	0.97	0.008	1.36 ± 0.18	0.28	0.25
$StrideL_{CV}$	0.017 ± 0.006	0.01*	0.38	0.66	0.00062**	0.9	0.001	0.02 ± 0.008	0.6	0.12
$StrideT_{CV}$	0.013 ± 0.004	0.008**	0.42	0.82	<0.0001**	0.78	0.002	0.014 ± 0.009	0.12	0.37
LatStepDev	3.55 ± 1.25	0.01*	0.4	0.74	<0.0001**	0.899	0.254	4.02 ± 1.39	0.001**	0.78
SPcmp	0.456 ± 0.29	0.02*	0.35	0.72	0.00011**	0.911	0.06	0.65 ± 0.7	0.03*	0.50
$Toe\text{-}out\ angle_{SD}$	1.62 ± 0.54	0.04**	0.32	0.75	<0.0001**	0.4	0.75	1.72 ± 0.66	0.42	0.18

Note: Cross-sectional analyses: Between-group differences in HC and SCA2 participants for clinical and gait measures. Stars indicate significant between-group differences (* ≡ $P < 0.05$, ** ≡ $P < 0.0083$ Bonferroni-corrected, *** ≡ $P < 0.001$). δ indicates the effect size as determined by Cliff's δ. Correlations between gait measures and clinical ataxia severity (SARA total score, $SARA_{p\&g}$ subscore) are shown for the SCA2 group. The three items of the SARA assessing gait and posture (gait, stance, sitting) were grouped into the $SARA_{p\&g}$ subscore.[64,65] Effect sizes of correlations are reported using Spearman's ρ. Longitudinal analyses of 1-year follow-up assessments: paired statistics for within-subject comparisons of clinical scores and gait measures for the two walking conditions (*P*-values, Wilcoxon signed-rank test; effect sizes r_{prb} determined by matched pairs rank biserial correlation).[37] Analyses are shown for the group of SCA2 subjects at baseline ($SCA2^{BL}$) and 1-year follow-up ($SCA2^{FU}$). Estimated time from onset was defined as the difference between present age and estimated age at onset,[20] with estimated disease onset calculated based on the individual's CAG repeats, as described in Tezenas du Montcel et al.[21]
Abbreviations: SCA2, spinocerebellar ataxia type 2; HC, healthy controls; ICC, intraclass correlation coefficient; MDC, minimal detectable change; m, mean; sd, standard deviation; SARA, Scale for the Assessment and Rating of Ataxia; $SARA_{p\&g}$, $SARA_{posture\&gait}$; $StrideL_{CV}$, stride length coefficient of variation; $StrideT_{CV}$, stride time coefficient of variation LatStepDev, lateral step deviation; Corr SARA, Spearman correlations between gait measures and the SARA score; SPcmp, composite measure of spatial step variability.

TABLE 3 *Results of cross-sectional and longitudinal analyses for the $SCA2_{ATX}$ population*

$SCA2_{ATX}$	Baseline m ± sd	HC vs SCA2		Corr SARA				1-year follow-up		
		P	δ	r	*P*	ICC	MDC_{90}	m ± sd	*P*	r_{prb}
Age at examination	43.7 ± 9.8	0.51	0.1	0.01	0.96	–	–	–	–	–
Estimated time from onset	5.3 ± 5.6	–	–	0.31	0.29	–	–	–	–	–
SARA	7.4 ± 3.6	<0.001**	0.98	–	–	–	–	7.39 ± 4.21	0.83	0.05
$SARA_{p\&g}$	1.85 ± 1.6	<0.001**	0.93	–	–	–	–	2.21 ± 1.9	0.188	0.44
Speed	1.34 ± 0.157	0.93	0.02	0.02	0.95	0.97	0.01	1.35 ± 0.2	0.9	0.04
$StrideL_{CV}$	0.019 ± 0.006	0.005**	0.53	0.68	0.0078**	0.9	0.001	0.021 ± 0.01	0.67	0.143
$StrideT_{CV}$	0.015 ± 0.004	0.0003**	0.67	0.62	0.019*	0.783	0.002	0.0175 ± 0.01	0.29	0.33
LatStepDev	4.13 ± 1.15	0.00036**	0.67	0.58	0.031*	0.904	0.259	4.59 ± 1.33	0.008**	0.771
SPcmp	0.587 ± 0.3	0.001**	0.61	0.57	0.033*	0.91	0.06	0.813 ± 0.6	0.21	0.39
Toe-out $angle_{SD}$	1.87 ± 0.5	0.0005**	0.65	0.59	0.027*	0.42	0.69	1.91 ± 0.64	0.76	0.1

Note: Cross-sectional analyses: Differences between groups of HC and SCA2 subjects for clinical and gait measures. Stars indicate significant between-group differences (* ≡ $P < 0.05$, ** ≡ $P < 0.0083$ Bonferroni corrected, *** ≡ $P < 0.001$). δ indicates the effect size as determined by Cliff's δ. Correlations between gait measures and clinical ataxia severity (SARA total score, $SARA_{p\&g}$ subscore) are given for the SCA2 group. The three items of the SARA assessing gait and posture (gait, stance, sitting) were grouped into the $SARA_{p\&g}$ subscore.[64,65] Effect sizes of correlations are reported using Spearman's ρ. Longitudinal analyses of 1-year follow-up assessments: Paired statistics for within-subject comparisons of clinical scores and gait measures for the two walking conditions (*P*-values, Wilcoxon signed-rank test; effect sizes r_{prb} determined by matched pairs rank biserial correlation[37]). Shown are analyses for the group of SCA2 subjects at baseline $SCA2^{BL}_{ATX}$ and 1-year follow-up $SCA2^{FU}_{ATX}$. Estimated time from onset was defined as the difference between present age and estimated age at onset,[20] with estimated disease onset calculated based on the individual's CAG repeats, as described in Tezenas du Montcel et al.[21]
Abbreviations: SCA2, spinocerebellar ataxia type 2; $SCA2_{ATX}$, SCA2 ataxia; HC, healthy controls; ICC, intraclass correlation coefficient; MDC, minimal detectable change; m, mean; sd, standard deviation; SARA, Scale for the Assessment and Rating of Ataxia; $SARA_{p\&g}$, $SARA_{posture\&gait}$; $StrideL_{CV}$, stride length coefficient of variation; $StrideT_{CV}$, stride time coefficient of variation LatStepDev, lateral step deviation; Corr SARA, Spearman correlations between gait measures and the SARA score; SPcmp, composite measure of spatial step variability (SPcmp).

progression or treatment response—in upcoming treatment trials.[1,2,4,45]

This study aimed to test the sensitivity of gait measures to detect ataxia-related longitudinal changes in a trial-relevant time frame (1 year) and disease severity stratum (early stage) in a SCA2 population in a multicenter setting. Analyses showed that gait measures (1) correlate with cross-sectional clinical ataxia severity, indicating a valid capture of clinical ataxia dysfunction; and in particular (2) capture longitudinal change between baseline and 1-year follow-up with high effect sizes, substantially outperforming the currently most widely used clinical ataxia scale.

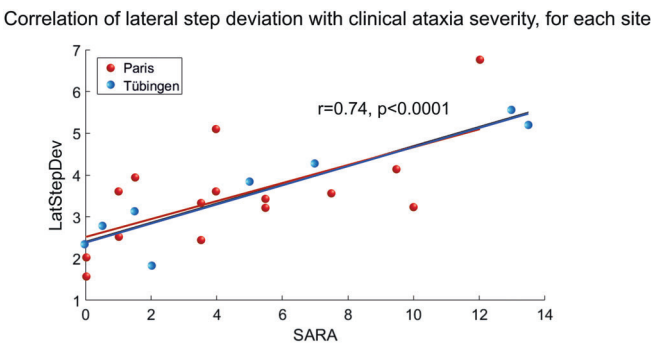

FIG. 1. Relationship between the gait measure LatStepDev and the SARA score separately color coded for participants from both sites, Paris (red) and Tübingen (blue). The lines represent linear fits of the data for each site. Participants from both centers together show a close relationship between LatStepDev and SARA ($r = 0.74$, $P < 0.0001$)***. LatStepDev, lateral step deviation; SARA, Scale for the Assessment and Rating of Ataxia. [Color figure can be viewed at wileyonlinelibrary.com]

Gait Measures Are Sensitive to Cross-Sectional Ataxia Severity

Our analysis of gait variability measures confirmed the cross-sectional results of previous studies (reviews in Ilg et al,[6] Milne et al,[11] and Buckley et al[13]), including those on SCA2,[14,15] which showed (1) a significant difference between HC and ataxia patients; and (2) a high correlation with ataxia severity as measured by the SARA score (Tables 2 and 3).

Importantly, our results validate these findings in a multicenter setting and in an early-stage SCA2 cohort (SARA score: mean, 4.7 points), suggesting their applicability to early disease stages of SCA, which presents the disease severity stratum targeted by upcoming interventional trials.[3,4,46]

At the same time, our cross-sectional results illustrate the impact of ataxia severity even within the early-stage study population. When distinguishing between SCA2 patients and healthy subjects, the $SCA2_{ATX}$ subpopulation increased the effect size compared to the overall

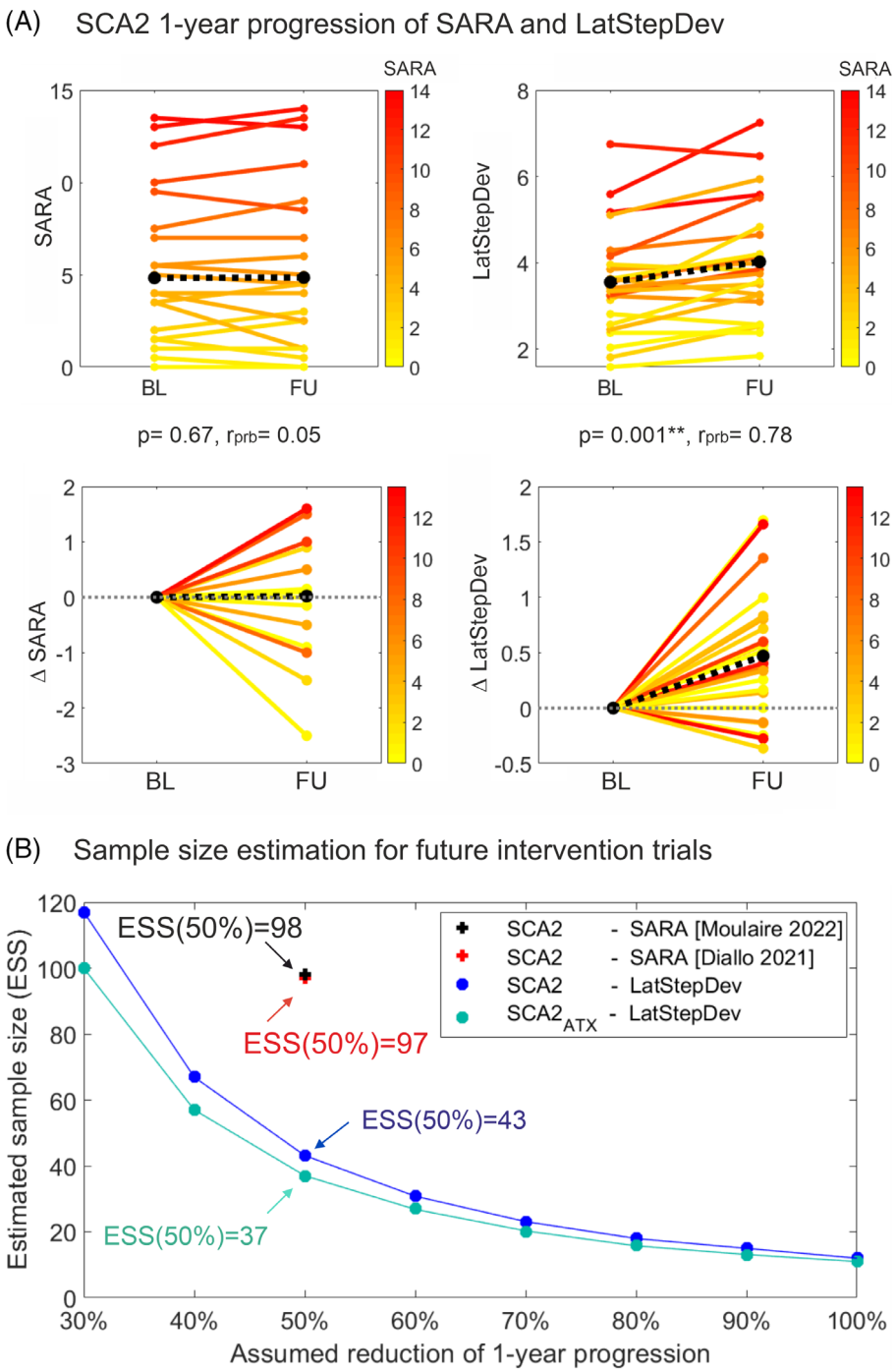

FIG. 2. (**A**) Longitudinal analyses of the 1-year follow-up assessments: within-subject changes between baseline and 1-year follow-up for the group of SCA2 subjects. Upper panel: Within-subject changes in SARA score and the gait measure LatStepDev at baseline (BL) and 1-year follow-up (FU). Lower panel: Within-subject changes between baseline and 1-year follow-up, expressed as Δ. In all panels, SARA scores of individual cerebellar subjects are color coded. Black dotted line = mean change across all subjects. Stars indicate significant differences between time points (* ≡ $P < 0.05$, ** ≡ $P < 0.0083$ Bonferroni corrected, *** ≡ $P < 0.001$). Effect sizes r_{prb} were determined by matched-pairs rank biserial correlation. (**B**) Sample size estimates were performed for future intervention trials showing different levels of progression reduction for the gait measure LatStepDev for both the entire SCA2 population and the subpopulation $SCA2_{ATX}$. The estimated number of subjects per study arm is plotted against the hypothesized therapeutic effect for reducing the 1-year progression in SCA2 subjects. Concrete numbers of sample sizes are given to detect a 50% reduction in natural history progression with a hypothetical intervention (80% power and two-sided 5% type I error). For comparison, sample sizes of n = 97 (Diallo et al,[43] red cross), and n = 98 (Moulaire et al,[44] black cross) have recently been reported. SCA2, spinocerebellar ataxia type 2; SARA, Scale for the Assessment and Rating of Ataxia; LatStepDev, lateral step deviation. [Color figure can be viewed at wileyonlinelibrary.com]

population SCA2, as pre-ataxic participants SCA2 showed less change in gait measures compared to healthy subjects (Tables 2 and 3).

In contrast, the overall SCA2 population shows a larger effect size (compared to $SCA2_{ATX}$) in the correlation of gait measures with the severity of ataxia as measured by the SARA score, because of the wider range of disease stages (namely, including the pre-ataxic stage) (Tables 2 and 3).

Gait Measures, Not SARA Score, Capture Longitudinal Change within 1 Year

In addition to the concurrent validity shown by the correlation with the SARA score, it is crucial for future interventional studies that sensitivity to change is demonstrated by quantifying individual changes in short, trial-like time frames. To date, very few longitudinal gait studies have been conducted in cerebellar ataxia,[30,47-49] most of them monocentric with heterogeneous populations and gait assessment approaches that are not easily transferable to international multicenter trials. Wearable inertial measurement units (IMUs) sensor technology for gait quantification has recently become feasible and reliable for large, multicenter clinical trials without sophisticated gait laboratories or expert researchers, making IMUs easy to use in clinical settings.[17]

Here, we now show in a multicenter setting using wearable motion sensors that the gait measure LatStepDev can quantify these longitudinal changes within a 1-year duration in an early-stage SCA2 population (SARA, 4.87 ± 4.28; including nine pre-ataxic mutation carriers).

In contrast, we did not observe a 1-year longitudinal change in the SARA score in either the entire SCA2 population or the subpopulation $SCA2_{ATX}$. Previous studies in SCA2 that found a longitudinal change in SARA score[43,44,50] were performed with more advanced disease stages (eg, mean SARA ≥10). These differences can be explained by previous results,[51] reporting an annual Δ in SARA of 2.45 points in SCA2 for patients with a disease duration of more than 10 years, but only an average progression of 0.35 SARA points for patients with a disease duration of <10 years. This finding again highlights the need to analyze the performance metrics of outcome measures (eg, clinical, digital-motor) in a disease stage-specific fashion.

Sample Size Estimates for Future Trials and MDC

For future disease-modifying drug trials in SCA, the primary goal will be to slow disease progression in a limited trial period, ideally within 1 year.[3,4,45] To demonstrate a 50% reduction in natural history with a hypothetical intervention using LatDevStep as the primary outcome measure, $n = 43$ subjects would be required for an early SCA2 population including pre-ataxic mutation carriers, and $n = 37$ for an ataxic SCA2 population including only ataxic mutation carriers. MDC analysis confirms the accuracy of detecting a 50% reduction in identified 1-year changes (Table 2).

In summary, the large effect sizes and good reliability of this digital-motor measure also in multicenter settings allow for substantially reduced sample size estimates compared to the SARA for the detection of reduced disease progression within 1 year (Fig. 2). This reduction in sample size could be decisive for the feasibility of a treatment trial: although trials with, for example, 100 SCA2 subjects per trial arm (as required for SARA as outcome) are almost impossible, 37 SCA2 subjects (as required for the gait performance measure LatStepDev in $SCA2_{ATX}$) are well feasible.

Meaningfulness and Ecological Validity

To properly evaluate treatment effects in both clinical trials and individual patient treatment settings, it is crucial to identify outcome measures that can detect meaningful changes for patients.[52,53] Gait assessment can provide meaningful outcome measures for evaluating treatment interventions, as cerebellar ataxia patients report gait and functional mobility impairments as having the greatest impact on their daily lives.[8-10] Although longitudinal studies relating differences in gait measures to patient-reported outcomes are still lacking, we have shown in Ilg et al[33] that the gait performance measure LatStepDev is highly correlated with the patient-reported subjective balance confidence (ABC score).[54] In particular, LatStepDev has been shown to capture ataxia-related gait impairments in real-life walking behavior, the latter being particularly important for demonstrating ecological relevance.[33,55,56] In addition, LatStepDev has recently been shown to be sensitive to short-term therapy-induced improvements in SCA27B[35] in correspondence with a change in a key patient-reported outcome (Patient Global Impression).[53]

Study Limitations

Our findings are limited by the relatively small cohort size. In particular, our study cohort was not sufficiently powered for detecting longitudinal change within the pre-ataxic group only. Therefore, larger future studies, including a larger number of pre-ataxic subjects, are needed to further validate the promises of gait measures and relate longitudinal changes in gait to patient-centered outcomes and patient-meaningful aspects of health[53,57,58] as well as to corresponding changes in molecular (such as blood neurofilament light chain)[59,60] and imaging biomarkers.[61]

Conclusion

Our study demonstrates that digital gait measures allow capturing natural history progression change of SCA2 within 1 year, with effect sizes exceeding the main clinical rating scale (SARA), which is still the most widely established outcome measure in this field. The proposed gait measures can be reliably captured by wearable motion sensors in multicenter studies including centers without sophisticated motion laboratories and expert researchers. In particular, the digital gait measure LatStepDev represents a promising performance outcome for future SCA intervention trials, particularly in the early stages of the disease, which are also more representative of the disease strata that will be enrolled in future trials than the advanced stages of the disease.[4,46,62,63]

Acknowledgments: This work was supported by the International Max Planck Research School for Intelligent Systems (to J.S.) and the Else Kröner-Fresenius-Stiftung Medical Scientist programme "ClinbrAIn" (to W.I.) as well as the Else Kröner-Fresenius Stiftung Clinician Scientist programme "PRECISE.net" (to M.S.). Work on this project was supported, in part, by the Deutsche Forschungsgemeinschaft (German Research Foundation) no. 441409627, as part of the PROSPAX consortium under the frame of the European Joint Programme on Rare Diseases, under the EJP RD COFUND-EJP no. 825575 (to M.S. and A.D.). Open Access funding enabled and organized by Projekt DEAL.

Data Availability Statement

Data available on request due to privacy/ethical restrictions.

References

1. Ashizawa T, Oz G, Paulson HL. Spinocerebellar ataxias: prospects and challenges for therapy development. Nat Rev Neurol 2018; 14(10):590–605.
2. Scoles DR, Pulst SM. Antisense therapies for movement disorders. Mov Disord 2019;34(8):1112–1119.
3. Klockgether T, Ashizawa T, Brais B, et al. Paving the way toward meaningful trials in ataxias: an ataxia global initiative perspective. Mov Disord 2022;37(6):1125–1130.
4. Coarelli G, Coutelier M, Durr A. Autosomal dominant cerebellar ataxias: new genes and progress towards treatments. Lancet Neurol 2023;22(8):735–749.
5. Globas C, du Montcel ST, Baliko L, et al. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. Mov Disord 2008;23(15): 2232–2238.
6. Ilg W, Branscheidt M, Butala A, et al. Consensus paper: neurophysiological assessments of ataxias in daily practice. Cerebellum 2018; 17(5):628–653.
7. Luo L, Wang J, Lo RY, et al. The initial symptom and motor progression in spinocerebellar ataxias. Cerebellum 2017;16(3):615–622.
8. Rosen A, Hagen S, Trace K, Compton A. The Voice of the Patient: Living with Polglutamine Spinocerebellar Ataxias (SCA) and Dentatorubal-Pallidoluysion Atrophy (DRPLA). Minneapolis, MN: National Ataxia Foundation; 2021. https://www.ataxia.org/ataxiapfdd/.
9. Lowit A, Greenfield J, Cutting E, Wallis R, Hadjivassiliou M. Symptom burden of people with progressive ataxia, and its wider impact on their friends and relatives: a cross-sectional study. AMRC Open Res 2023;3:28.
10. Gorcenco S, Karremo C, Puschmann A. Patients' perspective in hereditary ataxia. Cerebellum 2024;23(1):82–91.
11. Milne SC, Murphy A, Georgiou-Karistianis N, Yiu EM, Delatycki MB, Corben LA. Psychometric properties of outcome measures evaluating decline in gait in cerebellar ataxia: a systematic review. Gait Posture 2018;61:149–162.
12. Ilg W, Timmann D. Gait ataxia—specific cerebellar influences and their rehabilitation. Mov Disord 2013;28(11):1566–1575.
13. Buckley E, Mazza C, McNeill A. A systematic review of the gait characteristics associated with cerebellar ataxia. Gait Posture 2018; 60:154–163.
14. Velazquez-Perez L, Rodriguez-Labrada R, Gonzalez-Garces Y, et al. Prodromal spinocerebellar ataxia type 2 subjects have quantifiable gait and postural sway deficits. Mov Disord 2021;36(2):471–480.
15. Shah VV, Rodriguez-Labrada R, Horak FB, et al. Gait variability in spinocerebellar ataxia assessed using wearable inertial sensors. Mov Disord 2021;36(12):2922–2931.
16. Janse RJ, Hoekstra T, Jager KJ, et al. Conducting correlation analysis: important limitations and pitfalls. Clin Kidney J 2021;14(11): 2332–2337.
17. Byrom B, Watson C, Doll H, et al. Selection of and evidentiary considerations for wearable devices and their measurements for use in regulatory decision making: recommendations from the ePRO consortium. Value Health 2018;21(6):631–639.
18. Schmitz-Hubsch T, Coudert M, Bauer P, et al. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. Neurology 2008;71(13):982–989.
19. Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006;66(11):1717–1720.
20. Jacobi H, Reetz K, du Montcel ST, et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. Lancet Neurol 2013;12(7):650–658.
21. Tezenas du Montcel S, Durr A, Rakowicz M, et al. Prediction of the age at onset in spinocerebellar ataxia type 1, 2, 3 and 6. J Med Genet 2014;51(7):479–486.
22. Mancini M, King L, Salarian A, Holmstrom L, McNames J, Horak FB. Mobility lab to assess balance and gait with synchronized body-worn sensors. J Bioeng Biomed Sci 2011;Suppl 1:007.
23. Washabaugh EP, Kalyanaraman T, Adamczyk PG, Claflin ES, Krishnan C. Validity and repeatability of inertial measurement units for measuring gait parameters. Gait Posture 2017;55:87–93.
24. Morris R, Stuart S, McBarron G, Fino PC, Mancini M, Curtze C. Validity of mobility lab (version 2) for gait assessment in young adults, older adults and Parkinson's disease. Physiol Meas 2019; 40(9):095003.
25. Serrao M, Pierelli F, Ranavolo A, et al. Gait pattern in inherited cerebellar ataxias. Cerebellum 2012;11(1):194–211.
26. Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Speed-dependent temporospatial gait variability and long-range correlations in cerebellar ataxia. Gait Posture 2013;37(2):214–218.
27. Rochester L, Galna B, Lord S, Mhiripiri D, Eglon G, Chinnery PF. Gait impairment precedes clinical symptoms in spinocerebellar ataxia type 6. Mov Disord 2014;29(2):252–255.
28. Ilg W, Christensen A, Mueller OM, Goericke SL, Giese MA, Timmann D. Effects of cerebellar lesions on working memory interacting with motor tasks of different complexities. J Neurophysiol 2013;110(10):2337–2349.
29. Zhou H, Nguyen H, Enriquez A, et al. Assessment of gait and balance impairment in people with spinocerebellar ataxia using wearable sensors. Neurol Sci 2022;43(4):2589–2599.
30. Ilg W, Muller B, Faber J, et al. Digital gait biomarkers allow to capture 1-year longitudinal change in spinocerebellar ataxia type 3. Mov Disord 2022;37(11):2295–2301.
31. Schniepp R, Wuehr M, Schlick C, et al. Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. J Neurol 2014;261(1):213–223.
32. Winter DA. Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological. 2nd ed. Waterloo, Canada: Wiley-Interscience Publication; 1991.

33. Ilg W, Seemann J, Giese M, et al. Real-life gait assessment in degenerative cerebellar ataxia: toward ecologically valid biomarkers. Neurology 2020;95(9):e1199–e1210.
34. APDM. Whitepaper Mobility Lab; 2015. https://www.apdm.com/wp-content/uploads/2015/05/02-Mobility-Lab-Whitepaper.pdf.
35. Seemann J, Traschutz A, Ilg W, Synofzik M. 4-aminopyridine improves real-life gait performance in SCA27B on a single-subject level: a prospective n-of-1 treatment experience. J Neurol 2023;270(11):5629–5634.
36. Cliff N. Answering ordinal questions with ordinal data using ordinal statistics. Multivariate Behav Res 1996;31(3):331–350.
37. Kerby DS. The simple difference formula: an approach to teaching nonparametric correlation. Compr Psychiatry 2014;3:11.IT–13.11.
38. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009;41(4):1149–1160.
39. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15(2):155–163.
40. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420–428.
41. Mohandas Nair P, George Hornby T, Behrman L. AJTiscir. Minimal detectable change for spatial and temporal measurements of gait after incomplete spinal cord injury. Top Spinal Cord Inj Rehabil 2012;18(3):273–281.
42. Beckerman H, Roebroeck ME, Lankhorst GJ, Becher JG, Bezemer PD, Verbeek AL. Smallest real difference, a link between reproducibility and responsiveness. Qual Life Res 2001;10(7):571–578.
43. Diallo A, Jacobi H, Tezenas du Montcel S, Klockgether T. Natural history of most common spinocerebellar ataxia: a systematic review and meta-analysis. Journal of neurology 2021;268(8):2749–2756.
44. Moulaire P, Poulet PE, Petit E, et al. Temporal dynamics of the scale for the assessment and rating of ataxia in spinocerebellar ataxias. Mov Disord 2023;38(1):35–44.
45. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers 2019;5(1):24.
46. Saute JAM, Jardim LB. Planning future clinical trials for Machado-Joseph disease. In: Nóbrega C, Pereira de Almeida L, eds. Polyglutamine Disorders. Cham: Springer International Publishing; 2018:321–348.
47. Serrao M, Chini G, Casali C, et al. Progression of gait ataxia in patients with degenerative cerebellar disorders: a 4-year follow-up study. Cerebellum 2017;16(3):629–637.
48. Shirai S, Yabe I, Takahashi-Iwata I, et al. The responsiveness of triaxial accelerometer measurement of gait ataxia is higher than that of the scale for the assessment and rating of ataxia in the early stages of spinocerebellar degeneration. Cerebellum 2019;18(4):721–730.
49. Morton SM, Tseng YW, Zackowski KM, Daline JR, Bastian AJ. Longitudinal tracking of gait and balance impairments in cerebellar disease. Mov Disord 2010;25(12):1944–1952.
50. Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. Lancet Neurol 2015;14(11):1101–1108.
51. Monte TL, Reckziegel ER, Augustin MC, et al. The progression rate of spinocerebellar ataxia type 2 changes with stage of disease. Orphanet J Rare Dis 2018;13(1):20.
52. FDA. Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making. Silver Spring, MD: U.S. Food & Drug Administration (FDA); 2023. https://www.regulations.gov/docket/FDA-2023-D-0026.
53. Byrom B, Breedon P, Tulkki-Wilke R, Platko JV. Meaningful change: defining the interpretability of changes in endpoints derived from interactive and mHealth technologies in healthcare and clinical research. J Rehabil Assist Technol Eng 2020;7:2055668319892778.
54. Powell LE, Myers AM. The activities-specific balance confidence (ABC) scale. The journals of gerontology Series A, Biological sciences and medical sciences 1995;50A(1):M28–M34.
55. Cabaraux P, Agrawal SK, Cai H, et al. Consensus paper: ataxic gait. Cerebellum 2023;22(3):394–430.
56. Thierfelder A, Seemann J, John N, et al. Real-life turning movements capture subtle longitudinal and Preataxic changes in cerebellar ataxia. Mov Disord 2022;37(5):1047–1058.
57. Manta C, Patrick-Lake B, Goldsack JC. Digital measures that matter to patients: a framework to guide the selection and development of digital measures of health. Digit Biomark 2020;4(3):69–77.
58. Ilg W, Milne S, Schmitz-Hübsch T, et al. Quantitative gait and balance outcomes for ataxia trials: consensus recommendations by the ataxia global initiative working group on digital-motor biomarkers. Cerebellum 2023. https://doi.org/10.1007/s12311-023-01625-2
59. Wilke C, Haas E, Reetz K, et al. Neurofilaments in spinocerebellar ataxia type 3: blood biomarkers at the preataxic and ataxic stage in humans and mice. EMBO Mol Med 2020;12(7):e11803.
60. Coarelli G, Darios F, Petit E, et al. Plasma neurofilament light chain predicts cerebellar atrophy and clinical progression in spinocerebellar ataxia. Neurobiol Dis 2021;153:105311.
61. Faber J, Schaprian T, Berkan K, et al. Regional brain and spinal cord volume loss in spinocerebellar ataxia type 3. Mov Disord 2021;36(10):2273–2281.
62. Maas R. Preparing for disease-modification trials in degenerative cerebellar ataxias: which endpoints to choose? Mov Disord 2023;38(6):917–923.
63. Matilla-Duenas A, Ashizawa T, Brice A, et al. Consensus paper: pathological mechanisms underlying neurodegeneration in spinocerebellar ataxias. Cerebellum 2014;13(2):269–302.
64. Lawerman TF, Brandsma R, Verbeek RJ, et al. Construct validity and reliability of the SARA gait and posture sub-scale in early onset ataxia. Front Hum Neurosci 2017;11:605.
65. Ilg W, Fleszar Z, Schatton C, et al. Individual changes in preclinical spinocerebellar ataxia identified via increased motor complexity. Mov Disord 2016;31(12):1891–1900.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

SGML and CITI Use Only
DO NOT PRINT

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

W.I.: 1A, 1B, 2A, 2B, 3A.
J.S.: 1C, 2C, 3B.
M.S.: 1A, 2C, 3A.
G.C.: 1B, 1C, 3B.
A.D.: 1B, 2C, 3B.
L.D.: 1B, 1C, 3B.
M.C.: 1B, 1C, 3B.
J.C.L.: 1B, 1C, 3B.
M.L.W.: 1B, 1C, 3B.
M.G.: 1B, 1C, 3B.

Financial Disclosures

J.S., L.D., M.C., J.L., M.L.W., A.G., and G.C. report no disclosures. A.D. serves as an advisor to Critical Path Ataxia Therapeutics Consortium; her institution (Paris Brain institute) receives her consulting fees from Pfizer, Huntix, UCB, Reata, PTC Therapeutics as well as research grants from the National Institutes of Health, Biogen, Servier, and the National Clinical Research Program; and she holds partly a Patent B 06291873.5 on "Anaplerotic Therapy of Huntington's disease and other polyglutamine diseases" (2006). M.S. has received consultancy honoraria from Ionis, UCB, Prevail, Orphazyme, Servier, Reata, GenOrph, AviadoBio, Biohaven, Zevra, and Lilly, all unrelated to the present manuscript. W.I. received consultancy honoraria by Ionis Pharmaceuticals, unrelated to the present work.