The natural history of spinocerebellar ataxia type 3 in mainland China: a 2-year cohort study

Hong Jiang, MD

Department of Neurology

Xiangya Hospital, Central South University

Background

- **Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is caused by CAG expansion of *ATXN3*.**

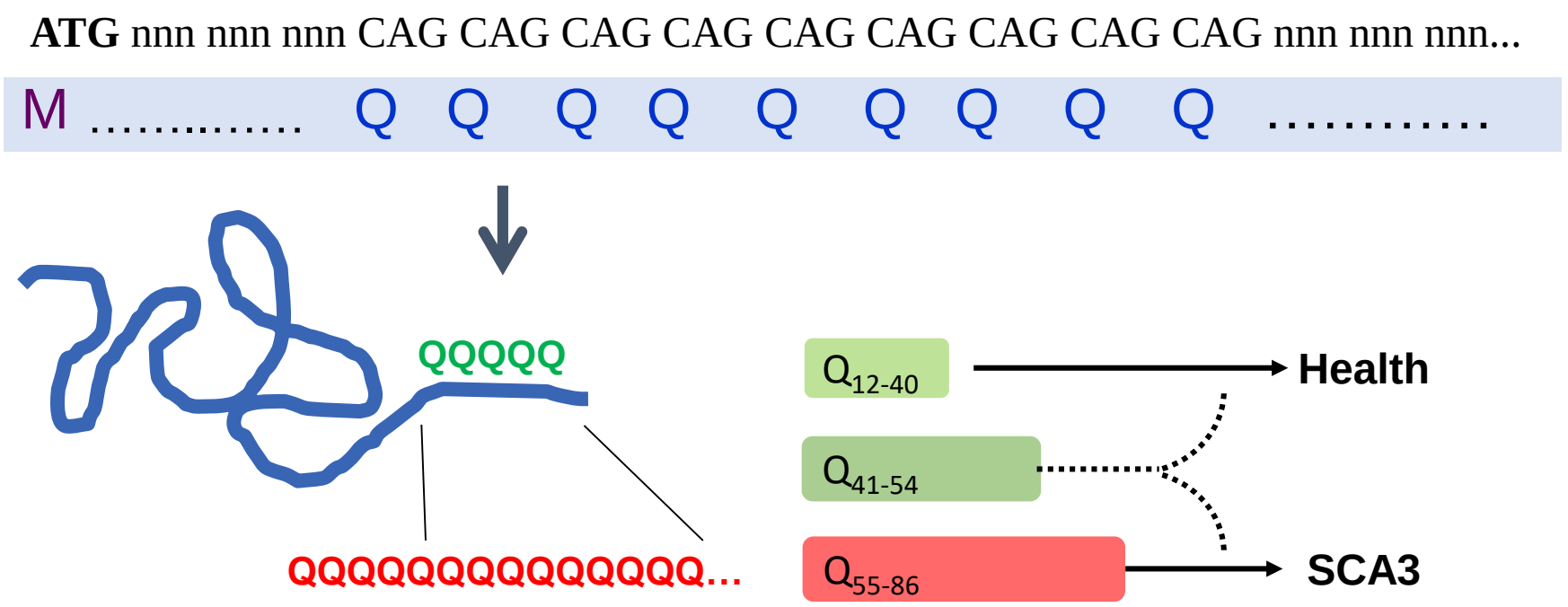


Figure 1 CAG repeat of *ATXN3* (M: methionine; Q: glutamine)

J Neurochem, 2019, 148(1):8-28.

Background

- **Spinocerebellar ataxia type 3 (SCA3) is one of the most common SCAs.**

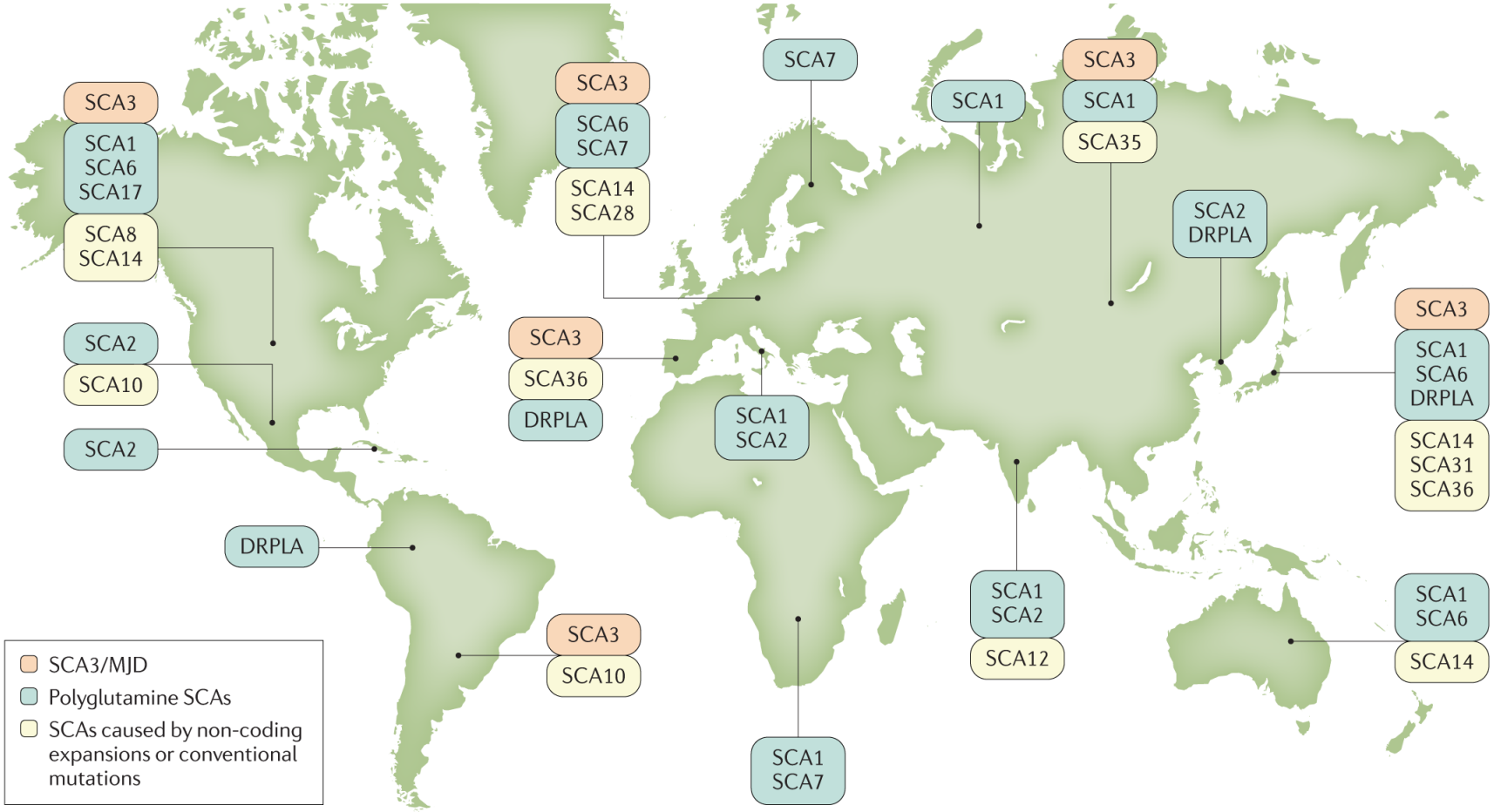


Figure 2. Geographical distribution of SCAs.

Nat Rev Dis Primers, 2019, 5(1):24.

Background

- **Highly variable phenotype of SCA3**

Subtype	Characteristic
1	AAO < 20, progress more quickly, prominent pyramidal signs and extrapyramidal features as well as ataxia.
2	20 ≤ AAO ≤ 50, the most common type, cerebellar ataxia, progressive external ophthalmoplegia and pyramidal signs.
3	40 ≤ AAO ≤ 75, peripheral signs such as motor neuropathy and muscle atrophy together with atxia.
4	Parkinsonism associated with other core clinical features, the rarest presentation.
5	Pure spastic paraplegia.

AAO = age at onset

Prog Neurobiol, 2012, 97(2):239-257.

Background

- **Divergent results in natural history studies of SCA3 (Till Sep 2015).**

Number	Region	Sample size	Follow-up duration	Outcome	Progression rate (points/year), mean (95% CI)	Affecting factor	Year of Publish
1	EUROSCA	122	2 y	SARA INAS	1.61 (1.37-1.85) 0.30 (0.14-0.46)	Disease duration Gender (Female)	2011
2	EUROSCA	122	8 y	SARA INAS	1.56 (1.42-1.70) NA	Not found Gender (Female)	2015
3	France	58	3 y	SARA	1.70 (1.31-2.09)	Not found	2012
4	US (CRC-SCA)	138	2 y	SARA	0.65 (0.18-1.12)	Not found	2013
5	Brazile	105	2-10 y	NESSCA	1.26	CAGexp AAO	2010
6	Taiwan	45	8-38 m	SARA	3.00 (2.56-3.44)	Not reported	2011

SARA = the Scale for the Assessment and Rating of Ataxia; INAS = the Inventory of Non-Ataxia Signs; CAGexp refers to the CAG repeat of expanded allele of *ATXN3*; AAO = age at onset

Question

- **What’s about the natural history of SCA3 in mainland China?**

- **Is there any population specific characteristic of natural history of SCA3 in mainland China?**

Study design

- **A 2-year longitudinal cohort study, followed annually.**
- **Recruited time: October 1, 2015 to September 30, 2016.**
- **Accomplished time: October 2018.**
- **Registered with Chictr.org on Sep 15, 2015, ChiCTR-OOC-15007124.**
- **Inclusion criteria.**
  - **With pathogenic allele (CAG repeats ≥ 55) in *ATXN3*.**
  - **Be able to understand and provide written informed consent to participate in the study.**
- **Primary outcome: SARA.**
- **Second outcomes: INAS and SCA Functional Index (SCAFI).**

Primary outcome

- **Scale for the Assessment and Rating of Ataxia (SARA)**

Item	Score range	Item	Score range
Gait	0-8	Finger chase	0-4
Stance	0-6	Nose-finger test	0-4
Sitting	0-4	Fast alternating hand movements	0-4
Speech disturbance	0-6	Heel-shin slide	0-4
Total	0-40		

Note: 0 representing no ataxia; 40 representing the most severe ataxia

Second outcomes

Inventory of Non-Ataxia Signs (INAS)

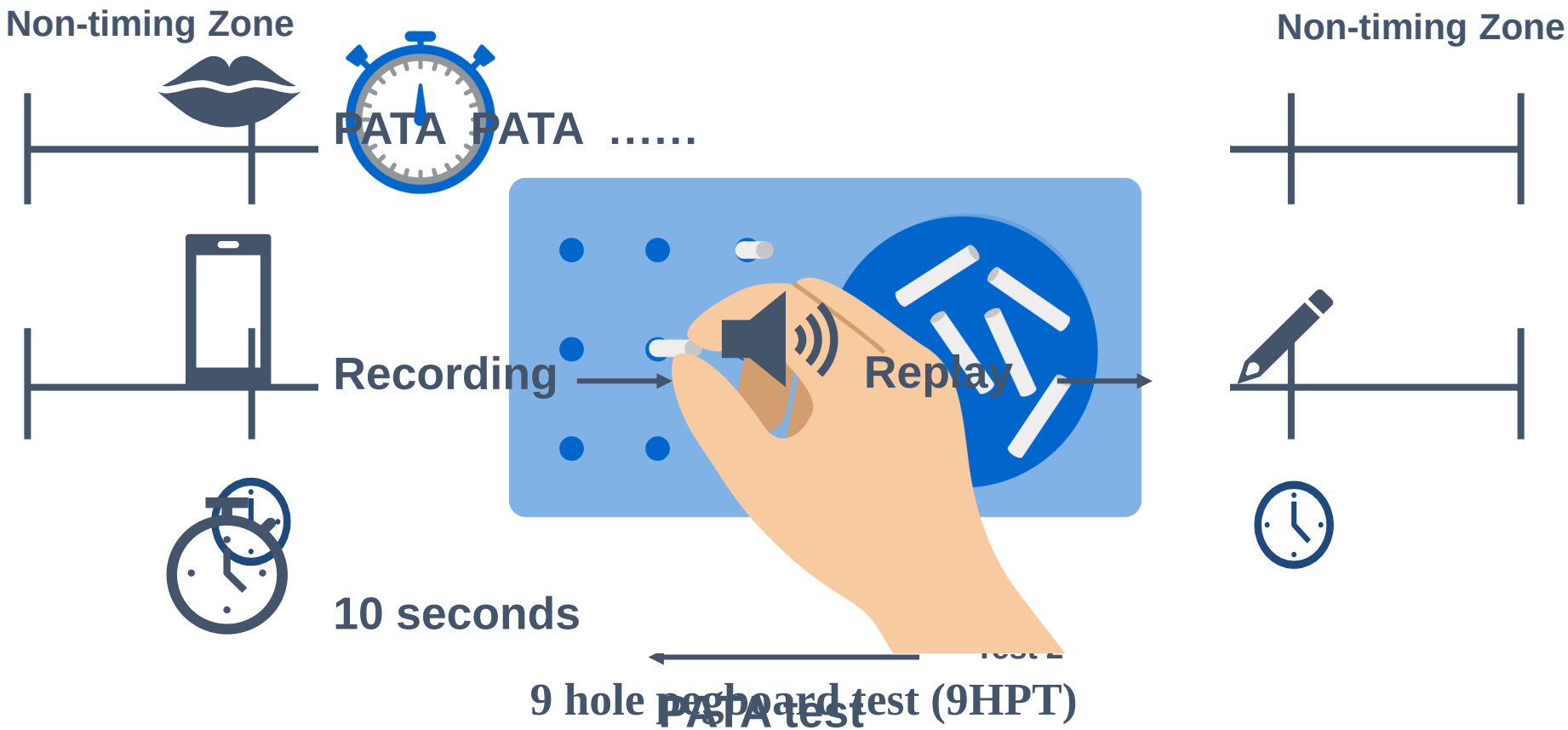
Item	Yes/No	Item	Yes/No
Hyperreflexia	1/0	Rigidity	1/0
Areflexia	1/0	Chorea/dyskinesia	1/0
Extensor plantar	1/0	Dystonia	1/0
Spasticity	1/0	Resting tremor	1/0
Paresis	1/0	Sensory symptoms	1/0
Muscle atrophy	1/0	Urinary dysfunction	1/0
Fasciculation	1/0	Cognitive dysfunction	1/0
Myoclonus	1/0	Brainstem oculomotor signs	1/0
Total	0-16		

These 16 binary variables can be summed up to a simple sum score, 16 representing all of non-ataxia signs.

Second outcomes

- **SCA Functional Index (SCAFI)**

- **A comprehensive index of 8MW, 9HPT, and PATA test.**
- **A higher SCAFI score represent a better functional status.**



Study profile

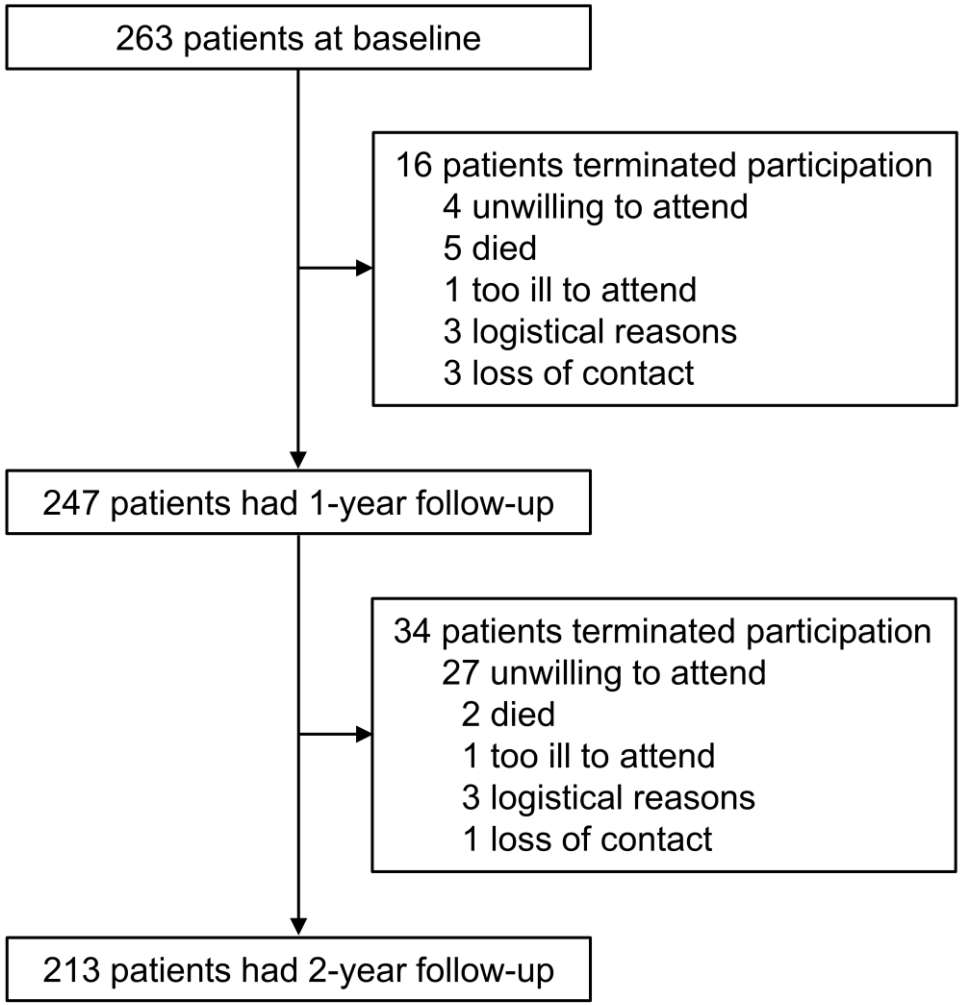


Figure 3. Study Profile.

Data shows the patient number at each visit and the reasons of dropout.

Result

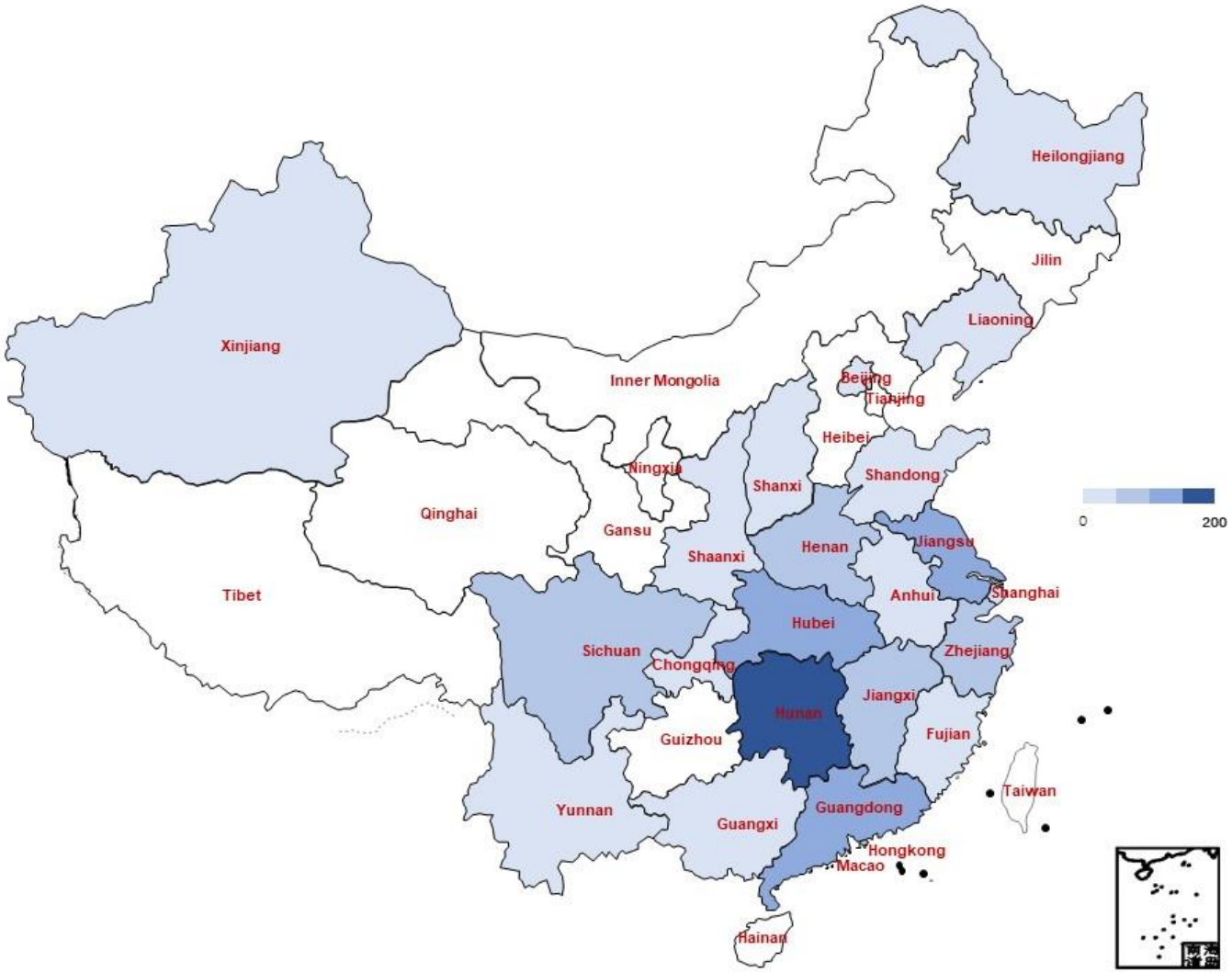


Figure 4. Geographical distribution of SCA3 patients in this study.

Result

Table 1 Baseline characteristics of the SCA3 cohort.

	Full cohort	Subgroup with at least one follow-up	Statistics (χ^2 or *U*)	*P*
No.	263	247	NA	NA
No. of families	165	155	NA	NA
Women (%)	138 (52.5%)	131 (53.0%)	0.02	0.898
Age at baseline (years)	44.67 ± 11.29	44.42 ± 10.81	32140.00	0.838
Age at onset (years)	36.29 ± 10.22	36.15 ± 9.86	32298.50	0.913
Disease duration (years)	8.38 ± 5.08	8.27 ± 5.10	31985.50	0.765
Length of expanded allele (repeat units)	71.88 ± 3.43	71.83 ± 3.31	32452.50	0.986
Length of normal allele (repeat units) [a]	19.98 ± 5.95	20.00 ± 5.99	32224.50	0.999
SARA score	15.61 ± 7.94	15.45 ± 7.83	32049.50	0.795
INAS count	4.84 ± 2.35	4.86 ± 2.36	32347.50	0.936
SCAFI score [b]	-0.35 ± 1.20	-0.32 ± 1.19	19581.00	0.857

Result

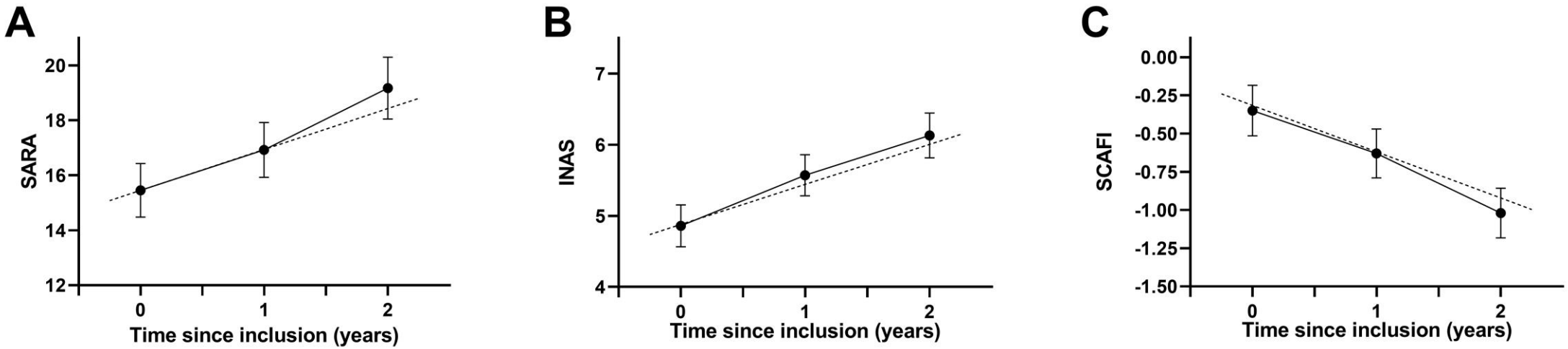


Figure 5. Progression of SARA, INAS, and SCAFI in SCA3 patients.

Result

Table 2 Linear mixed effect modeling for multivariable affecting SARA, INAS, and SCAFI progression.

Response variable	Variables in fixed effect	Estimate	SE	95% CI	*t*	*P*
SARA	Time	1.491	0.079	1.336~1.646	18.938	4.398e-50
	SARA at baseline	0.999	0.004	0.991~1.007	245.779	0.000
	Time*Length of expanded allele	0.107	0.024	0.060~0.154	4.493	1.1e-5
INAS	Time	0.547	0.046	0.457~0.638	11.898	4.951e-26
	INAS at baseline	0.953	0.023	0.909~0.998	42.149	1.298e-122
	Time*INAS at baseline	-0.099	0.020	-0.138~-0.060	-4.999	1e-6
SCAFI	Time	-0.272	0.011	-0.293~-0.251	-25.391	4.061e-60
	SCAFI at baseline	0.996	0.007	0.982~1.010	139.931	3.340e-195
	Time*Length of normal allele	0.004	0.002	0.0002~0.0071	2.060	0.041
	Time*SCAFI at baseline	-0.094	0.009	-0.111~-0.076	-10.669	9.163e-21

Result

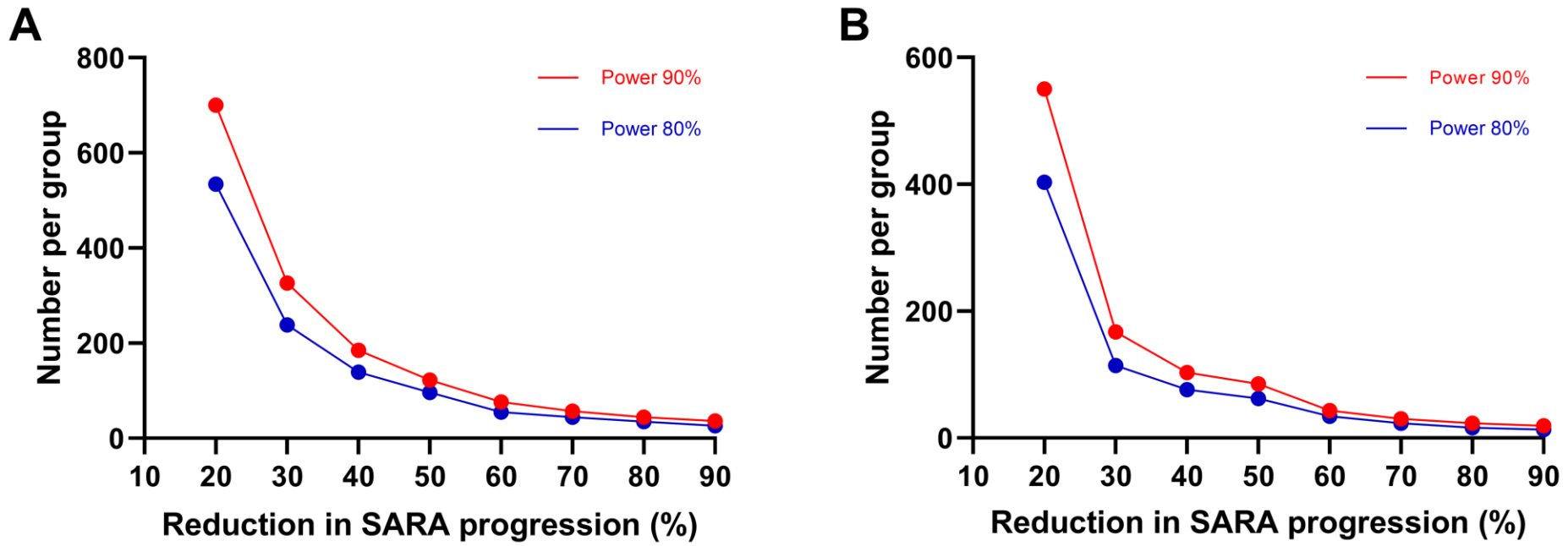


Figure 6. Sample size estimates.

Required sample size per group in two-armed clinical trial for 1-year (A) and 2-years duration (B), to detect various differences in SARA progression as a function of treatment efficacy and a statistical power of 80% and 90%.

Progression of Ataxia in different SCA3 studies

Number	Region	Sample size	Follow-up duration	Outcome	Progression rate (points/year), mean (95% CI)	Affecting factor	Year of Publish
1	EUROSCA	122	2 y	SARA	1.61 (1.37-1.85)	Baseline duration (+)	2011
2	EUROSCA	122	8 y	SARA	1.56 (1.42-1.70)	Not found	2015
3	France	58	3 y	SARA	1.70 (1.31-2.09)	Not found	2012
4	US (CRC-SCA)	138	2 y	SARA	0.65 (0.18-1.12)	Not found	2013
5	Taiwan	45	8-38 m	SARA	3.00 (2.56-3.44)	Not reported	2011
6	Taiwan	118	5 y	SARA	1.60 (1.33-1.87)	CAG_{exp} (+)	2019
7	Netherlands	82	15 y	ICARS	2.57 (2.27-2.86)	CAG_{exp} (+)	2021
8	This study	247	2 y	SARA	1.49 (1.33-1.65)	CAG_{exp} (+)	2022

Progression of Ataxia based on Meta-analysis

Table 1 Baseline studies and patients characteristics

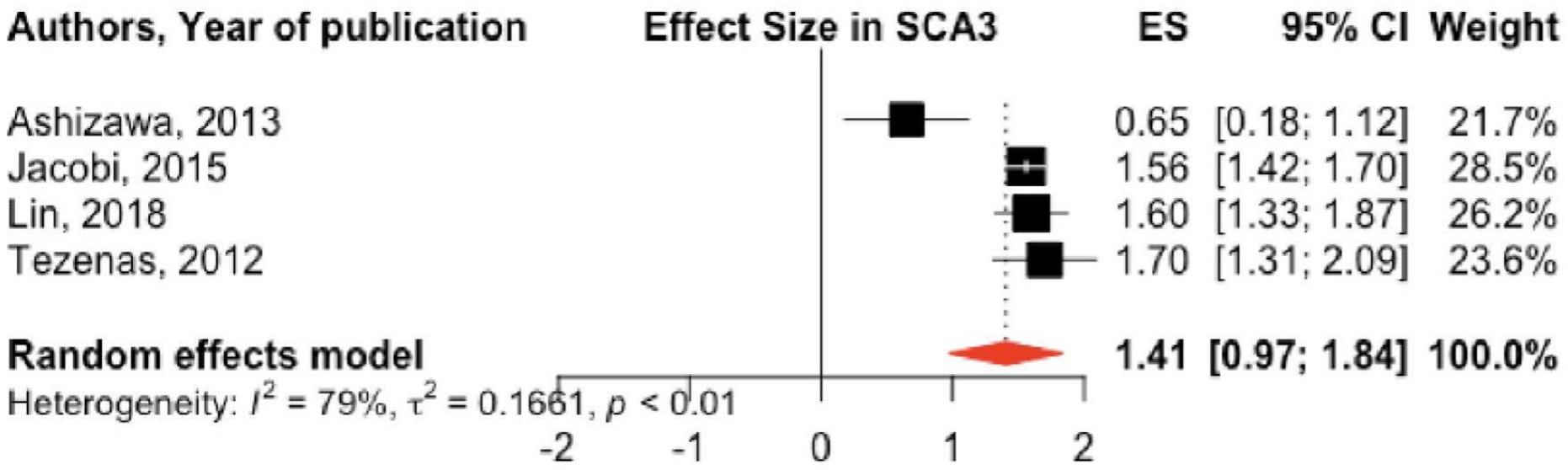
Subtype disease	Study	Location	Sample	Men (*n*)	Age	CAG	Disease duration	Age at onset	SARA	Maximum follow-up
SCA1	Tezenas, 2012	France	25	17	48	NR	9	40	16.9	3
	Ashizawa, 2013	USA	60	48	49.28	NR	8.93	40.41	14.16	2
	Jacobi, 2015	Europe	107	66	46	49	9	37	14.8	8
	Lin, 2018	Taiwan	10	4	53.60	46.20	5.40	48.20	13.45	5
SCA2	Tezenas, 2012	France	35	16	45	NR	13	32	15.4	3
	Ashizawa, 2013	USA	75	54	49.81	NR	13.46	36.85	16.82	2
	Jacobi, 2015	Europe	146	68	46	40	11	35	15.7	8
	Lin, 2018	Taiwan	37	19	45.57	40.24	5.08	40.49	9.53	5
	Monte, 2018	Brazil	49	27	46.35	40.35	12.94	33.23	18.42	2
SCA3	Tezenas, 2012	France	58	23	48	NR	11	37	13.8	3
	Ashizawa, 2013	USA	138	129	50.34	NR	10.92	39.25	14.98	2
	Jacobi, 2015	Europe	122	61	50	71	12	38	14.1	8
	Lin, 2018	Taiwan	118	48	47.79	70.91	7.46	40.33	12.22	5
SCA6	Tezenas, 2012	France	5	1	57	NR	11	46	12.7	3
	Ashizawa, 2013	USA	72	62	63.94	NR	11.76	52.18	14.13	2
	Yasui, 2014	Japan	46	23	63.0	23.2	15.0	48.0	15.9	3
	Jacobi, 2015	Europe	87	48	65	22	10	55	15.0	8
	Lin, 2018	Taiwan	25	9	58.68	23.56	7.12	46.56	11.81	5

Data are summarized by mean for continuous variable and number for categorical variables

CAG length of expanded repeats allele, *SARA* Scale for the Assessment and Rating Ataxia, *SCA* spinocerebellar ataxia, *NR* not reported

J Neurol, 2021, 268(8):2749-56.

Progression of Ataxia based on Meta-analysis



J Neurol, 2021, 268(8):2749-56.

Is CAGexp a population-specific affecting factor?

Number	Region	Sample size	Follow-up duration	Outcome	Progression rate (points/year), mean (95% CI)	Affecting factor	Year of Publish
1	EUROSCA	122	2 y	SARA	1.61 (1.37-1.85)	Baseline duration (+)	2011
2	EUROSCA	122	8 y	SARA	1.56 (1.42-1.70)	Not found	2015
3	France	58	3 y	SARA	1.70 (1.31-2.09)	Not found	2012
4	US (CRC-SCA)	138	2 y	SARA	0.65 (0.18-1.12)	Not found	2013
5	Taiwan	45	8-38 m	SARA	3.00 (2.56-3.44)	Not reported	2011
6	Taiwan	118	5 y	SARA	1.60 (1.33-1.87)	CAG_{exp} (+)	2019
7	Netherlands	82	15 y	ICARS	2.57 (2.27-2.86)	CAG_{exp} (+)	2021
8	This study	247	2 y	SARA	1.49 (1.33-1.65)	CAG_{exp} (+)	2022

Progression of non-ataxia signs in SCA3 studies

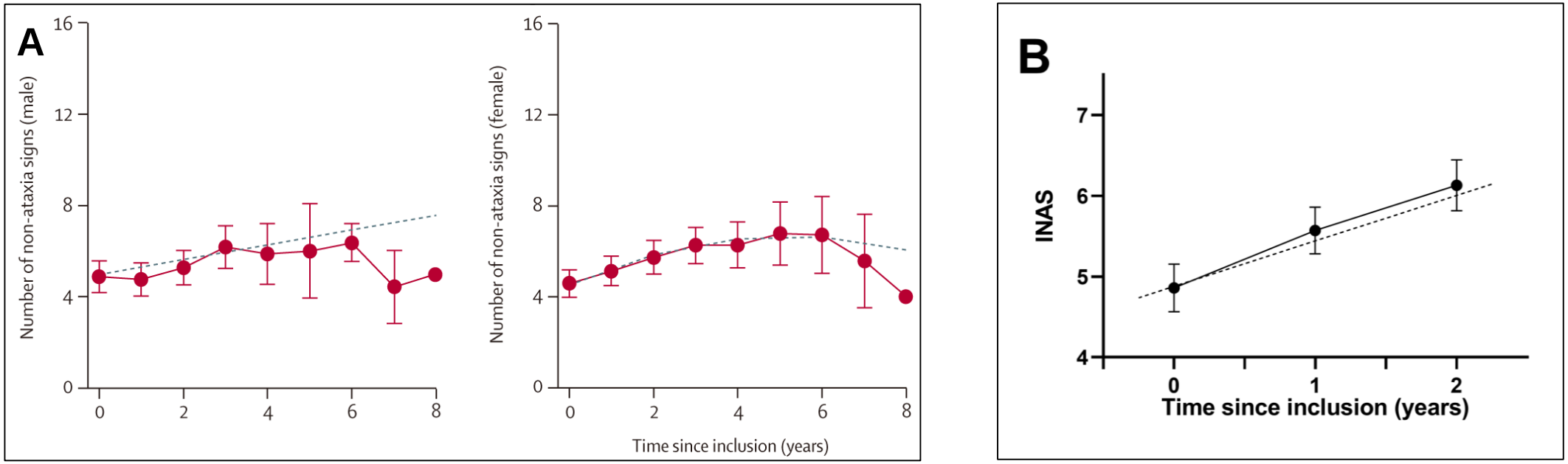


Figure 7. Progression of INAS in EUROSCA (A) and this study (B).

Summary

- **This study provide quantitative data on the progression of SCA3 in mainland China.**
- **This study identified the expanded CAG as a factor for faster progression of ataxia symptoms.**
- **This study provide useful information for sample size calculation and patient stratification in the future SCA3 clinical trials.**

Future direction

- **Collect other longitudinal data such as neuroimaging data and longitudinal biofluid data, to establish a more comprehensive profile of disease progression of SCA3.**

- **Multicenter and international cooperation.**

Acknowledgments

Jiang Lab

- Key Laboratory of Hunan Province in Neurodegenerative Disorders
- Laboratory of Medical Genetics, Central South University
- National Clinical Research Center for Geriatric Diseases (Xiangya)

- National Key R&D Program of China (No. 2021YFA0805200)
- National Natural Science Foundation of China (No. 81974176 and No. 82171254)

Our collaborators

- **Prof. Thomas Klockgether (University of Bonn)**
- **Prof. Tetsuo Ashizawa (Houston Methodist)**
- **Dr. Mark Williamson (University of North Dakota)**