nature reviews neurology
https://doi.org/10.1038/s41582-026-01218-7

Supplementary information

MRI end-points for clinical trials in ataxias: recommendations from the Ataxia Global Initiative MRI Biomarkers Working Group

In the format provided by the authors and unedited

Supplementary Box 1 | Supplementary methods

Ataxia Global Initiative MRI Biomarker Validation Checklist

Instructions

1. Based on currently available literature, identify a small set of potential biomarkers that may be sensitive to disease status (e.g., high cross-sectional correlations with disease severity & high effect sizes versus control populations) and/or disease progression (e.g., sensitivity to longitudinal change).

   This should **NOT** be a comprehensive review of all imaging literature, although a broad literature search may be necessary to identify all relevant candidate biomarkers and all supporting evidence.

   In general, for any given MR modality (i.e., structural MRI, diffusion MRI, MRS), no more than 3 markers should be considered.

2. Complete one table (template below) for each identified candidate marker for ONE disease. Provide as much quantitative information as possible (i.e., effect sizes), including data from multiple studies/publications/sources where available. Short narrative entries are allowable to clarify complex data.

   Where information is not yet available for a cell in the table, please indicate 'NA'. Do not leave cells empty.

3. For autosomal dominant diseases, please complete SEPARATE TABLES for the presymptomatic and symptomatic disease stages, where possible.

4. In the last entry table, please identify one or more potential Contexts of Use (CoU) using FDA-NIH criteria: https://www.fda.gov/drugs/biomarker-qualification-program/context-use

   As indicated in this link, a CoU statement includes both a BEST biomarker category and a potential drug development use.

   It is anticipated that most MRI biomarkers for ataxias will fall in the following BEST categories (https://www.ncbi.nlm.nih.gov/books/NBK326791/):

   - 'Response'
     - 'Pharmacodynamic' (i.e., reversible change)
     - 'Surrogate Endpoint' (i.e., non-reversible – only slowing of progression)
   - 'Prognostic'
   - 'Safety'

   For 'Response' biomarkers, specify whether the anticipated treatment effect is a "slowing of worsening" (e.g., reduced rate of brain atrophy), likely needing >1 year to detect, or a "reversal" scenario (e.g., normalization of mI levels), which might be detected relatively acutely, say weeks to a few months.

The ‘Monitoring’ biomarker should not be used, as it is an umbrella term that can include Response, Prognostic, and Safety biomarkers.

TEMPLATE: For each identified potential biomarker, generate a new table. Please include references for all empirical data (with a bibliography below the table). If no published data is available for a row, insert ‘NA’.

Entries should be empirical and using the measures described wherever possible (some measures should be derived if not reported in the paper and all required info is available – e.g., Cohen’s d). Narrative entries are permissible when quantitative data is complex or not explicitly available.

Red text in the example table below provides instructions. Black text are example entries.

MR Modality:	One of sMRI, dMRI, QSM, MRS, fMRI, etc. e.g., sMRI
Marker:	Indicate the specific outcome measure & measurement tool/method, e.g.: Smith (2020): Pons Volume, Freesurfer Jones (2020): Pons Volume, Manual Segmentation
Test-retest variability	Evidence from healthy control studies over short or long intervals (days to years); or from patient studies over short intervals (<weeks). Report: (i) within-subject standard deviation (wSD) and/or CV (wCV), and/or intra class correlation coefficient (including the specific ICC definition used), and/or other reliability measure, (ii) timeframe between testing, (iii) cohort. Smith (2020): wCV=0.62 over 1 year, healthy people 40-60 years
Cross-sectional group differences vs controls	Report group-mean averages and SD for each group, and absolute and statistical effect sizes (Cohen’s d preferred; other standard metrics acceptable, such as partial eta squared). Include mean or range of disease severity. e.g., Smith (2022): control mean (SD) = 102mL (53), patient mean (SD) = 63mL (23), d = 1.3, SARA mean = 21 Jones (2021): control mean (SD) = 97mL (41), patient mean (SD) = 59mL (36), d = 0.8, SARA mean = 14
Cross-sectional correlations with clinical scales	Report effect sizes (Pearson’s r preferred). Include range of disease severity. E.g., Smith (2022): r = 0.53 vs SARA, SARA range: 5-25
Cross-sectional correlations with PROMs	Report effect sizes (Pearson’s r preferred). Include range of PROM. E.g.,

	Smith (2022): r = 0.32 vs FARS-ADLs, ADLs range: 9-23
Longitudinal change vs controls	Report within-group mean and standard deviation of annual change from each group (absolute change/yr, % change/yr, or standardised response mean) and between-group (Cohen's d preferred) effects; study timeframe & number of timepoints; mean disease severity at baseline. E.g., Smith (2022): control mean (SD) change/yr = 8% (23%), patient mean (SD) change/yr = 76% (35%), d = 0.4, 2 year trial with 2 timepoints, baseline SARA range = 5-12
Longitudinal change in the marker vs. concurrent longitudinal change in clinical scales AND/OR PROMs?	Report correlation between marker change and disease severity change, study timeframe, and mean disease severity at baseline. E.g., Smith (2022): r = 0.4 vs SARA change over 1 year, baseline SARA mean = 12
Does the baseline value of the marker (categorical split or continuous) predict subsequent clinical change?	Report correlations between marker baseline values and subsequent longitudinal clinical change (Pearson r). Include clinical scale, follow-up timeframe, and disease severity at baseline. E.g., Smith (2022): r = 0.6 vs SARA change over 1 year, SARA baseline mean = 12
Does longitudinal rate of change depend on disease stage/severity (categorical split or continuous variable)?	Report any subgroup analyses or relevant correlations between baseline clinical scale and longitudinal marker change. As per previous. Smith (2022): Rate of SARA change was significantly greater in patients with baseline susceptibility was >100mL vs <100mL
Has the marker been used in interventional trials?	Identify the trial
Differences between treated and placebo group?	Report mean and statistical uncertainty of change in placebo group, mean and statistical uncertainty of change in treated group(s), and mean and statistical uncertainty of comparison between groups. Specify the units of change (e.g., mm3, or % change) and the metric of statistical uncertainty (e.g., 95%CI, or SD).
Proposed Context(s) of Use	See Instructions Page, e.g.: (i) Response (surrogate endpoint) biomarker for detecting slowing of neurodegeneration (ii) Prognostic biomarker for disease stratification

Citations:
[1]Smith et al, (2020), An MR biomarker study in SCAs, Journal of Research
[2]Jones et al, (2021), Another MR biomarker study in SCAs, Journal of Science

Supplementary box 2 **| Development and details of supplementary tables**

Four supplementary tables are provided, one for each of Spinocerebellar Ataxia (SCA) Type 1 (SCA1), SCA2, SCA3, and Friedreich Ataxia (FRDA). Each Table contains a detailed listing the of the data collated by the authorship group from published literature using the consensus guidelines developed by the Ataxia Global Initiative MRI Biomarkers Working Group (see paper Methods and Supplementary Methods). This is not a comprehensive catalogue of all imaging outcomes that have been published in these diseases to date. Rather, this is the full set of data that supports the selection of the most promising candidate imaging biomarkers which are described in the accompanying paper. A subset of these data is presented in Tables 1-4 in the main manuscript.

In most cases, data were extracted directly from the relevant publication, but where necessary, missing information was sought via communication with the corresponding author. Effect size measures are reported as Cohen's d (cross-sectional group comparisons) or Standardised Response Mean (SRM). Effect sizes were derived using the published data (or as provided by corresponding author) if necessary. Clinical disease severity is reported using the Scale for the Assessment and Rating of Ataxia (SARA), with conversion from ICARS or FARS when necessary according to Rummey et al.[1].

Imaging studies employing diffusion-weighted imaging (DWI) or magnetic resonance spectroscopy (MRS) typically report multiple outcome measures for each region-of-interest (ROI). For example, DWI studies commonly report fractional anisotropy (FA) and mean, axial, and radial diffusivity (MD, AD, RD). Here, we tabulate only the outcome measure with the highest cross-sectional and/or longitudinal effect size for each ROI in each study. Similarly, in cases where outcomes are reported separately for the left and right hemisphere of an ROI, the higher effect size is tabulated. In cases where outcomes are reported independently for a preataxic and an ataxic cohort, data are tabulated separately for each cohort.

Supplementary table 1 | **The most promising candidate imaging endpoints in spinocerebellar ataxia type 1**

Cross-sectional									
Region	**Measure**	**Processing**	**Effect size (d)**	**nSCA1**	**nCTRL**	**SARA (mean or median)**	**Correlation with COA?**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
Ataxic or Mixed Cohorts									
Brainstem	Volume	Semi-automated	3.8	48	31	12 (Ataxic)	Yes	Schulz, 2010, NeuroImage[2]	Table 4†
Brainstem	Volume	Semi-automated	2.5	16	20	-	Yes	Guerrini, 2004, Brain[3]	Table 1†
Brainstem	Volume	SPM-VBM	-	10	10	18 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Table 1†
Brainstem	Volume	FreeSurfer	1.6	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
Brainstem	Volume	CAT12-VBM	1.6	119	126	11 (Mixed)	Yes	Robertson, 2026, medRxiv[6]	Figure 1
Pons	Volume	Semi-automated	3.5	48	31	12 (Ataxic)	Yes	Schulz, 2010, NeuroImage[2]	Table 4†
Pons	Volume	FreeSurfer	1.5	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
Pons	Volume	FreeSurfer	2.8	28	20	13 (Ataxic)	Yes	Prooije, 2024, Ann Neurol[7]	Fig. 3, Sup Mat
Pons	Volume	CAT12-VBM	1.8	119	126	11 (Mixed)	Yes	Robertson, 2026, medRxiv[6]	Figure 1
Medulla	Volume	FreeSurfer	1.6	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
Cerebellum WM	Volume	SPM-VBM	-	10	10	18 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Table 1†
Cerebellum WM	Volume	CerebNet	4.7	12	292	12 (Ataxic)	Yes	Ferreira, 2024, Cerebellum[8]	Figure S10.2
Cerebellum WM	Volume	CAT12-VBM	2.3	119	126	11 (Mixed)	Yes	Robertson, 2026, medRxiv[6]	Figure 1
SCP	Volume	FreeSurfer	2.7	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
SCP	Volume	CAT12-VBM	1.6	119	126	11 (Mixed)	Yes	Robertson, 2026, medRxiv[6]	Figure 1
Spinal cord (C2-C3)	CSA	SpineSeg	3.3	31	31	15 (Ataxic)	Yes	Martins, 2017, Cerebellum[9]	Table 1
Spinal cord (C2)	CSA	SCT	2.0	75	70	12 (Mixed)	Yes	Rezende, 2024, JNNP[10]	Fig. 2, Sup Mat
Preataxic Cohorts									
Brainstem	Volume	FreeSurfer	1.1	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
Pons	Volume	FreeSurfer	1.1	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
Medulla	Volume	FreeSurfer	1.4	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a
SCP	Volume	FreeSurfer	1.6	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 1a

Magnetic Resonance Spectroscopy (MRS)									
Ataxic or Mixed Cohorts									
Pons	tNAA	AMARES/MRUI	1.5	16	20	- (Ataxic)	Yes	Guerrini, 2004, Brain[3]	Table 3†
Pons	tNAA/mIns	LCModel	2.6	9	15	9 (Ataxic)	-	Öz, 2011, Cerebellum[11]	Fig. 4‡
Pons	tNAA/tCr	LCModel	1.5	16	33	11 (Ataxic)	-	Adanyeguh, 2015, Mov Disord[12]	Fig. 1
Pons	tNAA/mIns	LCModel	2.6	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 3b
Pons	tNAA	LCModel	2.2	27	21	13 (Ataxic)	Yes	Prooije, 2024, Ann Neurol[7]	Suppl Materials
Pons	tNAA/tCr	LCModel	3.5	18	22	8 (Mixed)	No	Joers, 2018, Ann Neurol[13]	Suppl Table 1§, Cohen's d provided by first author
Cerebellum WM	tNAA/mIns	LCModel	3.7	9	15	9 (Ataxic)	-	Öz, 2011, Cerebellum[11]	Fig. 4‡
Cerebellum WM	tNAA/tCr	LCModel	2.4	18	22	8 (Mixed)	No	Joers, 2018, Ann Neurol[13]	Suppl Table 1§, Cohen's d provided by first author
Cerebellum WM	tNAA/mIns	LCModel	1.8	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 3a
Preataxic Cohorts									
Pons	tNAA/tCr	LCModel	1.9	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 3b
Cerebellum WM	tNAA/tCr	LCModel	1.0	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 3a
Diffusion Weighted Imaging (DWI)									
Ataxic or Mixed Cohorts									
MCP	MD	ROI	3.7	16	20	-	Yes	Guerrini, 2004, Brain[3]	Table 2†
MCP	MD	FSL-ROI	2.4	11	9	7 (Mixed)	No	Park, 2020, Front Neurol[14]	Suppl Table
ICP, SCP	FA	FSL-TBSS	2.1	12	21	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Suppl eTable
ICP, SCP	FA	FSL-TBSS	-	10	10	18 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Tables 2, 3†
ICP	FA	FSL-ROI	2.2	11	9	7 (Mixed)	No	Park, 2020, Front Neurol[14]	Suppl Table
ICP	RD	FSL-ROI	3.3	14	17	8 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 2d
CST	FDC	MRTrix-FBA	1.9	12	21	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Suppl eTable
Brainstem	MD	FSL-TBSS	-	10	10	18 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Tables 2, 3†

ICP	FDC	MRTrix-FBA	3.1	14	16	8 (Ataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Tables 4, S3, S6
ICP	FA	FSL-ROI	3.8	26	21	12 (Mixed)	Yes	Kapteijns, 2025, NeuroImage Clin[17]	Fig 2, Table S2
Preataxic Cohorts									
ICP	FA	FSL-ROI	1.9	11	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 2a
ICP	FDC	MRTrix-FBA	1.8	10	16	1 (Preataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Tables 4, S3, S6
Quantitative Susceptibility Mapping (QSM)									
Ataxic Cohorts									
Dentate nucleus	Volume	Manual	1.6	16	16	14 (Ataxic)	No	Deistung, 2022, Brain Commun[18]	Fig 4
Dentate nucleus	Susceptibility	In-house pipeline	1.1	16	16	14 (Ataxic)	No	Deistung, 2022, Brain Commun[18]	Fig 4
Longitudinal									
Region	**Measure**	**Processing**	**Effect size (SRM)**	**nSCA1**	**nCTRL**	**Baseline SARA (mean or median)**	**Follow-up duration**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
Ataxic or Mixed Cohorts									
Brainstem	Volume	Semi-automated	-1.6	37	37	12 (Ataxic)	25mo	Reetz, 2013, Brain[19]	Table 5†
Brainstem	Volume	FastSurfer	-1.0	23	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 7
Pons	Volume	Semi-automated	-1.5	37	37	12 (Ataxic)	25mo	Reetz, 2013, Brain[19]	Table 5†
Pons	Volume	FreeSurfer	-1.8	15	24	11 (Ataxic)	25mo	Adanyeguh, 2018, NeuroImage Clin[15]	Table 2
Pons	Volume	FreeSurfer	-2.2	16	21	9 (Ataxic)	19, 36mo	Deelchand, 2019, Mov Disord Clin Pract[21]	Table 2
Pons	Volume	FreeSurfer	-0.88	25	21	7 (Mixed)	12 mo	Nigri, 2022, Cerebellum[22]	Suppl Mat
Pons	Volume	FreeSurfer	-2.1	28	20	13 (Ataxic)	12 mo	Prooije, 2024, Ann Neurol[7]	Fig. 4, Table
Pons	Volume	FastSurfer	-1.3	23	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 7
Cerebellum	Volume	FreeSurfer	-1.7	15	24	11 (Ataxic)	25 mo	Adanyeguh, 2018, NeuroImage Clin[15]	Table 2
Cerebellum WM	Volume	CerebNet	-0.9	23	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 6
VTN	Volume	FreeSurfer	-1.5	9	14	6.5 (Ataxic)	12 mo	Grisoli, 2024, Radiol Med[23]	In Text
VTN	Volume	FreeSurfer	-1.3	8	14	0.5 (Preataxic)	12 mo	Grisoli, 2024, Radiol Med[23]	In Text
Magnetic Resonance Spectroscopy (MRS)									

Ataxic or Mixed Cohorts									
Pons	tNAA/mIns	LCModel	-0.8	16	21	9 (Ataxic)	19, 36mo	Deelchand, 2019, Mov Disord Clin Pract[21]	Table 2
Pons	tNAA/mIns	LCModel	-0.6	28	21	13 (Ataxic)	12mo	Prooije, 2024, Ann Neurol[7]	Fig. 4, Table
Pons	tNAA/tCr	LCModel	-0.4	23	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 14
Cerebellum WM	tNAA/mIns	LCModel	-0.6	23	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 13
Diffusion Weighted Imaging (DWI)									
Ataxic or Mixed Cohorts									
MCP	AD	FSL-ROI	1.5	9	9	7 (Mixed)	20,44,67mo	Park, 2020, Front Neurol[14]	Suppl Table
MCP	RD	FSL-ROI	1.2	10	9	7 (Mixed)	6mo	Rezende, 2024, Mov Dis[24]	Suppl Mat
MCP	MD	FSL-ROI	0.7	23	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 11
ICP	FA	FSL-ROI	-1.5	26	21	12 (Mixed)	12, 24mo	Kapteijns, 2025, NeuroImage Clin[17]	Table S4, SRM at 1-year follow up provided by first author

General Acronyms: d, Cohen's d; SRM, standardised response mean; SARA, Scale for the Assessment and Rating of Ataxia; COA, clinical outcome assessment
Morphometry Acronyms: VBM, voxel-based morphometry; WM, white matter; GM, grey matter; CSA, cross-sectional area; VTN, ventral thalamic nucleus
DWI Acronyms: TBSS, tract-based spatial statistics; ROI, region-of-interest; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; ICP, inferior cerebellar peduncle; CST, cortico-spinal tract; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FBA, fixel-based analysis; FDC, fiber density and cross-section
MRS Acronyms: tNAA, total N-acetylaspartate; tCr, total creatine; mIns, myo-inositol
Mixed cohorts include individuals who are ataxic and preataxic

* Data collected at 3 tesla (T) except where indicated
† Data collected at 1.5T
‡ Data collected at 4T
§ Data collected at 7T

Supplementary Table 2 **| The most promising candidate imaging endpoints in spinocerebellar ataxia type 2**

Cross-sectional									
Region	**Measure**	**Processing**	**Effect size (d)**	**nSCA2**	**nCTRL**	**SARA (mean or median)**	**Correlation with COA?**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
Ataxic or Mixed Cohorts									
Brainstem	Volume	Semi-automated	3.8	48	31	12 (Ataxic)	Yes	Schulz, 2010, NeuroImage[2]	Table 4†
Brainstem	Volume	SPM-VBM	-	10	10	13 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Table 4†
Brainstem	Volume	CAT12-VBM	2.2	110	128	12 (Mixed)	Yes	Robertson, 2025, Mov Disord[25]	Figure 1
Pons	Volume	Manual/SPM-VBM	2.4	26	18	14 (Ataxic)	No	Reetz, 2018, ACTN[26]	Table 2‖
Pons	Volume	CAT12-VBM	2.8	110	128	12 (Mixed)	Yes	Robertson, 2025, Mov Disord[25]	Figure 1
Midbrain	Volume	Manual/SPM-VBM	1.4	26	18	14 (Ataxic)	No	Reetz, 2018, ACTN[26]	Table 2‖
Cerebellum	Volume	Manual/SPM-VBM	3.1	26	18	14 (Ataxic)	Yes	Reetz, 2018, ACTN[26]	Table 2‖
Cerebellum GM	Volume	SPM-VBM	-	10	10	13 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Table 4†
Cerebellum WM	Volume	SPM-VBM	-	10	10	13 (Ataxic)	Yes	Della Nave, 2008, NeuroImage[4]	Table 4†
Cerebellum GM	Volume	SPM-VBM	-	20	20	13 (Ataxic)	Yes	Della Nave, 2008, Mov Disord[27]	Table 1†
Cerebellum WM	Volume	SPM-VBM	-	20	20	13 (Ataxic)	Yes	Della Nave, 2008, Mov Disord[27]	Table 1†
Cerebellum WM	Volume	CAT12-VBM	3.4	110	128	12 (Mixed)	Yes	Robertson, 2025, Mov Disord[27]	Figure 1
Spinal cord (C2)	CSA	Spinal Cord Toolbox	2.1	102	101	14 (Ataxic)	Yes	Rezende, 2024, JNNP[10]	Figure 2
Spinal cord (C2)	CSA	Spinal Cord Toolbox	2.8	16	16	15 (Ataxic)	No	de Borba 2024, J Neurol[28]	Table 2
Preataxic Cohorts									
Brainstem	Volume	Manual/SPM-VBM	1.2	16	18	0.8 (Preataxic)	Yes	Reetz, 2018, ACTN[26]	Table 2‖
Pons	Volume	Manual/SPM-VBM	1.2	16	18	0.8 (Preataxic)	No	Reetz, 2018, ACTN[26]	Table 2‖
Cerebellum	Volume	Manual/SPM-VBM	1.1	16	18	0.8 (Preataxic)	No	Reetz, 2018, ACTN[26]	Table 2‖
Spinal cord (C2)	CSA	Spinal Cord Toolbox	1.8	9	14	1.2 (Preataxic)	Yes	Rezende, 2024, JNNP[10]	Suppl Table 12
Diffusion Weighted Imaging (DWI)									
Ataxic or Mixed Cohorts									
SCP	FA	FSL-TBSS	2.0	12	24	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Fig. 4
SCP	FA	FSL-ROI	2.8	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Suppl Table 1
MCP	FA	FSL-TBSS	1.6	12	24	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Fig. 4
MCP	FA	FSL-ROI	4.1	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Suppl Table 1
ICP	FA	FSL-TBSS	1.9	12	24	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Fig. 4

ICP	FA	FSL-ROI	5.1	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Suppl Table 1
Pontine crossing	FA	FSL-TBSS	1.7	12	24	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Fig. 4
Pontine crossing	FA	FSL-ROI	2.5	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Suppl Table 1
Cerebral peduncle	FA	FSL-TBSS	2.0	12	24	13 (Ataxic)	Yes	Adanyeguh, 2018, NeuroImage Clin[15]	Fig. 4
Cerebral peduncle	FA	FSL-ROI	2.2	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Suppl Table 1
CST	FA	FSL-ROI	2.6	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Suppl Table 1
Thalamic radiation	FA	FSL-TBSS	-	9	9	10 (Ataxic)	No	Park, 2020, Front Neurol[14]	Fig. 3
<u>Magnetic Resonance Spectroscopy (MRS)</u>									
<u>Ataxic or Mixed Cohorts</u>									
Pons	tNAA/tCr	LCModel	6.9	7	15	10 (Ataxic)	No	Öz, 2011, Cerebellum[11]	Fig. 4[‡]
Pons	tNAA/mIns	LCModel	3.0	12	33	13 (Ataxic)	No	Adanyeguh, 2015, Mov Disord[12]	Fig. 1
Pons	tNAA/tCr	LCModel	4.5	19	22	10 (Mixed)	Yes	Joers, 2018, Ann Neurol[13]	Suppl Table 1[§], Cohen's d provided by first author
Pons	NAA	AMARES/MRUI	1.5	9	20	- (Ataxic)	No	Guerrini, 2004, Brain[3]	Table 3[†]
Cerebellum WM	tNAA/tCr	LCModel	6.3	7	15	10 (Ataxic)	No	Öz, 2011, Cerebellum[11]	Fig. 4[‡]
Cerebellum WM	tNAA/mIns	LCModel	4.3	19	22	10 (Mixed)	Yes	Joers, 2018, Ann Neurol[13]	Suppl Table 1[§], Cohen's d provided by first author
Cerebellum WM	NAA	AMARES/MRUI	2.8	9	20	- (Ataxic)	No	Guerrini, 2004, Brain[3]	Table 3[†]
<u>Quantitative Susceptibility Mapping (QSM)</u>									
<u>Ataxic Cohorts</u>									
Dentate Nuclei	Volume	Manual	1.3	14	14	13 (Ataxic)	No	Deistung, 2022, Brain Comm[18]	Table 2
Longitudinal									
Region	**Measure**	**Processing**	**Effect size (SRM)**	**nSCA2**	**nCTRL**	**Baseline SARA (mean or median)**	**Follow-up duration**	**Reference**	**Figure or Table***
<u>Morphometry (Brain T1)</u>									
<u>Ataxic or Mixed Cohorts</u>									
Pons	Volume	FreeSurfer	-2.2	14	15	9 (Ataxic)	12mo	Nigri, 2020, Front Neurol[29]	Table 3
Pons	Volume	FreeSurfer	-1.6	12	24	13 (Ataxic)	24mo	Adanyeguh, 2018, NeuroImage Clin[15]	Figure 3
Pons	Volume	FreeSurfer/CERES	-0.6	15	10	4 (Mixed)	12mo	Coarelli, 2024, Neurology[30]	Table 4

Cerebellum	Volume	FreeSurfer	-1.1	14	15	9 (Ataxic)	12mo	Nigri, 2020, Front Neurol[29]	Table 3
Cerebellum	Volume	FreeSurfer	-2.1	12	24	13 (Ataxic)	24mo	Adanyeguh, 2018, NeuroImage Clin[15]	Figure 3
Cerebellum	Volume	FreeSurfer/CERES	-0.6	15	10	4 (Mixed)	12mo	Coarelli, 2024, Neurology[30]	Table 4
Preataxic Cohorts									
Cerebellum	Volume	FreeSurfer	-1.0	13	15	0 (Preataxic)	12mo	Nigri, 2020, Front Neurol[29]	Table 3

General Acronyms: d, Cohen's d; SRM, standardised response mean; SARA, Scale for the Assessment and Rating of Ataxia; COA, clinical outcome assessment
Morphometry Acronyms: VBM, voxel-based morphometry; WM, white matter; GM, grey matter; CSA, cross-sectional area
DWI Acronyms: TBSS, tract-based spatial statistics; ROI, region-of-interest; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; ICP, inferior cerebellar peduncle; CST, cortico-spinal tract; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FBA, fixel-based analysis; FDC, fiber density and cross-section
MRS Acronyms: tNAA, total N-acetylaspartate; tCr, total creatine; mIns, myo-inositol
Mixed cohorts include individuals who are ataxic and preataxic

* Data collected at 3 tesla (T) except where indicated
† Data collected at 1.5T
‡ Data collected at 4T
§ Data collected at 7T
‖ Data collected at 0.23T

Supplementary Table 3 | **The most promising candidate imaging endpoints in spinocerebellar ataxia type 3**

Cross-sectional									
Region	**Measure**	**Processing**	**Effect size (d)**	**nSCA3**	**nCTRL**	**SARA (mean or median)**	**Correlation with COA?**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
Ataxic or Mixed Cohorts									
Pons	Volume	FreeSurfer	2.0	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 4a
Pons	Volume	MRICloud	1.8	91	91	14 (Ataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 1
Pons	Volume	FreeSurfer	2.6	207	62	12 (Ataxic)	Yes	Faber, 2021, Mov Dis[32]	Table 2, 4
Pons	Volume	CAT12-VBM	1.9	339	276	10 (Mixed)	Yes	Robertson, 2025, bioRxiv[33]	Figure 1‡
Pons	Volume	FreeSurfer	2.7	94	45	10 (Ataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
Brainstem	Volume	FreeSurfer	1.9	19	19	14 (Ataxic)	No	Arruda, 2020, Cerebellum[35]	Table S1
Brainstem	Volume	CAT12-VBM	1.7	339	276	10 (Mixed)	Yes	Robertson, 2025, bioRxiv[33]	Figure 1‡
Medulla	Volume	FreeSurfer	2.3	207	62	12 (Ataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Medulla	Volume	CAT12-VBM	1.5	339	276	10 (Mixed)	Yes	Robertson, 2025, bioRxiv[33]	Figure 1‡
Medulla	Volume	FreeSurfer	3.0	94	45	10 (Ataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
SCP	Volume	FreeSurfer	2.9	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 4a
SCP	Volume	CAT12-VBM	2.0	339	276	10 (Mixed)	Yes	Robertson, 2025, bioRxiv[33]	Figure 1‡
SCP	Volume	FreeSurfer	2.6	94	45	10 (Ataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
Cerebellum GM	Volume	FreeSurfer	1.3	49	49	15 (Ataxic)	No	Rezende, 2015, Eur J Neurol[36]	Table 3, Cohen's d provided by first author
Cerebellum WM	Volume	FreeSurfer	1.7	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Supple Table 4a

Cerebellum WM	Volume	FreeSurfer	3.6	49	49	15 (Ataxic)	No	Rezende, 2015, Eur J Neurol[36]	Table 3, Cohen's d provided by first author
Cerebellum WM	Volume	SUIT	0.4	207	62	12 (Ataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Cerebellum WM	Volume	FreeSurfer	3.4	19	19	14 (Ataxic)	Yes	Arruda, 2020, Cerebellum[35]	Table S1
Cerebellum WM	Volume	CerebNet	3.4	62	62	13 (Ataxic)	Yes	Ferreira, 2024, Cerebellum[8]	Figure S10.2
Cerebellum WM	Volume	CAT12-VBM	2.3	339	276	10 (Mixed)	Yes	Robertson, 2025, bioRxiv[33]	Figure 1‡
Cerebellum WM	Volume	CerebNet	2.8	94	45	10 (Ataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
Thalamus	Volume	FreeSurfer	1.4	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 4a
Thalamus	Volume	FreeSurfer	1.4	49	49	15 (Ataxic)	No	Rezende, 2015, Eur J Neurol[36]	Table 3, Cohen's d provided by first author
Thalamus	Volume	FreeSurfer	1.2	19	19	14 (Ataxic)	No	Arruda, 2020, Cerebellum[35]	Table S1
Pallidum	Volume	FreeSurfer	1.1	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 4a
Pallidum	Volume	FreeSurfer	1.8	49	49	15 (Ataxic)	No	Rezende, 2015, Eur J Neurol[36]	Table 3, Cohen's d provided by first author
Pallidum	Volume	FreeSurfer	1.5	19	19	14 (Ataxic)	No	Arruda, 2020, Cerebellum[35]	Table S1
Pallidum	Volume	FreeSurfer	1.6	207	62	12 (Ataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Caudate	Volume	FreeSurfer	1.1	49	49	15 (Ataxic)	No	Rezende, 2015, Eur J Neurol[36]	Table 3, Cohen's d provided by first author
Caudate	Volume	CAT12-VBM	0.52	339	276	10 (Mixed)	No	Robertson, 2025, bioRxiv[33]	Figure 1‡
Spinal Cord (C2)	CSA	SpineSeg	2.2	91	91	14 (Ataxic)	No	Rezende, 2018, Ann Neurol[31]	Table S1
Spinal Cord (C2)	CSA	SCT	2.6	191	59	12 (Ataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Spinal Cord (C2)	CSA	SCT	2.0	192	178	11 (Ataxic)	Yes	Rezende, 2024, JNNP[10]	Figure 2, Suppl Table 9
Spinal Cord (C2)	CSA	Spinal Cord Toolbox	1.9	26	26	9.4 (Ataxic)	No	de Borba, 2024, J Neurol[28]	Table 2
Preataxic Cohorts									
Pons	Volume	MRICloud	1.2	12	12	1.8 (Preataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 1
Pons	Volume	FreeSurfer	1.0	47	62	1.3 (Preataxic)	Yes	Faber, 2021, Mov Dis[32]	Table 2, 4
Pons	Volume	FreeSurfer	1.1	32	45	1.0 (Preataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d

									provided by last author
Medulla	Volume	FreeSurfer	1.1	47	62	1.3 (Preataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Medulla	Volume	FreeSurfer	1.6	32	45	1.0 (Preataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
SCP	Volume	FreeSurfer	1.4	28	17	1.3 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 4a
SCP	Volume	FreeSurfer	1.2	32	45	1.0 (Preataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
Cerebellum WM	Volume	CerebNet	0.7	32	45	1.0 (Preataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
Pallidum	Volume	FreeSurfer	0.7	47	62	1.3 (Preataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Spinal Cord (C2)	CSA	Spinal Cord Toolbox	1.3	47	59	1.3 (Preataxic)	No	Faber, 2021, Mov Dis[32]	Table 2, 4
Spinal Cord (C2)	CSA	Spinal Cord Toolbox	1.7	36	24	1.1 (Preataxic)	Yes	Rezende, 2024, JNNP[10]	Suppl Table 13
<u>Diffusion Weighted Imaging (DWI)</u>									
<u>Ataxic or Mixed Cohorts</u>									
SCP	MD	FSL-ROI	2.1	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 5c
SCP	FA	MRICloud	2.3	91	91	14 (Ataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 4
SCP	RD	FSL-ROI	3.2	7	9	7.4 (Ataxic)	No	Park, 2020, Front Neurol[14]	Table S1
SCP	FDC	MRtrix-FBA	1.8	36	16	6.9 (Ataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Suppl Table 3
SCP	FA	MRtrix-ROI	2.0	94	45	10 (Ataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
MCP	FA	MRICloud	2.0	91	91	14 (Ataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 4
MCP	MD	FSL-ROI	1.6	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 5c
MCP	FDC	MRtrix-FBA	2.5	36	16	6.9 (Ataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Suppl Table 3

ICP	FA	FSL-ROI	3.3	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 5a
ICP	FA	MRICloud	3.0	91	91	14 (Ataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 4
ICP	FA	FSL-ROI	4.4	7	9	7.4 (Ataxic)	No	Park, 2020, Front Neurol[14]	Table S1
ICP	FA	MRtrix-ROI	2.9	94	45	10 (Ataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
ICP	FDC	MRtrix-FBA	3.5	36	16	6.9 (Ataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Suppl Table 3
Preataxic Cohorts									
SCP	MD	FSL-ROI	0.8	28	17	1.3 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 5c
SCP	FA	MRICloud	1.5	12	12	1.8 (Preataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 4
SCP	FDC	MRtrix-FBA	0.9	24	16	1.0 (Preataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Suppl Table 3
SCP	FA	MRtrix-ROI	1.0	32	45	1.0 (Preataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
MCP	FA	MRICloud	1.9	12	12	1.8 (Preataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 4
MCP	MD	MRICloud	1.2	32	20	0.5 (Preataxic)	No	de Oliveira, 2023, J Neurol[37]	Table 2
MCP	FDC	MRtrix-FBA	0.9	24	16	1.0 (Preataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Suppl Table 3
ICP	FA	FSL-ROI	2.1	28	17	1.3 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 5a
ICP	FA	MRICloud	2.4	12	12	1.8 (Preataxic)	No	Rezende, 2018, Ann Neurol[31]	Figure 4
ICP	FA	MRICloud	1.5	32	20	0.5 (Preataxic)	No	de Oliveira, 2023, J Neurol[37]	Table 2
ICP	FDC	MRtrix-FBA	2.0	24	16	1.0 (Preataxic)	Yes	Arpin, 2025, Ann Clin Transl Neurol[16]	Suppl Table 3
ICP	FA	MRtrix-ROI	1.2	32	45	1.0 (Preataxic)	No	Berger, 2025, Lancet Reg Health[34]	Appendix Table 6, Cohen's d provided by last author
Magnetic Resonance Spectroscopy (MRS)									
Ataxic or Mixed Cohorts									
Pons	tNAA/mIns	LCModel	2.7	21	33	13 (Ataxic)	No	Adanyeguh, 2015, Mov Disord[12]	Fig. 1, 2

Pons	tNAA/mIns	LCModel	2.8	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 6b
Pons	tNAA/mIns	LCModel	2.7	21	22	7 (Mixed)	No	Joers, 2018, Ann Neurol[13]	Suppl Table 1§, Cohen's d provided by first author
Cerebellum Hemisphere	NAA/Cr	Functool (GE XVi)	1.1	18	44	11 (Ataxic)	No	Chen, 2014, Cerebellum & Ataxias[38]	Table 2†
Cerebellum Hemisphere	NAA/Cr	Functool (GE XVi)	1.5	58	44	-	Yes	Lirng, 2012, Plos One[39]	Table 2†
Cerebellum WM	tNAA/tCr	LCModel	2.3	37	17	7 (Ataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 6a
Cerebellum WM	tNAA/tCr	LCModel	2.6	21	22	7 (Mixed)	No	Joers, 2018, Ann Neurol[13]	Suppl Table 1§, Cohen's d provided by first author
Preataxic Cohorts									
Pons	tNAA/mIns	LCModel	1.0	28	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 6b
Cerebellum WM	tNAA/mIns	LCModel	0.7	28	17	1 (Preataxic)	Yes	Chandrasekaran, 2023, Ann Neurol[5]	Suppl Table 6a
Quantitative Susceptibility Mapping (QSM)									
Ataxic Cohorts									
Substantia Nigra	Susceptibility	MEDI	2.3	41	32	12.3 (Ataxic)	Yes	Qiu, 2025, Eur J Neurol[40]	Table 3
Dentate Nucleus	Susceptibility	MEDI	1.1	41	32	12.3 (Ataxic)	Yes	Qiu, 2025, Eur J Neurol[40]	Table 3
Preataxic Cohorts									
Substantia Nigra	Susceptibility	MEDI	1.8	19	18	0.6 (Preataxic)	Yes	Qiu, 2025, Eur J Neurol[40]	Table 3
Longitudinal									
Region	**Measure**	**Processing**	**Effect size (SRM)**	**nSCA3**	**nCTRL**	**Baseline SARA (mean or median)**	**Follow-up duration**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
Ataxic or Mixed Cohorts									
Pons	Volume	FreeSurfer	-2.4	20	24	13 (Ataxic)	25mo	Adanyeguh, 2018, Neuroimage Clin[15]	Fig 2, 3; Table 2
Pons	Volume	Semi-automated	-0.9	19	19	12 (Ataxic)	29mo	Reetz, 2013, Brain[19]	Table 5†
Pons	Volume	FreeSurfer	-1.9	65	27	9.5 (Mixed)	12mo (24, 36, …)	Berger, 2025, Lancet Reg Health[34]	Table 3, SRM at 1-year follow up

									provided by last author
Pons	Volume	FastSurfer	-1.3	63	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 7
Medulla	Volume	FreeSurfer	-0.6	65	27	9.5 (Mixed)	12mo (24, 36, …)	Berger, 2025, Lancet Reg Health[34]	Table 3, SRM at 1-year follow up provided by last author
Brainstem	Volume	FastSurfer	-1.0	63	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 7
Cerebellum	Volume	FreeSurfer	-1.7	20	24	13 (Ataxic)	25mo	Adanyeguh, 2018, Neuroimage Clin[15]	Fig 2, 3; Table 2
Cerebellum GM	Volume	CERES/SUIT	-2.1#	23	22	13 (Ataxic)	61mo	Piccinin, 2020, Mov Dis[41]	Suppl Material, Table 1
Cerebellum	Volume	Semi-automated	-0.5	19	19	12 (Ataxic)	29mo	Reetz, 2013, Brain[19]	Table 5†
Cerebellum	Volume	CERES	-0.5	25	9	2 (Mixed)	6mo	Rezende, 2024, Mov Dis[24]	Suppl Table 3
Cerebellum WM	Volume	FreeSurfer	-1.2	65	27	9.5 (Mixed)	12mo (24, 36, …)	Berger, 2025, Lancet Reg Health[34]	Table 3, SRM at 1-year follow up provided by last author
Cerebellum WM	Volume	CerebNet	-0.9	63	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 6
Putamen	Volume	MRICloud	-0.6#	23	22	13 (Ataxic)	61mo	Piccinin, 2020, Mov Dis[41]	Suppl Material, Table 1
Putamen	Volume	Semi-automated	-1.5	19	19	12 (Ataxic)	29mo	Reetz, 2013, Brain[19]	Table 5†
Caudate	Volume	Semi-automated	-1.6	19	19	12 (Ataxic)	29mo	Reetz, 2013, Brain[19]	Table 5†
Thalamus	Volume	MRICloud	-0.8#	23	22	13 (Ataxic)	61mo	Piccinin, 2020, Mov Dis[41]	Suppl Material, Table 1
<u>Diffusion Weighted Imaging (DWI)</u>									
<u>Ataxic or Mixed Cohorts</u>									
SCP	MD	MRICloud	1.1	21	20	13 (Ataxic)	61mo	Piccinin, 2020, Mov Dis[41]	Suppl Material, Table 1
MCP	FA	FSL-ROI	-0.6	25	9	2 (Mixed)	6mo	Rezende, 2024, Mov Dis[24]	Suppl. Table 9
ICP	RD	MRICloud	1.3	21	20	13 (Ataxic)	61mo	Piccinin, 2020, Mov Dis[41]	Suppl Material, Table 1
ICP	MD	FSL-ROI	0.5	28	0	10.9 (Ataxic)	12mo	Tang, 2025, Neuroscience[42]	Table 2
MCP	MD	FSL-ROI	0.5	63	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 11

Preataxic Cohorts									
MCP	MD	MRICloud	0.2	14	9	0.5 (Preataxic)	30mo	de Oliveira, 2023, J Neurol[37]	Table 4
ICP	FA	MRICloud	0.2	14	9	0.5 (Preataxic)	30mo	de Oliveira, 2023, J Neurol[37]	Table 4
Magnetic Resonance Spectroscopy (MRS)									
Mixed Cohorts									
Pons	tNAA/mIns	LCModel	-0.7	63	14	4.5 (Mixed)	6, 12, 24, 36, 48mo	Rezende, 2026, Ann Clin Transl Neurol[20]	Suppl. Table 14
Quantitative Susceptibility Mapping (QSM)									
Mixed Cohorts									
Substantia Nigra	Susceptibility	MEDI	2.3	12	0	6.0 (Mixed)	12mo	Qiu, 2025, Eur J Neurol[40]	Table 4
Dentate Nucleus	Susceptibility	MEDI	1.1	12	0	6.0 (Mixed)	12mo	Qiu, 2025, Eur J Neurol[40]	Table 4

General Acronyms: d, Cohen's d; SRM, standardised response mean; SARA, Scale for the Assessment and Rating of Ataxia; COA, clinical outcome assessment
Morphometry Acronyms: VBM, voxel-based morphometry; WM, white matter; GM, grey matter; SPM, statistical parametric mapping; CSA, cross-sectional area
DWI Acronyms: TBSS, tract-based spatial statistics; ROI, region-of-interest; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; ICP, inferior cerebellar peduncle; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FBA, fixel-based analysis; FDC, fiber density and cross-section
MRS Acronyms: tNAA, total N-acetylaspartate; tCr, total creatine; mIns, myo-inositol
Mixed cohorts include individuals who are ataxic and preataxic

* Data collected at 3 tesla (T) except where indicated
† Data collected at 1.5T
‡ Data collected at 3T, except for one site (out of 11) where data were collected at 1.5T
§ Data collected at 7T
# Longitudinal effect size is Cohen's d for slope difference between patients and controls

Supplementary Table 4 | **The most promising candidate imaging endpoints in Friedreich ataxia**

Cross-sectional									
Region	**Measure**	**Processing**	**Effect size (d)**	**nFRDA**	**nCTRL**	**SARA (mean or median)**	**Correlation with COA?**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
SCP	Volume	SPM/SUIT-VBM	2.3	248	262	18	Yes	Harding, 2021, Ann Neurol[43]	Fig 1
SCP	Volume	FreeSurfer	2.0	28	20	9	No	Adanyeguh, 2023, Brain Comm[44]	Table 2
SCP	Volume	Manual	4.2	12	13	21	Yes	Akhlaghi, 2011, Cerebellum[45]	Text (Results)
SCP	Volume	SPM/SUIT-VBM	1.3	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
Medulla	Volume	SPM/SUIT-VBM	2.6	248	262	18	-	Harding, 2021, Ann Neurol[43]	Fig 1
Medulla	Volume	FreeSurfer	2.8	28	20	9	No	Adanyeguh, 2023, Brain Comm[44]	Table 2
Medulla	Volume	ANTS	1.8	21	22	21	No	Dogan, 2019, JNNP[47]	Table 1
Brainstem	Volume	FreeSurfer	1.7	31	40	19	Yes	Rezende, 2016, Mov Dis[48]	Table 2
Brainstem	Volume	SPM/SUIT-VBM	1.7	248	262	18	Yes	Harding, 2021, Ann Neurol[43]	Fig 1
Cerebellum**	Volume	ACAPULCO	0.5	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
Spinal cord (C2-3)	CSA	SpineSeg	4.0	33	30	19	Yes	Chevis, 2013, Cerebellum[49]	Table 1
Spinal cord (C1)	CSA	SCT	2.6	256	223	17	Yes	Rezende, 2023, Mov Dis[50]	Text (Results)
Spinal cord (C2-3)	CSA	SCT	3.9	28	20	9	Yes	Joers, 2022, Brain Comm[51]	Table 2
Spinal cord (C2)	CSA	SCT	2.8	30	30	16	Yes	Hernandez, 2022, Mov Dis[52]	Table 2
Spinal cord (C1)	CSA	ITK-SNAP	2.9	21	22	21	Yes	Dogan, 2019, JNNP[47]	Table 1
Spinal Cord (C1-2)	CSA	SCT	2.9	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
Diffusion Weighted Imaging (DWI)									
SCP	FA	FSL-ROI	2.4	28	20	9	Yes	Adanyeguh, 2023, Brain Comm[44]	Table 2
SCP	FA	FSL-ROI	3.9	36	31	19	Yes	Selvadurai, 2020, Hum Brain Mapp[53]	-
SCP	FA	Vendor-provided (Siemens)	2.3	10	10	-	-	Straub, 2020, J Neurosci Res[54]	Table 3
SCP	FA	FSL-ROI	3.4	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
SCP	FDC	MRTrix-FBA	3.6	28	20	9	Yes	Adanyeguh, 2023, Brain Comm[44]	Table 2
SCP	FW	DIPY, custom	2.2	14	14	19	No	Fernandez, 2024, Mov Dis[55]	Table S2
Spinal cord (C3-6)	FA	SCT, RESTORE	2.5	28	20	9	Yes	Joers, 2022, Brain Comm[51]	Table 2
Spinal cord (C2)	FA	SCT, RESTORE	2.9	30	30	16	Yes	Hernandez, 2022, Mov Dis[52]	Table 1
Spinal cord (C3-5)	FA	SCT, RESTORE	3.1	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
Magnetic Resonance Spectroscopy (MRS)									
Spinal cord	tNAA/mIns	LCModel	3.4	28	20	9	No	Joers, 2022, Brain Comm[51]	Table 2
Spinal cord	tNAA/mIns	LCModel	2.8	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2

Quantitative Susceptibility Mapping (QSM)									
Dentate Nucleus	Volume	Manual	1.8	15	15	24	No	Deistung, 2022, Brain Comm[18]	Fig 4
Dentate Nucleus	Volume	Manual	0.6	30	33	18	Yes	Harding, 2016, JNNP[56]	Table 1
Dentate Nucleus	Volume	Manual	1.4	20	18	18	Yes	Ward, 2019, Mov Dis[57]	Table 2
Dentate Nucleus	Volume	DentateSeg (AI)	1.5	169	95	14	No	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
Dentate Nucleus	Susceptibility	STI-Suite	1.2	30	33	18	Yes	Harding, 2016, JNNP[56]	Table 1
Dentate Nucleus	Susceptibility	STI-Suite	1.3	20	18	18	Yes	Ward, 2019, Mov Dis[57]	Table 2
Dentate Nucleus	Susceptibility	STAR-QSM	1.5	10	10	-	-	Straub, 2020, J Neurosci Res[54]	Table 3
Dentate Nucleus	Susceptibility	JHU/KKI	0.9	169	95	14	Yes	Georgiou-Karistianis, 2025, Ann Neurol[46]	Table 2
Red Nucleus	Susceptibility	Manual	1.6	10	10	-	-	Straub, 2020, J Neurosci Res[54]	Table 3
Longitudinal									
Region	**Measure**	**Processing**	**Effect size (SRM)**	**nFRDA**	**nCTRL**	**Baseline SARA (mean or median)**	**Follow-up duration**	**Reference**	**Figure or Table***
Morphometry (Brain T1)									
SCP	Volume	SPM-ROI	-0.5	28	29	18	24mo	Selvadurai, 2021, J Neurol[58]	Fig 3
SCP	Volume	FreeSurfer	-0.4	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Cerebellum	Volume	CERES	-1.1	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Cerebellum WM	Volume	CERES	-1.1	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Cerebellum GM	Volume	CERES	-1.0	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Brainstem	Volume	FreeSurfer	-0.8	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Suppl. Table 5
Thalamus	Volume	FreeSurfer	-0.8	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Ventral DC	Volume	FreeSurfer	-0.9	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
4th ventricle	Volume	FreeSurfer	0.9	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Spinal cord (C1-2)	CSA	SCT	-1.2	28	20	9	24mo	Joers, 2022, Brain Comm[51]	Suppl. Table 3
Diffusion Weighted Imaging (DWI)									
SCP	RD	FSL-ROI	1.0	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
SCP	FA	FSL-ROI	-0.7	29	27	17	24mo	Selvadurai, 2021, J Neurol[58]	Table S15
SCP	FDC	MrTrix-FBA	-1.0	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
PLIC	FDC	MrTrix-FBA	-1.0	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
SCR	FDC	MrTrix-FBA	-1.0	28	20	9	14,27,45mo	Adanyeguh, 2023, Brain Comm[44]	Table 3
Quantitative Susceptibility Mapping (QSM)									
Dentate Nucleus	Susceptibility	STI-Suite	0.9	20	18	18	24mo	Ward, 2019, Mov Dis[57]	Table 2

General Acronyms: d, Cohen's d; SRM, standardised response mean; SARA, Scale for the Assessment and Rating of Ataxia; COA, clinical outcome assessment

Morphometry Acronyms: VBM, voxel-based morphometry; WM, white matter; GM, grey matter; CSA, cross-sectional area

DWI Acronyms: TBSS, tract-based spatial statistics; ROI, region-of-interest; SCP, superior cerebellar peduncle; Ventral DC, Ventral diencephalon; PLIC, posterior limb of internal capsule; SCR, superior corona radiata; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FBA, fixel-based analysis; FDC, fiber density and cross-section

MRS Acronyms: tNAA, total N-acetylaspartate; tCr, total creatine; mIns, myo-inositol

* Data collected at 3 tesla except where indicated
** Cerebellum volume is included despite its small cross-sectional effect size to document its correlation with COA

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