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# Comparable progression of spinocerebellar ataxias between Caucasians and Chinese

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ABSTRACT

*Introduction:* The aim of this study is to reappraise the progression of the five most common spinocerebellar ataxias (SCAs) in the Chinese population and to establish a much-needed critical comparison with that in other ethnic groups. There are very few longitudinal cohort studies of SCAs in Asian populations. An intriguing finding in an earlier study demonstrated a faster progression of SCA among Chinese than that among Caucasians.
*Methods:* Patients with SCA1, SCA2, SCA3, SCA6 or SCA17 were consecutively assessed using the scale for the assessment and rating of ataxia (SARA) for five years. A linear mixed model was used to compare the annual progression rates measured using the SARA among patients with different SCA subtypes. Predictors of the progression rates were analyzed.
*Results:* A total of 199 patients with SCA (10 with SCA1, 37 with SCA2, 118 with SCA3, 25 with SCA6 and 9 with SCA17) were enrolled. The mean annual increase in SARA scores was 1.23 points for SCA1, 1.52 points for SCA2, 1.60 points for SCA3, 0.99 points for SCA6 and 3.26 points for SCA17. A larger CAG repeat length ($\geq$74) was associated with faster progression in SCA3, whereas a lower total SARA score at the first visit ($<$ 12) was associated with faster clinical progression in SCA6.
*Conclusion:* The results of this study confirm that the annual progression rates of SCA2 and SCA3 are comparable between Han Chinese and other ethnic populations. More studies are warranted to confirm the rapid progression of SCA17 observed in our cohort.

## 1. Introduction

Spinocerebellar ataxias (SCAs) are rare inherited neurodegenerative diseases with clinical and genetic heterogeneities [1,2]. The prevalence of SCA subtypes varies across different populations [3–5]. SCA1, SCA2, and SCA3 are the most common subtypes in Caucasians, while SCA2, SCA3, SCA6 and dentatorubral-pallidoluysian atrophy (DRPLA) are more frequently encountered in Japanese and Chinese people [6,7].

The phenotypic features [8,9] and disease progression [10–13] of SCA1, SCA2, SCA3 and SCA6 have previously been illustrated in a few studies, mostly in Caucasians [8–13]. However, studies in Asians, including one of ours, appear to convey a different perspective in terms of disease progression and raise the concern that different genetic backgrounds may play a role in SCAs [14,15].

In this article, we longitudinally and quantitatively investigated the severity and progression of five common SCA subtypes over a long follow-up period among a large group of Han Chinese patients in Taiwan using the scale for the assessment and rating of ataxia (SARA). We aimed to identify factors that determine the disease severity and progression. We also examined the longitudinal changes in SARA subscores for different SCA subtypes since they may potentially indicate the preferential involvement of pathophysiological pathways in each subtype. As potential treatments for SCAs will be emerging, knowledge of the natural history and progression of each SCA subtype in each population is essential to assess therapeutic effects.

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## 2. Methods

### 2.1. Study design and participants

We consecutively enrolled 199 Chinese patients with SCA1, SCA2, SCA3, SCA6 or SCA17 from the Neurology Clinic of Taipei Veterans General Hospital between Oct. 2007 and Oct. 2016. Molecular testing was performed according to the practice guideline recommended by the SCAbase website (www.scabase.eu) [16]. Polymerase chain reaction (PCR) was performed with fluorescent-labeled primer sets to amplify the trinucleotide repeat regions in the ataxin 3 (*ATXN3*), ataxin 2 (*ATXN2*), calcium voltage-gated channel subunit alpha 1 A (*CACNA1A*), ataxin 1 (*ATXN1*), and TATA-box binding protein (*TBP*) genes separately. We used similar primer designs and PCR conditions as those employed in a previous study [7]. Fragment length analysis was conducted on an ABI Prism 3700 Genetic Analyzer (Applied Biosystems, Waltham, MA). The study was approved by the Ethics Committee of Taipei Veterans General Hospital. All participants were of Han Chinese descent and had provided written informed consent prior to participating in the study.

### 2.2. Clinical evaluations

The age at onset (AO) was defined as the age at which the earliest symptoms of ataxia occurred according to statements from the patients or their caregivers. Disease duration was defined as the length of time from symptom onset to the first visit to our clinic. Since most studies on cerebellar ataxia used SARA, a reliable and validated measure to evaluate the severity of ataxia [17,18], we also used the 40-point (0 being normal) SARA to score the clinical severity of ataxia. Between Oct. 2007 and Oct. 2016, 199 study participants were rated annually ( ± 3 months) by a single board-certified neurologist (B.W.S.) using the SARA for a total of 721 ratings. Because the numbers of patients attending our out-patient clinic regularly for more than 5 years in a row were limited, only the first to the 5th SARA scores obtained annually were included in the analyses. The 199 patients were examined 2 to 5 times (mean ± SD: 3.07 ± 1.04) over a follow-up period of 9–60 months, resulting in a total of 610 assessments.

### 2.3. Statistical analysis

To compare the characteristics of study participants across different SCA subtypes, we used the chi-squared test for dichotomous variables and one-way analysis of variance (ANOVA) for continuous variables. Fisher's least significant difference (LSD) test for the post hoc analysis was employed for pairwise comparisons between SCA3 and one of the other SCA subtypes (i.e., SCA1, SCA2, SCA6 or SCA17). To investigate factors that influence SARA total scores at the first visit, multivariate stepwise regression was performed with the variables AO, disease duration and CAG repeat length of the expanded alleles. Sex and repeat length of the normal alleles were excluded from the multivariate regression model since neither variable was associated with SARA total scores in the univariate regression analysis.

The annual progression rate of SARA total score was calculated in each SCA subtype using a linear mixed model with random effects on the intercept and slope [19]. We first tested for a linear, quadratic or cubic effect of time, and the linear model was selected according to the Akaike information criterion. The linear mixed model was used to investigate differences in the slope (i.e., progression rates of SARA total scores) across SCA subtypes. Since half of the subjects enrolled in this study suffered from SCA3, pairwise comparison of the annual increase in the SARA total score was conducted between patients with SCA3 and those with the other SCA subtypes.

To identify factors that might influence the annual progression of SARA total score in each SCA subtype, we used several scenarios to divide the patients into two groups. We only performed subgroup analyses for SCA2, SCA3, and SCA6 because the small sample sizes of SCA1 and SCA17 patients may lead to insufficient power in statistical analysis. The cutoff values used to dichotomize subjects within the SCA2, SCA3, and SCA6 subgroups were as the follows: (1) the mean CAG repeat length of the expanded alleles, (2) the mean SARA total score upon enrollment, and (3) the mean disease duration. We used a linear mixed model to compare the progression in the SARA total scores between two subgroups.

Similar analyses were conducted again to compare the SARA subscores at the first visit and the annual progression of each subscore across different SCA subtypes. For SARA subscores at the first visit, ANOVA and LSD post hoc analyses were performed for group comparisons and pairwise comparisons, respectively. A linear mixed model was employed to compare the progression of each SARA subscore between SCA3 and the other SCA subtypes.

To compare the clinical progression of ataxia between Chinese patients and patients of other ethnic groups, literature reports investigating the annual progression rate in terms of the SARA were included [10–12,14]. SPSS software version 15.0 (SPSS, Inc., Chicago, IL) was used for the statistical analysis. All tests were two-sided, and a $p$ value $< 0.05$ was considered significant.

## 3. Results

### 3.1. Baseline characteristics at the first visit

The average AO and age at the first evaluation of the study participants were significantly older in SCA1 and SCA6 than those in the other SCA subtypes. The disease durations and SARA scores at the first visit were similar among patients with SCA1, SCA2, SCA3, SCA6 or SCA17 (see Table 1).

Multivariate stepwise regression analysis was conducted to ascertain the factors that were significantly related to SARA total scores at the first visit in each SCA subtype (see Suppl. Table 1). For SCA2, disease duration and CAG repeat length of the expanded alleles were related to SARA total scores. For SCA3, AO, disease duration, and CAG repeat length of the expanded alleles were strong predictors of a higher SARA score at the first clinic visit. For SCA6, an older age at the first evaluation significantly contributed to a higher SARA total score at the first visit. We failed to identify any predictive factors for SARA scores at the first visit for SCA1 and SCA17, which may be due to the small sample sizes.

### 3.2. Longitudinal changes in SARA total scores

A linear mixed model was used to estimate annual progression in terms of SARA total scores in each SCA subtype. For all SCA subtypes, SARA scores increased significantly over annual follow-ups ($p < 0.05$, see Suppl. Table 2). The average annual increase in the SARA total score was 1.23 points per year for SCA1, 1.52 points per year for SCA2, 1.60 points per year for SCA3, 0.99 points per year for SCA6 and 3.26 points per year for SCA17. Because the case number was significantly larger for SCA3, pairwise comparisons of annual progression according to SARA scores were performed between patients with SCA3 and those with other SCA subtypes (see Fig. 1A–D). The annual progression rates in terms of SARA total scores were similar between SCA1 and SCA3 ($p = 0.41$), as well as between SCA2 and SCA3 ($p = 0.83$). The annual increase in SARA total scores in SCA6 was significantly smaller than that in SCA3 ($p = 0.046$). In contrast, progression seemed to be significantly faster in patients with SCA17 than that in patients with SCA3 ($p = 0.006$).

To identify other factors that have an impact on annual progression in terms of SARA total score in SCA2, SCA3 and SCA6, a mixed linear model was used after patients in each subtype were divided into two groups according to the average CAG repeat length of the expanded alleles (see Table 2). For patients with SCA3, those carrying a larger

**Table 1**
Characteristics of study participants.

| Mean ± SD (95% Confidence interval) | SCA1 | SCA2 | SCA3 | SCA6 | SCA17 | *p* value[a] |
|---|---|---|---|---|---|---|
| N | 10 | 37 | 118 | 25 | 9 | |
| Male (%) | 40.00% | 51.35% | 40.67% | 36.00% | 22.22% | 0.52 |
| CAG repeat length, expanded alleles | 46.20 ± 2.53 (44.39–48.01) | 40.24 ± 2.95 (39.26–41.23) | 70.92 ± 4.67 (70.06–71.77) | 23.56 ± 1.12 (23.10–24.02) | 45.22 ± 3.15 (42.80–47.65) | – |
| CAG repeat length, normal alleles | 29.20 ± 2.44 (27.45–30.95) | 21.84 ± 1.17 (21.45–22.23) | 20.42 ± 6.53 (19.23–21.61) | 13.68 ± 1.15 (13.21–14.15) | 36.67 ± 2.24 (34.35–38.39) | – |
| Age at first evaluation (year) | 53.60 ± 5.42 (49.72–57.48) | 45.57 ± 14.13 (40.86–50.28) | 47.79 ± 12.34 (45.54–50.04) | 53.68 ± 8.86 (50.02–57.34) | 44.11 ± 12.83 (34.25–53.97) | 0.04 |
| Age at onset (year) | 48.20 ± 5.67 (44.14–52.26) | 40.49 ± 13.91 (35.85–45.13) | 40.33 ± 11.68 (38.20–42.46) | 46.56 ± 8.80 (42.93–50.19) | 38.11 ± 11.03 (29.63–46.59) | 0.04 |
| Disease duration (year) | 5.40 ± 5.21 (1.67–9.13) | 5.08 ± 3.44 (3.93–6.23) | 7.46 ± 6.63 (6.25–8.67) | 7.12 ± 5.36 (4.91–9.33) | 6.00 ± 5.34 (1.90–10.10) | 0.25 |
| SARA total score during first visit | 13.45 ± 6.92 (8.50–18.40) | 9.53 ± 4.36 (8.07–10.98) | 12.22 ± 8.48 (10.67–13.76) | 11.81 ± 6.79 (9.01–14.61) | 15.33 ± 7.69 (9.42–21.24) | 0.20 |
| Follow-up times | 3.20 ± 0.92 (2.54–3.86) | 3.22 ± 0.98 (2.89–3.54) | 3.11 ± 1.08 (2.91–3.31) | 2.84 ± 1.03 (2.42–3.26) | 2.33 ± 0.50 (1.95–2.72) | 0.14 |

SARA = the scale for the assessment and rating of ataxia.
[a] Analysis of variance (ANOVA) or Chi-squared test where appropriate.

expanded CAG repeat length had significantly faster disease progression (estimated annual increase: 2.35 points) than those with a smaller expanded CAG repeat length (estimated annual increase: 1.35 points) ($p = 0.003$). For patients with SCA2 or SCA6, annual progression according to SARA scores was similar between those with larger expanded CAG repeat lengths and those with smaller expanded repeat lengths.

Similar subgroup analyses were performed by dividing the patients by average SARA total scores at the first visit (see Table 2). SCA6 patients with a milder disease at the first visit (SARA score < 12) seemed to have faster disease progression than those with a SARA score ≥ 12 at the first visit (estimated annual increases of 1.60 points and 0.29 points, respectively). For SCA6, although the CAG repeat lengths were similar, those with a baseline SARA score lower than 12 tended to have a shorter disease duration (p = 0.01) and a younger age at the first clinic visit (p = 0.003) (see Suppl. Table 3).

For patients with SCA2 or SCA3, disease severity at the first visit did not have any impact on disease progression at longitudinal follow-ups (see Table 2). For SCA2, those with a higher SARA score at the first visit tended to have a longer disease duration and a larger expanded CAG repeat length (p = 0.04 and 0.01, respectively; see Suppl. Table 3). SCA3 patients with a higher SARA score at the first visit tended to have a longer disease duration (p < 0.001) as well as longer CAG expansion (p = 0.01). We failed to find any significant association between disease duration and SARA progression for SCA2, SCA3 or SCA6 when similar analyses were conducted using the cutoff value of average disease duration (see Table 2).

### 3.3. SARA subscores at the first visit and longitudinal follow-ups

We analyzed the SARA score at the first visit and the annual progression of SARA subscores in each SCA subtype. At the first visit, patients with SCA6 had significantly higher SARA subscores in the heel-knee-shin slide test than those with SCA3 (2.03 points and 1.42 points for SCA6 and SCA3, respectively; $p = 0.004$) (see Suppl. Table 4). No significant differences were found among SCA1, SCA2, SCA3, SCA6 and SCA17 at the first visit in other SARA subscores.

At the longitudinal follow-ups, patients with SCA6 exhibited a slower deterioration of stance (see Fig. 1E). Patients with SCA17 seemed to present faster deterioration in finger chase (annual increases of 0.38 and 0.08 for SCA17 and SCA3, respectively) and fast alternating hand movements (annual increases of 0.47 and 0.13 for SCA17 and SCA3, respectively).

### 3.4. Comparison of SARA progression across different ethnic groups

Table 3 shows the annual progression rate of total SARA scores for each SCA subtype in the present cohort and literature reports. From this study, the annual increases in SARA total scores in the Chinese population were 1.23, 1.52, 1.60, 0.99 and 3.26 points per year for SCA1, SCA2, SCA3, SCA6, and SCA17, respectively. In the latest European integrated project on spinocerebellar ataxias (EUROSCA study) involving 462 patients from 17 ataxia referral centers in ten European countries [11], SCA1 progressed fastest, followed by SCA3, SCA2 and SCA6, with annual progression rates of 2.11, 1.56, 1.49, and 0.80 SARA points per year, respectively. The annual progression rates were similar between the earlier EUROSCA study with a follow-up period of 2 years [10] and their latest report with a longer follow-up for up to 8 years [11]. Slower progression was reported by the Clinical Research Consortium for Spinocerebellar Ataxia (CRC-SCA) in the United States, in which the annual increases in SARA score for SCA1, SCA2, SCA3, and SCA6 were 1.61, 0.71, 0.65, and 0.87 points per year, respectively [12]. Only one study longitudinally assessed the progression of ataxia in Japanese patients with SCA6 and found an annual increase of 1.33 SARA points per year [14].

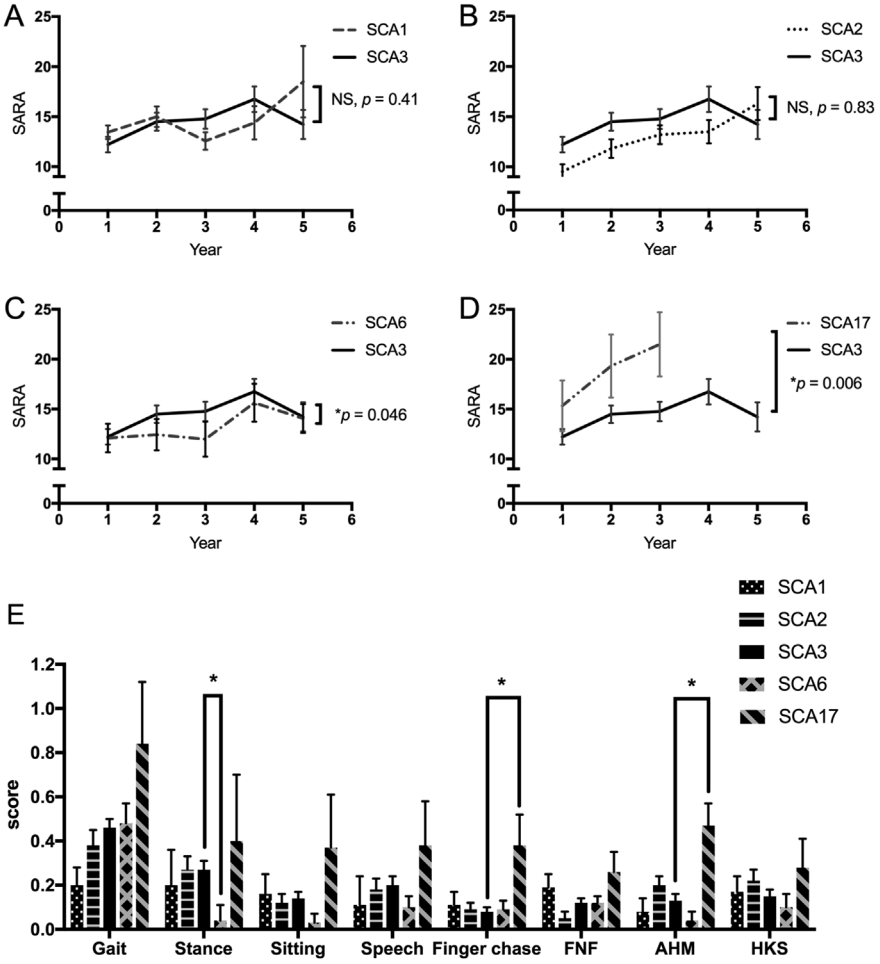


**Fig. 1. Comparison of the annual progression rates of SARA total scores and SARA sub-scores across SCA subtypes**. Pairwise comparison of the annual increase in **(A–D)** SARA total scores and **(E)** SARA sub-scores between SCA3 and other subtypes. The *p* value was calculated using a linear mixed model when comparing between SCA3 and either one of other SCA subtypes. $*p < 0.05$. AHM: alternating hand movements, FNF: finger-nose-finger test, HKS: heel-knee-shin test.

**Table 2**
Subgroup analysis using cutoff values of average CAG repeat length of the expanded alleles, average baseline SARA scores, or average disease duration.

| | Average CAG repeats of the expanded allele | | | Average SARA score at baseline | | | Average disease duration | | |
|---|---|---|---|---|---|---|---|---|---|
| | CAG repeats | N | ΔSARA/yr (95% CI) | SARA | N | ΔSARA/yr (95% CI) | Duration (yr) | N | ΔSARA/yr (95% CI) |
| SCA2 | ≥41 | 18 | 1.54 (0.99–2.08) | ≥10 | 18 | 1.03 (0.51–1.56) | ≥5 | 28 | 1.34 (0.86–1.82) |
| | < 41 | 19 | 1.54 (0.80–2.29) | < 10 | 19 | 0.70 (0.15–1.25) | < 5 | 14 | 1.79 (0.41–3.16) |
| | *p* value* | | 0.94 | | | 0.58 | | | 0.41 |
| SCA3 | ≥74 | 31 | 2.35 (1.73–2.97) | ≥18 | 24 | 1.41 (0.90–1.92) | ≥5 | 90 | 1.40 (1.14–1.66) |
| | < 74 | 87 | 1.35 (1.06–1.64) | < 18 | 94 | 1.14 (0.89–1.40) | < 5 | 40 | 1.45 (0.86–2.05) |
| | *p* value* | | 0.003* | | | 0.49 | | | 0.49 |
| SCA6 | ≥24 | 7 | 1.06 (0.33–1.79) | ≥12 | 11 | 0.29 (−0.21–0.78) | ≥5 | 19 | 0.81 (0.49–1.12) |
| | < 24 | 18 | 0.97 (0.35–1.59) | < 12 | 14 | 1.60 (0.95–2.25) | < 5 | 6 | 0.93 (−0.74–2.30) |
| | *p* value* | | 0.95 | | | 0.002* | | | 0.43 |

*Statistics analysis was performed from linear mixed model when comparing annual SARA progression rates between two subgroups.
*yr = year(s), SARA = the scale for the assessment and rating of ataxia.

## 4. Discussion

This study assessed the longitudinal progression of different SCA subtypes over a long period of time in a large group of patients of Han Chinese descent and compared the data with those collected from other ethnic groups. The annual progression rates of SCA2, SCA3, and SCA6 in Han Chinese are comparable to those reported in European populations [11]. The cohort of SCA17 in this longitudinal study is the first of its kind. Because of the limited sample size, the findings that the progression of SCA17 appeared to be twice as fast as that of SCA3 and SCA2 and of slower progression of SCA1 in the Chinese population await further validation. For SCA3, a higher CAG repeat length in the expanded alleles significantly predicted faster progression of ataxia symptoms. Regarding SCA2 or SCA6, the annual changes in SARA scores were similar between those with a higher CAG expanded repeat length and those with a lower CAG expanded repeat length. To our surprise, SCA6 patients with a lower SARA total score at the first visit were associated with faster deterioration of SARA scores during the

**Table 3**
Comparison of clinical progression of ataxia in terms of SARA in different ethnic groups.

| | | SCA1 | SCA2 | SCA3 | SCA6 | SCA17 | Follow-up (months) | | Ref., |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | interval | duration | published year |
| CRC-SCA (USA) | N | 39 | 52 | 93 | 54 | – | 6 | 24 | Ref 12, 2013 |
| | ΔSARA/yr | 1.61 | 0.71 | 0.65 | 0.87 | | | | |
| | $(CAG)_n$ | NA | NA | NA | NA | – | | | |
| EUROSCA (Europe) | N | 107 | 146 | 122 | 87 | – | 12 | 49 (35–72)* | Ref 11, 2015 |
| | ΔSARA/yr | 2.11 | 1.49 | 1.56 | 0.80 | – | | | |
| | $(CAG)_n$ | 47.4 ± 5.2 | 39.3 ± 3.2 | 68.8 ± 4.6 | 22.4 ± 0.9 | – | | | |
| | N | 113 | 155 | 125 | 86 | | 12 | 24 | Ref 10, 2011 |
| | ΔSARA/yr | 2.18 | 1.40 | 1.61 | 1st year: 0.35 2nd year: 1.40 | | | | |
| | $(CAG)_n$ | 49 ± 6 | 40 ± 4 | 71 ± 4 | 22 ± 1 | | | | |
| Chinese (Taiwan) | N | 10 | 37 | 118 | 25 | 9 | 12 | 36 (24–48)* | Present study |
| | ΔSARA/yr | 1.23 | 1.52 | 1.60 | 0.99 | 3.26 | | | |
| | $(CAG)_n$ | 46.20 ± 2.53 | 40.24 ± 2.95 | 70.92 ± 4.67 | 23.56 ± 1.12 | 45.22 ± 3.15 | | | |
| | N | – | 11 | 45 | 9 | 5 | 6 | 6–38 | Ref 15, 2011 |
| | ΔSARA/yr | – | 2.88 | 3.00 | 2.04 | 4.50 | | | |
| | $(CAG)_n$ | | 42.4 ± 5.4 | 71.5 ± 8.1 | 23.4 ± 1.4 | 43.4 ± 0.5 | | | |
| Japanese | N | – | – | – | 46 | – | 12 | 36 | Ref 14, 2014 |
| | ΔSARA/yr | – | – | – | 1.33 | – | | | |
| | $(CAG)_n$ | | | | 23.2 ± 1.4 | | | | |

*Median (interquartile range).
(CAG)n = number of CAG repeats, yr = year, SARA = the scale for the assessment and rating of ataxia, NA = not available.

follow-ups, implying a steeper slope of disease progression in the early stage of SCA6.

The larger sample size with 3-times as many patients as in our previous report [15], together with extension of the observation period from 3 years to 5 years, strengthens the significance of our observation. For SCA2 and SCA3, the annual increases of 1.52 and 1.60 SARA points per year in the Chinese are very close to the progression rates of 1.49 and 1.56 points per year in European populations [11]. However, these progression rates are faster than the reported rates of 0.71 and 0.65 points per year, respectively, in the CRC-SCA study in the United States [12]. Since the average follow-up periods in the present study (36 months) and EUROSCA study (48 months) are longer than that of CRC-SCA study (24 months) [11,12], we believe that an annual increase of 1.5 points in the SARA total score is a reasonable estimate for SCA2 and SCA3 across different populations. Our findings justify the estimation that for a randomized case-control trial, sample sizes of 157 patients in the treatment arm for SCA1, 148 patients for SCA2, 191 patients for SCA3, 278 patients for SCA6, and 115 patients for SCA17 are needed to demonstrate the efficacy of a new therapy that would retard disease progression with a 50% reduction in SARA points over a one-year follow-up (alpha level, 0.05; power of 0.80) (http://glimmpse.samplesizeshop.org) [20,21].

SCA17 is a rare disease with complex clinical features, including Parkinsonism, chorea, dystonia, psychosis and/or dementia [22]. SCA17 accounted for 1.1% of all SCA cases in a large Caucasian cohort [23], but only 0.3% in a Japanese study [6]. In Taiwan, Korean and Thailand, SCA17 is more frequently encountered and should be considered in patients with ataxia and additionally atypical Parkinsonism [24–26]. We acknowledged that the small sample size in the current cohort may be insufficient to draw solid conclusions, but our study is the first to report the progression rate of SCA17. In this study, patients with SCA17 had a higher SARA total score at the first visit. In addition, the annual progression of SCA17 seemed to be twice as fast as that of SCA3 (3.26 vs. 1.60 points per year). Patients with SCA17 tended to exhibit faster deterioration in finger chase and fast alternating hand movements. Whether these features are attributable to coexisting Parkinsonism features requires further investigation [25–27].

The estimated annual changes in SARA total scores in our previous study were significantly higher than those reported in the current study [15]. Several factors may contribute to these discrepancies, including the smaller sample sizes in each SCA subtype, shorter observation interval, and different statistical methods used in the previous study. In the present study, we used a mixed linear model, which has become an increasingly popular statistical method of analysis with the advantage of managing repetitive measurements at different time points and missing data in a longitudinal study [11,19].

Controlling the factors that may result in faster disease progression in patients with the same SCA subtype is important since these confounding factors may attenuate statistical power in clinical trials. In this study, we noticed that a longer CAG repeat length in the expanded alleles is associated with faster progression in SCA3. The EUROSCA study showed that larger expanded repeats predicted faster progression in SCA1 but not SCA3 [11]. In the present Chinese cohort, the disease duration is 5 years shorter than that in the European study. The Asian genetic background and different disease stages at baseline may introduce discrepancies between the two studies. In SCA6, we found that a lower SARA score at the first visit seemed to be associated with a faster progression. Concordant with our observations, a lower SARA score at the first visit also correlated with faster progression in SCA6 in the EUROSCA and Japanese studies [11,14]. A shorter disease duration was associated with faster SARA score progression in SCA1 and SCA2 in the EUROSCA study [11]. However, disease duration was not found to be correlated with SARA progression in SCA2, SCA3 or SCA6 in the present study. In earlier reports, female gender was associated with faster progression of non-ataxia symptoms, increased risks of disability, and shortened survival [10,28]. Unfortunately, we did not evaluate non-ataxia symptoms in the present cohort, and we failed to find any gender effect on the progression of SARA score (data not shown).

This study has several limitations. First, only 39.6% and 22.6% of the patients completed the consecutive 4-year and 5-year follow-ups, respectively. Given that the patients who dropped out tended to be sicker and to exhibit profound disability, the SARA annual progression rate may have been underestimated. Second, the observations for SCA1 and SCA17 require further validation owing to the smaller sample sizes. Third, nonmotor features may also contribute to clinical disability, but this information was not collected with SARA which captured only ataxia symptoms. Parkinsonism may influence the evaluation of ataxia symptoms in some cases of SCA2 or SCA3 [29,30].

In conclusion, this longitudinal study made a much-needed comparison of disease progression for five common SCA subtypes between Chinese and other ethnic groups for the first time. The genotype (i.e., different SCA subtypes) is apparently the major determinant of annual

progression of SCAs in different populations. Recruiting a large number of participants from a single center is challenging in interventional trials. Basic knowledge of ethnicity-specific natural courses and confounding factors related to disease progression of a rare disease, such as SCA, is invaluable in upcoming clinical trials.

## Author roles

1) Statistical analysis: YC Lin and YC Liao
2) Conceptualization of the study: YC Lee and BW Soong
3) Patient enrollment: YC Lin, YC Lee, TY Hsu, YC Liao and BW Soong
4) Manuscript: YC Lin, YC Lee, YC Liao and BW Soong

## Declarations of interest

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## Appendix A. Supplementary data

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## References

[1] B.W. Soong, P.J. Morrison, Spinocerebellar ataxias, Handb. Clin. Neurol. 155 (2018) 143–174.
[2] T.D. Bird, Hereditary ataxia overview, in: R.A. Pagon, M.P. Adam, H.H. Ardinger, S.E. Wallace, A. Amemiya, L.J.H. Bean, T.D. Bird, N. Ledbetter, H.C. Mefford, R.J.H. Smith, K. Stephens (Eds.), GeneReviews(R), Seattle (WA), 1993.
[3] L. Schols, P. Bauer, T. Schmidt, T. Schulte, O. Riess, Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis, Lancet Neurol. 3 (5) (2004) 291–304.
[4] L. Ruano, C. Melo, M.C. Silva, P. Coutinho, The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies, Neuroepidemiology 42 (3) (2014) 174–183.
[5] B.W. Soong, H.L. Paulson, Spinocerebellar ataxias: an update, Curr. Opin. Neurol. 20 (4) (2007) 438–446.
[6] H. Maruyama, Y. Izumi, H. Morino, M. Oda, H. Toji, S. Nakamura, H. Kawakami, Difference in disease-free survival curve and regional distribution according to subtype of spinocerebellar ataxia: a study of 1,286 Japanese patients, Am. J. Med. Genet. 114 (5) (2002) 578–583.
[7] B.W. Soong, Y.C. Lu, K.B. Choo, H.Y. Lee, Frequency analysis of autosomal dominant cerebellar ataxias in Taiwanese patients and clinical and molecular characterization of spinocerebellar ataxia type 6, Arch. Neurol. 58 (7) (2001) 1105–1109.
[8] T. Schmitz-Hubsch, M. Coudert, P. Bauer, P. Giunti, C. Globas, L. Baliko, A. Filla, C. Mariotti, M. Rakowicz, P. Charles, P. Ribai, S. Szymanski, J. Infante, B.P. van de Warrenburg, A. Durr, D. Timmann, S. Boesch, R. Fancellu, R. Rola, C. Depondt, L. Schols, E. Zdienicka, J.S. Kang, S. Dohlinger, B. Kremer, D.A. Stephenson, B. Melegh, M. Pandolfo, S. di Donato, S.T. du Montcel, T. Klockgether, Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms, Neurology 71 (13) (2008) 982–989.
[9] H. Jacobi, K. Reetz, S.T. du Montcel, P. Bauer, C. Mariotti, L. Nanetti, M. Rakowicz, A. Sulek, A. Durr, P. Charles, A. Filla, A. Antenora, L. Schols, J. Schicks, J. Infante, J.S. Kang, D. Timmann, R. Di Fabio, M. Masciullo, L. Baliko, B. Melegh, S. Boesch, K. Burk, A. Peltz, J.B. Schulz, I. Dufaure-Gare, T. Klockgether, 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. 12 (7) (2013) 650–658.
[10] H. Jacobi, P. Bauer, P. Giunti, R. Labrum, M.G. Sweeney, P. Charles, A. Durr, C. Marelli, C. Globas, C. Linnemann, L. Schols, M. Rakowicz, R. Rola, E. Zdzienicka, T. Schmitz-Hubsch, R. Fancellu, C. Mariotti, C. Tomasello, L. Baliko, B. Melegh, A. Filla, C. Rinaldi, B.P. van de Warrenburg, C.C. Verstappen, S. Szymanski, J. Berciano, J. Infante, D. Timmann, S. Boesch, S. Hering, C. Depondt, M. Pandolfo, J.S. Kang, S. Ratzka, J. Schulz, S. Tezenas du Montcel, T. Klockgether, The natural history of spinocerebellar ataxia type 1, 2, 3, and 6: a 2-year follow-up study, Neurology 77 (11) (2011) 1035–1041.
[11] H. Jacobi, S.T. du Montcel, P. Bauer, P. Giunti, A. Cook, R. Labrum, M.H. Parkinson, A. Durr, A. Brice, P. Charles, C. Marelli, C. Mariotti, L. Nanetti, M. Panzeri, M. Rakowicz, A. Sulek, A. Sobanska, T. Schmitz-Hubsch, L. Schols, H. Hengel, L. Baliko, B. Melegh, A. Filla, A. Antenora, J. Infante, J. Berciano, B.P. van de Warrenburg, D. Timmann, S. Szymanski, S. Boesch, J.S. Kang, M. Pandolfo, J.B. Schulz, S. Molho, A. Diallo, T. Klockgether, Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study, Lancet Neurol. 14 (11) (2015) 1101–1108.
[12] T. Ashizawa, K.P. Figueroa, S.L. Perlman, C.M. Gomez, G.R. Wilmot, J.D. Schmahmann, S.H. Ying, T.A. Zesiewicz, H.L. Paulson, V.G. Shakkottai, K.O. Bushara, S.H. Kuo, M.D. Geschwind, G. Xia, P. Mazzoni, J.P. Krischer, D. Cuthbertson, A.R. Holbert, J.H. Ferguson, S.M. Pulst, S.H. Subramony, Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study, Orphanet J. Rare Dis. 8 (2013) 177.
[13] A. Moriarty, A. Cook, H. Hunt, M.E. Adams, L. Cipolotti, P. Giunti, A longitudinal investigation into cognition and disease progression in spinocerebellar ataxia types 1, 2, 3, 6, and 7, Orphanet J. Rare Dis. 11 (1) (2016) 82.
[14] K. Yasui, I. Yabe, K. Yoshida, K. Kanai, K. Arai, M. Ito, O. Onodera, S. Koyano, E. Isozaki, S. Sawai, Y. Adachi, H. Sasaki, S. Kuwabara, T. Hattori, G. Sobue, H. Mizusawa, S. Tsuji, M. Nishizawa, K. Nakashima, A 3-year cohort study of the natural history of spinocerebellar ataxia type 6 in Japan, Orphanet J. Rare Dis. 9 (2014) 118.
[15] Y.C. Lee, Y.C. Liao, P.S. Wang, I.H. Lee, K.P. Lin, B.W. Soong, Comparison of cerebellar ataxias: a three-year prospective longitudinal assessment, Mov. Disord. 26 (11) (2011) 2081–2087.
[16] J. Sequeiros, J. Martindale, S. Seneca, P. Giunti, O. Kamarainen, V. Volpini, H. Weirich, K. Christodoulou, N. Bazak, R. Sinke, A. Sulek-Piatkowska, J. Garcia-Planells, M. Davis, M. Frontali, P. Hamalainen, S. Wieczorek, C. Zuhlke, M.L. Saraiva-Pereira, J. Warner, E. Leguern, F. Thonney, B. Quintans Castro, J. Jonasson, K. Storm, A. Andersson, A. Ravani, L. Correia, I. Silveira, I. Alonso, C. Martins, J. Pinto Basto, P. Coutinho, A. Perdigao, D. Barton, M. Davis, N. European molecular quality genetics, EMQN best practice guidelines for molecular genetic testing of SCAs, Eur. J. Hum. Genet. 18 (11) (2010) 1173–1176.
[17] T. Schmitz-Hubsch, S.T. du Montcel, L. Baliko, J. Berciano, S. Boesch, C. Depondt, P. Giunti, C. Globas, J. Infante, J.S. Kang, B. Kremer, C. Mariotti, B. Melegh, M. Pandolfo, M. Rakowicz, P. Ribai, R. Rola, L. Schols, S. Szymanski, B.P. van de Warrenburg, A. Durr, T. Klockgether, R. Fancellu, Scale for the assessment and rating of ataxia: development of a new clinical scale, Neurology 66 (11) (2006) 1717–1720.
[18] I. Yabe, M. Matsushima, H. Soma, R. Basri, H. Sasaki, Usefulness of the scale for assessment and rating of ataxia (SARA), J. Neurol. Sci. 266 (1–2) (2008) 164–166.
[19] G. Verbeke, G. Molenberghs, Pattern-mixture Models, Linear Mixed Models for Longitudinal Data, Springer New York, New York, NY, 2000, pp. 275–293.
[20] Y. Guo, H.L. Logan, D.H. Glueck, K.E. Muller, Selecting a sample size for studies with repeated measures, BMC Med. Res. Methodol. 13 (2013) 100.
[21] S.M. Kreidler, K.E. Muller, G.K. Grunwald, B.M. Ringham, Z.T. Coker-Dukowitz, U.R. Sakhadeo, A.E. Baron, D.H. Glueck, GLIMMPSE: online power computation for linear models with and without a baseline covariate, J. Stat. Software 54 (10) (2013).
[22] A.C. Bruni, J. Takahashi-Fujigasaki, F. Maltecca, J.F. Foncin, A. Servadio, G. Casari, P. D'Adamo, R. Maletta, S.A. Curcio, G. De Michele, A. Filla, K.H. El Hachimi, C. Duyckaerts, Behavioral disorder, dementia, ataxia, and rigidity in a large family with TATA box-binding protein mutation, Arch. Neurol. 61 (8) (2004) 1314–1320.
[23] A. Rolfs, A.H. Koeppen, I. Bauer, P. Bauer, S. Buhlmann, H. Topka, L. Schols, O. Riess, Clinical features and neuropathology of autosomal dominant spinocerebellar ataxia (SCA17), Ann. Neurol. 54 (3) (2003) 367–375.
[24] L. Choubtum, P. Witoonpanich, S. Hanchaiphiboolkul, R. Bhidayasiri, O. Jitkritsadakul, S. Pongpakdee, S. Wetchaphanphesat, P. Boonkongchuen, T. Pulkes, Analysis of SCA8, SCA10, SCA12, SCA17 and SCA19 in patients with unknown spinocerebellar ataxia: a Thai multicentre study, BMC Neurol. 15 (2015) 166.
[25] J.Y. Kim, S.Y. Kim, J.M. Kim, Y.K. Kim, K.Y. Yoon, J.Y. Kim, B.C. Lee, J.S. Kim, S.H. Paek, S.S. Park, S.E. Kim, B.S. Jeon, Spinocerebellar ataxia type 17 mutation as a causative and susceptibility gene in parkinsonism, Neurology 72 (16) (2009) 1385–1389.
[26] Y.R. Wu, H.Y. Lin, C.M. Chen, K. Gwinn-Hardy, L.S. Ro, Y.C. Wang, S.H. Li, J.C. Hwang, K. Fang, H.M. Hsieh-Li, M.L. Li, L.C. Tung, M.T. Su, K.T. Lu, G.J. Lee-Chen, Genetic testing in spinocerebellar ataxia in Taiwan: expansions of trinucleotide repeats in SCA8 and SCA17 are associated with typical Parkinson's disease, Clin. Genet. 65 (3) (2004) 209–214.
[27] J.Y. Yun, W.W. Lee, H.J. Kim, J.S. Kim, J.M. Kim, H.J. Kim, S.Y. Kim, J.Y. Kim,

S.S. Park, Y.K. Kim, S.E. Kim, B.S. Jeon, Relative contribution of SCA2, SCA3 and SCA17 in Korean patients with parkinsonism and ataxia, Park. Relat. Disord. 17 (5) (2011) 338–342.
[28] T. Klockgether, R. Ludtke, B. Kramer, M. Abele, K. Burk, L. Schols, O. Riess, F. Laccone, S. Boesch, I. Lopes-Cendes, A. Brice, R. Inzelberg, N. Zilber, J. Dichgans, The natural history of degenerative ataxia: a retrospective study in 466 patients, Brain 121 (Pt 4) (1998) 589–600.
[29] C.S. Lu, H.C. Chang, P.C. Kuo, Y.L. Liu, W.S. Wu, Y.H. Weng, T.C. Yen, Y.H. Chou, The parkinsonian phenotype of spinocerebellar ataxia type 3 in a Taiwanese family, Park. Relat. Disord. 10 (6) (2004) 369–373.
[30] C.S. Lu, Y.H. Wu Chou, P.C. Kuo, H.C. Chang, Y.H. Weng, The parkinsonian phenotype of spinocerebellar ataxia type 2, Arch. Neurol. 61 (1) (2004) 35–38.