READISCA

An NIH-funded transatlantic observational study for SCA1 and SCA3

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READISCA Specific Aims

Aim 1. Establish the world's largest cohorts of premanifest and early stage SCA1 and SCA3 patients by combining and expanding existing cohorts, COA data and biofluid samples (blood, cerebrospinal fluid) from US and Europe

Aim 2. Validate MR morphological, biochemical and functional biomarkers in premanifest and early SCA1 and SCA3

Aim 3. Adapt recent developments on statistical design and analysis of small population trials to SCAs.

READISCA Goals

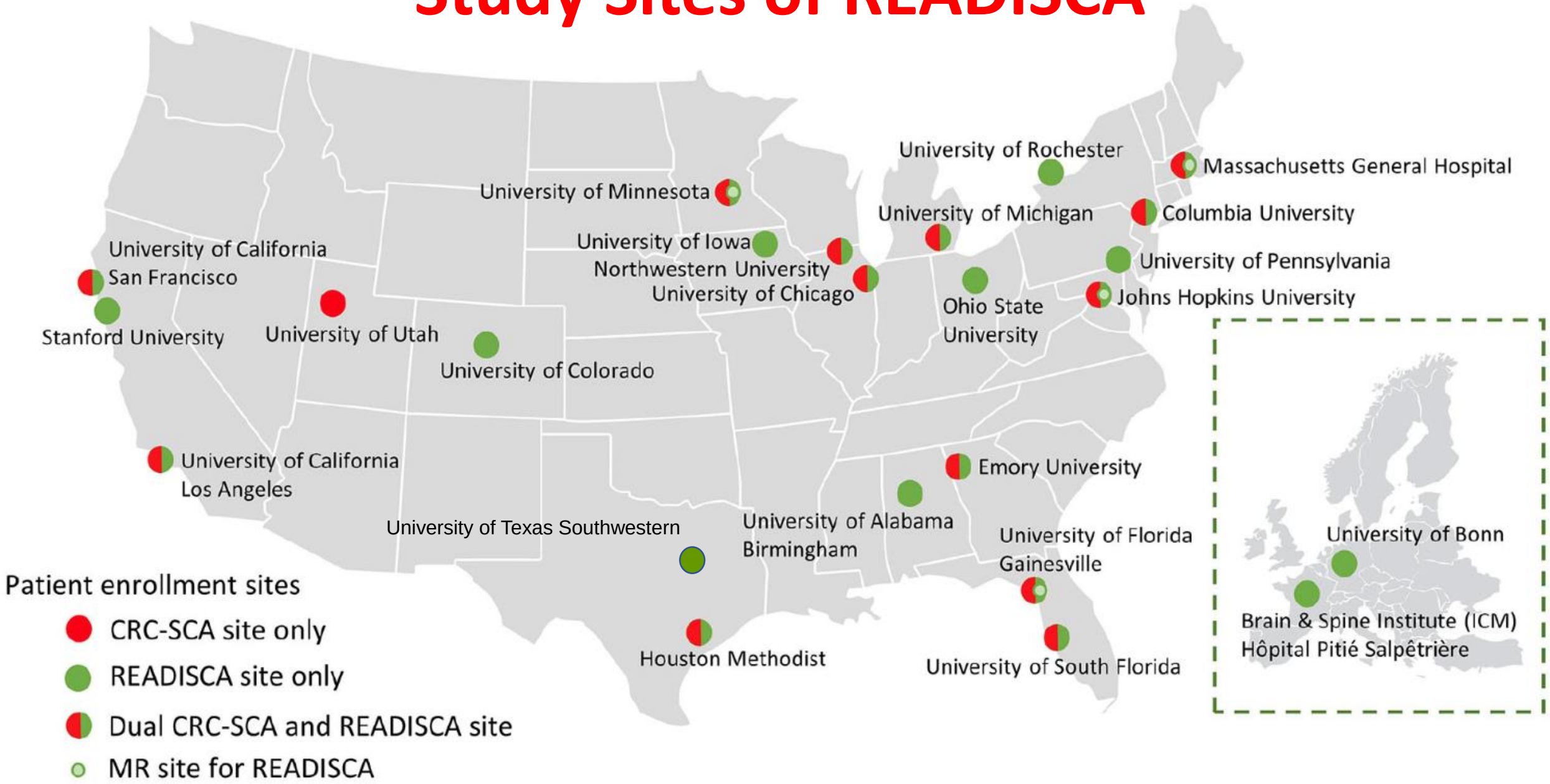
- Establish clinical trial readiness for two common SCAs (SCA1 & SCA3), in collaborations with NAF, Ataxia Global Initiative (AGI), and Critical Path to Therapeutics for the Ataxias (CPTA)
- Focusing on premanifest mutation carriers close to the predicted onset of ataxia and early-stage ataxic individuals with these SCAs
- Transatlantic (US & Europe) comparisons of data of study subjects from two continents to assess the feasibility of transatlantic trials (using previously collected data and new READISCA data).
- Longitudinal data collection (6-year span)
  - Clinical outcome assessment measures (SARA, INAS, PRO, etc.)
  - MRI (VBM, DTI, rs-fMRI) and MR spectroscopy data
- Longitudinal collection of plasma and CSF and fluid biomarker studies
- Establishing iPSC from representative study participants
- Optimization of clinical trial designs through simulations of various statistical models using the longitudinal data

READISCA Enrollment

Inclusion Criteria				
Study population category	**Genotype of SCA1/SCA3**	**Age (years)**	**SARA total score**	**Gait**
Early-stage patients	(+)	18-65	3-9.5	Ambulate without an assisting device (SARA gait score <5)
Premanifest carriers	(+)	27-65	0-2.5	Within the normal range (SARA total score <3)
Previously early stg	(+)	Any age	<10 in 2009-2012	Any state
Controls	(-)	18-65	0-2.5	Within the normal range (SARA total score <3)

Exclusion Criteria
• Subjects receiving investigational treatment • Subjects not willing to participate in the study • Genotype consistent with other types of ataxia • Changes in PT/OT within 2 months of enrollment • Concomitant condition(s) that affects assessment or severity of ataxia
• Exclusion criteria for Aim 2

Study Sites of READISCA



READISCA Baseline Evaluation (Aug 2018 – Dec 2020)

Visit Type	Baseline			
SCA type	SCA1	SCA3	Contr	Total
Clinic (Aim1)	54	123	42	**219**
Imaging (Aim 2)	27	67	16	**110**
Completed LPs	33	30	16	**79**

Temporal Dynamics of the SARA in SCAs

by Moulaire et al for the READISCA Consortium

Data from four cohorts (EUROSCA, RISCA, CRC-SCA, and SPATAX) comprising 1210 participants and 4092 visits.

The linearity of the progression and the variability were assessed using an ordinal Bayesian mixed-effect model (Leaspy).

Sample size calculations for therapeutic trials were performed with different scenarios to improve the responsiveness of the scale.

Results:

- Seven of the eight different items had a nonlinear progression
- The average time for a one-point increase for each item ranged from 3.5 years [3.4; 3.6] (median, 95% credible interval) to 11.4 [10.9; 12.0] years.
- The total SARA score had a linear progression with an average time for a one-point increase of 0.95 [0.92; 0.98] years.

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Mov Disorders 2022 Oct 23, PMID: 36273394

Baseline clinical and blood biomarker in patients with preataxic and early-stage disease spinocerebellar ataxia 1 and 3

Tezenas du Montcel et al for the READISCA Consortium

In SCA, ataxia onset can be preceded by mild clinical manifestation, cerebellar and/or brainstem alterations or biomarkers modifications.

200 ATXN1 or ATAXN3 mutation carriers, consisting of (1) 31 ataxic and 14 pre-ataxic SCA1, (2) 80 ataxic and 36 pre-ataxic SCA3, and (3) 39 controls, were enrolled at 18 US and two European ataxia referral centers.

Clinical, cognitive, motor, neuropsych measures and plasma NfL measurements were compared between mutation carriers with and without ataxia and controls.

- **Plasma NfL levels were higher in pre-ataxic mutation carrier than controls.**
- **Upper motor neuron signs were more frequent in pre-ataxic carrier than controls.**
- **Sensor impairment and diplopia were more frequent in pre-ataxic carrier than controls in SCA3.**
- **Functional scales, fatigue and depression scores, swallowing difficulties, and cognitive impairment were worse in mutation carriers with ataxia than those without ataxia.**
- **Ataxic SCA3 subjects showed extrapyramidal signs, urinary dysfunction and lower motor neuron signs significantly more often than mutation carriers without ataxia.**

These alterations in pre-ataxic SCA1 and SCA3 carriers, who are ~6 years before estimated ataxia onset, would be considered when selecting participants for future therapeutic trials and not restrict the selection to patients with cerebellar signs.

In the second cycle of review in Neurology

Clinically meaningful MR endpoints sensitive to preataxic and early ataxic stages of SCA1 and SCA3

Chandrasekaran et al.

The paper describes

- Cross-sectional neuroimaging results from ataxic and preataxic subjects with SCA1 and SCA3 enrolled in the READISCA study.
- Morphometric (volumetry), microstructural (diffusivity) and neurochemical (spectroscopy) data from 107 individuals (65 SCA3, 25 SCA1 and 17 controls) scanned at 3T in multiple sites were assessed.
- In the preataxic stage, we found volumetric and microstructural abnormalities in the brainstem and cerebellar peduncles as well as neurochemical changes in the pons. Looking separately at SCA1 and SCA3, neurochemical and microstructural metrics were respectively the most sensitive MRI parameters in the preataxic stage.

In the second cycle of review in Ann Neurology

READISCA Enrollment Status (Oct 2022)

Visit Type	Baseline				6-month (Aim2 only)				12-month				24-month				36-month			
SCA type	SCA1	SCA3	Contr	Total	SCA1	SCA3	Contr	Total	SCA1	SCA3	Contr	Total	SCA1	SCA3	Contr	Total	SCA1	SCA3	Contr	Total
Clinic (Aim1)	54	123	42	**219**	--	--	--	--	39	88	27	**154**	22	58	19	99	9	23	8	40
Imaging (Aim 2)	27	67	16	**110**	12	26	9	47	19	48	12	**79**	15	34	7	56	5	10	3	18
Completed LPs	33	30	16	**79**	--	--	--	--	5	9	0	**14**	3	12	1	16	6	3	0	9
	Contr: Controls																			

AIM1						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Total
SCA1 PM	18	13	7	5	1	**120**
SCA3 PM	31	24	18	3	0	
SCA1 ES	33	23	12	4	0	**268**
SCA3 ES	79	59	36	20	2	
SCA1 PrevES	4	3	2	0	0	**26**
SCA3 PrevES	10	5	2	0	0	
	BL	12M	24M	36M	48M	

AIM2						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Total
SCA1 PM	9	3	7	6	3	**96**
SCA3 PM	25	17	12	12	2	
SCA1 ES	16	9	11	8	2	**143**
SCA3 ES	36	25	20	8	8	
SCA1 PrevES	1	0	1	1	0	**15**
SCA3 PrevES	6	4	2	0	0	
	BL	6M	12M	24M	36M	

Visit Type	Withdrawals							
SCA Type	SCA1			SCA3			Control	Total
	ES	PM	PrevES	ES	PM	PrevES		
Clinic (Aim1)	8	0	0	9	0	1	2	**20**
Imaging (Aim 2)	3	1	0	4	1	0	1	**10**
Pending	6	1	2	6	1	2	4	**22**

READISCA Progress and Phenoconversions (Oct 2022)

Phenoconversions

Subject	Cohort	SCA Type	Baseline date	SARA Score	12M	SARA Score	24M	SARA Score	PC Date	Phenoconversion
PS-01-021	ES	SCA1	6/23/2020	2	7/2/2021	3	7/1/2022	2	7/2/2021	3 to 2
MI-01-030	ES	SCA1	11/28/2018	2.5	11/19/2019	3	withdrawn	withdrawn	11/19/2019	2.5 to 3
PS-01-007	ES	SCA1	11/19/2019	2.5	11/26/2020	3	12/10/2021	2	11/26/2020	3 to 2
AB-01-006	ES	SCA1	3/18/2021	2.5	4/6/2022	4	n/a	n/a	4/6/2022	2.5 to 4
SA-01-035	ES	SCA3	7/18/2019	0.5	4/27/2021	3.5	5/6/2022	3.5	4/27/2021	3.5 to 3.5
LA-01-079	ES	SCA3	12/16/2019	1	5/20/2021	5.5	6/1/2022	4.5	5/20/2021	5.5 to 4.5
UF-01-085	ES	SCA3	11/6/2020	1	1/10/2022	4.5	n/a	n/a	1/10/2022	1 to 4.5
MN-01-023	ES	SCA3	1/16/2019	2	1/8/2020	1	4/7/2021	6	4/17/2021	1 to 6
SA-01-031	ES	SCA3	3/26/2019	2	2/2/2021	3.5	3/4/2022	2	2/2/2021	3.5 to 2
MN-01-029	ES	SCA3	6/7/2019	2	2/24/2021	8.5	3/9/2022	10	2/24/2021	8.5 to 10

SCA Type	SCA1	SCA3
# of Phenoconverwions	4	6

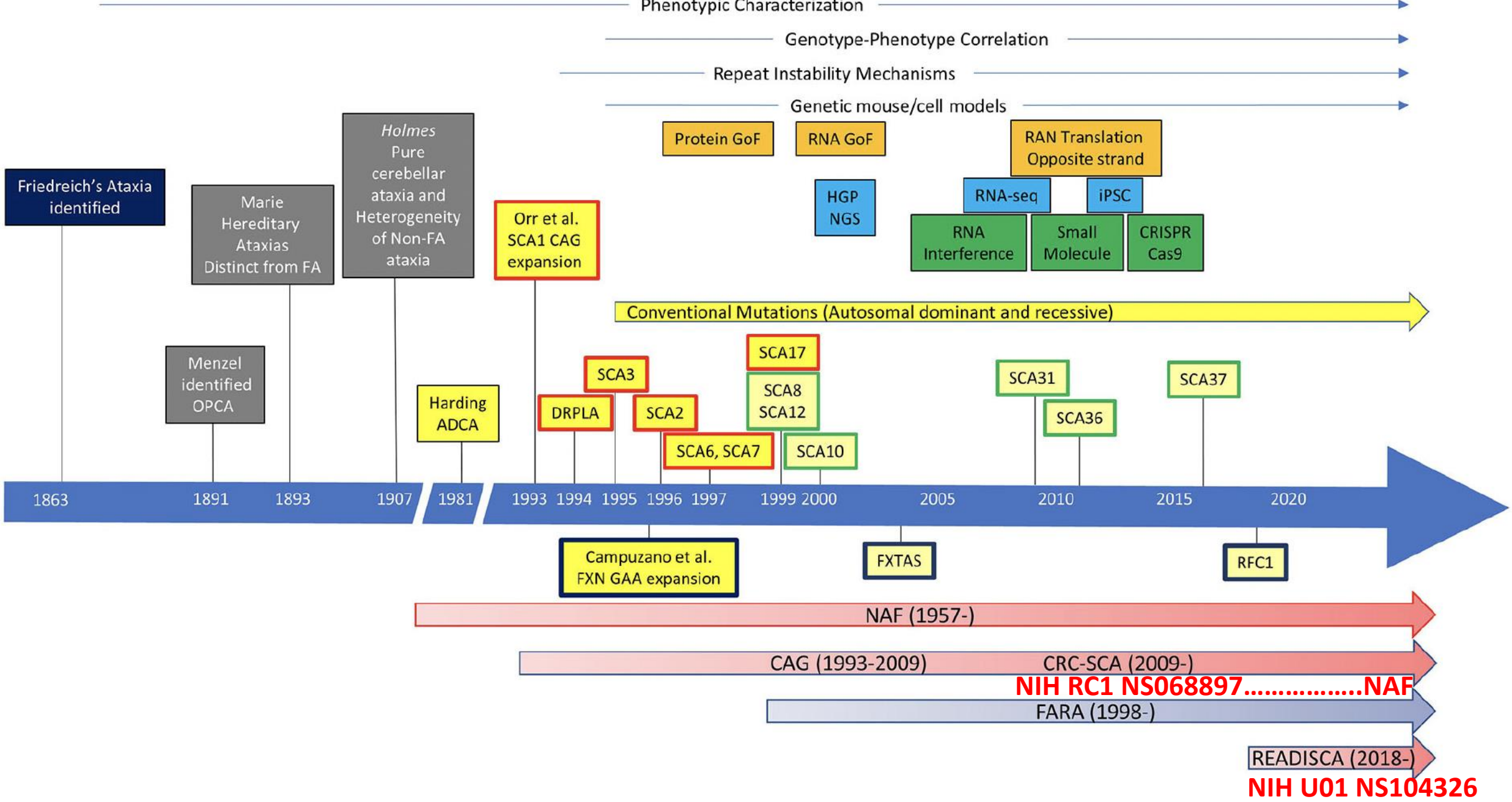
Visits Pending

Estimated Pending Visits	2022				2023			
SCA Type	Control	SCA1	SCA3	Total	Control	SCA1	SCA3	Total
Clinic (AIM1)	16	14	22	52	16	10	40	66
Imaging (AIM2)	6	7	6	19	6	4	20	30

What will happen when the READISCA study ends?

READISCA will end in December 2023 with the no-cost extension. By then:

- Analysis of longitudinal data of prior studies from the US and Europe have been published.
- Baseline and longitudinal clinical and MR data have been published and made available at the NIMH Data Archive (NDA).
- All samples will be stored at BioSEND (CSF, plasma and DNA) and NHCDR/Infinite BiologiX (PBMC - iPSC) and made available to investigators through the SCA Biospecimen Resource Access Committee (SCA-BRAC).
- All data and samples will be kept under supervision of Joint Controllers as long as the GDPR mandates until their storage is terminated.
- Sharing of non-NDA data with a third party will need separate permission according to the GDPR (see the READISCA Data Sharing Policy).
- READISCA study subjects who have also been enrolled in the CRC-SCA Natural Hx study under a shared study ID will continue the participation in the CRC-SCA study.
- READISCA subjects who are not in the CRC-SCA Natural Hx study will be asked to participate in the CRC-SCA study.



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Thank you

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