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Natural History and Phenotypic Spectrum of GAA-FGF14 Sporadic Late-Onset Cerebellar Ataxia (SCA27B)

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Mathilde Renaud and Mathieu Anheim contributed equally to this work and should be considered co-last authors.

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ABSTRACT: Background: Heterozygous GAA expansions in the *FGF14* gene have been related to autosomal dominant cerebellar ataxia (SCA27B-MIM:620174). Whether they represent a common cause of sporadic late-onset cerebellar ataxia (SLOCA) remains to be established.

Objectives: To estimate the prevalence, characterize the phenotypic spectrum, identify discriminative features, and model longitudinal progression of SCA27B in a prospective cohort of SLOCA patients.

Methods: *FGF14* expansions screening combined with longitudinal deep-phenotyping in a prospective cohort of 118 SLOCA patients (onset >40 years of age, no family history of cerebellar ataxia) without a definite diagnosis.

Results: Prevalence of SCA27B was 12.7% (15/118). Higher age of onset, higher Spinocerebellar Degeneration Functional Score, presence of vertigo, diplopia, nystagmus, orthostatic hypotension absence, and sensorimotor neuropathy were significantly associated with SCA27B. Ataxia progression was ≈ 0.4 points per year on the Scale for Assessment and Rating of Ataxia.

Conclusions: *FGF14* expansion is a major cause of SLOCA. Our natural history data will inform future *FGF14* clinical trials. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: cerebellar ataxia; genetics; *FGF14*; natural history; phenotyping; SCA27B

Heterozygous GAA expansions in intron 1 of the fibroblast growth factor 14 (*FGF14*) gene have recently been shown to cause a dominantly inherited cerebellar ataxia (CA), spinocerebellar ataxia 27B (SCA27B-MIM:620174).¹⁻³ The elevated populational allele frequency of $\approx 2\%$ of *FGF14* GAA_{≥250} repeat units expansion carriers¹ suggests a significant proportion of unidentified patients with SCA27B and highlights the need to pave the way to clinical trial readiness for this novel and frequent genetic disorder. While several international cohorts have documented that *FGF14* expansions are a major cause of autosomal dominant CA,

these have not specifically addressed the question of the relative importance in sporadic late-onset CA cases (SLOCA).^{1,2} Additionally, in-depth longitudinal phenotyping and prospective quantification of disease progression has still to be documented.^{1,2}

Here, we studied a cohort of SLOCA patients without a diagnosis despite comprehensive investigations, who were prospectively followed in the neurology department of Strasbourg University Hospital to (1) determine the prevalence of SCA27B in a French cohort of SLOCA, (2) isolate discriminative features, and (3) map disease progression using prospectively collected quantitative longitudinal data.

Methods

Patients

From January 2014 to June 2022, patients consecutively sent to our referral center for SLOCA were included. Inclusion criteria were: (i) CA; (ii) lack of family history of CA; (iii) onset of CA after 40 years; and (iv) CA duration longer than 6 months. Exclusion criteria were: (i) lack of consent and (ii) dementia. Patients underwent collection of clinical and imaging data at baseline, then a prospective follow-up including quantitative clinical assessment every 6 months. Some of these patients were previously reported.⁴⁻⁷

Baseline and Follow-up Evaluation

Comprehensive laboratory investigations and imaging were conducted for all patients as previously described (Data S1).⁴⁻⁸ Collected clinical data included: Scale for the Assessment and Rating of Ataxia (SARA) score,⁹ Spinocerebellar Degeneration Functional Score (SDFS) from 0 (no disability) to 7 (bedridden),¹⁰ as well as screening for cerebellar multiple system atrophy (MSA-C) diagnostic criteria.^{11,12} Sensory motor nerve conduction studies and electromyography in the upper and lower limbs were performed, in addition to brain MRI and brain dopamine transporter imaging ([¹²³I]-ioflupane scintigraphy).^{6,8} Patients were screened for expansions in *ATXN 1, 2, 3, 7, CACNA1A, TBP, ATN1, FXN, RFC1*, and *FMR1* genes. All undiagnosed patients after this screening underwent targeted gene panel analysis that included 392 CA-related genes (Data S1).

Genetic Screening for *FGF14* GAA Repeat Expansion

FGF14 GAA expansions were screened as reported elsewhere¹³ using a three-step procedure including fluorescent long-range polymerase chain reaction (PCR), bidirectional repeated-primed PCRs (RP-PCRs), and agarose gel electrophoresis of long-range PCR products

and Sanger sequencing. The detailed procedures are described in Data S1. (GAA)_{≥250} repeat units expansions were considered as pathogenic.

Groups Definition

Patients receiving a diagnosis of acquired cause of SLOCA (including MSA-C diagnosis according to either the 2008 or 2022 consensus criteria for MSA diagnosis^{11,12}) or a genetic cause (including *RFC1* expansions or *SPG7* pathogenic variants carriers) following baseline screening were excluded from the analysis. *FGF14* expansion (SCA27B) carriers were compared with patients not carrying *FGF14* expansion, namely idiopathic late-onset cerebellar ataxia (ILOCA).

Statistical Analysis

Statistical analysis was performed using the statistical software Rstudio® (R version 4.3.0). To identify SCA27B discriminative features, χ^2 and Fisher's exact tests were used to test for differences in proportions and Mann–Whitney test for comparisons of quantitative variables between the SCA27B and ILOCA groups. The sensitivity and specificity of those features were subsequently calculated, and a cut-off associated with optimal diagnostic value for quantitative variables was determined through receiver operating characteristics (ROC) curves plotting (*ROCR* package in R). Pearson and Spearman rank tests were used to identify correlations between SCA27B features and GAA expansions sizes. Survival analysis for disease age-of-onset in ILOCA and SCA27B groups were conducted using the Kaplan–Meier method and comparisons were performed using the log-rank test (*survival* and *survminer* packages in R).

Modeling of SARA and SDFS scores progression among ILOCA and SCA27B patients were performed using linear mixed-effects modeling (LMEM) restricted-maximum-likelihood method with random intercept and disease duration as fixed-effect (*lme4* package in R). From SARA modeling, we calculated sample sizes that would enable the detection of a variable reduction in SARA score in parallel-group interventional trials in an observation period of 2, 3, or 4 years (*pwr* package in R). $P < 0.05$ was considered statistically significant, and all tests were two-tailed.

Ethics

All patients gave written informed consent before enrolment in the study and genetic testing. Strasbourg University Hospital local ethics committee approved the study (DC-2014-2222).

TABLE 1 Baseline characteristics of idiopathic late-onset cerebellar ataxia (ILOCA) and SCA27B patients.

Parameter	SCA27B group	Missing values	ILOCA group	Missing values	P-value
General characteristics					
Patients (n)	15 (12.7%)	–	103 (87.3%)	–	–
Women (n (%))	4 (26.7%)	0	0.49	0	0.13
Age of onset (years)	67.5 ± 7	0	58.1 ± 10.8	0	0.01**
Age at inclusion (years)	72.4 ± 6.3	0	62.7 ± 10.3	0	<0.01**
Disease duration at inclusion (years)	4.8 ± 3.9	0	4.7 ± 4.88	0	0.5
Number of visits	3.9 ± 2.1	0	3.5 ± 1.9	0	0.42
Duration of follow-up (years)	1.6 ± 1	0	2.1 ± 1.13	0	0.11
SARA score	10.8 ± 4.6	0	10.8 ± 5.2	1	0.83
SDFS score	3.7 ± 1.1	0	3.2 ± 1.2	2	0.03*
Dominance-masking events	6.7%	0	10.7%	0	1
<i>FGF14</i> GAA expansions (size (median and range))	346 (281, 525) repeats	0	34.4 (9, 199) repeats	0	<0.01**
Clinical characteristics					
Vertigo	66.7%	0	17.8%	2	<0.01**
Intention tremor	64.3%	1	43.4%	4	0.30
Dysarthria	42.9%	1	28.3%	4	0.35
Dysphagia	14.3%	1	12.1%	3	0.68
Extrapyramidal syndrome	21.4%	1	35.4%	3	0.38
Rest tremor	14.3%	1	11.1%	3	0.66
Akinesia	35.7%	1	34.3%	3	1
Extrapyramidal rigidity	14.3%	1	31.3%	3	0.34
Pyramidal syndrome	21.4%	1	39.6%	2	0.31
Spasticity	0%	2	7.9%	2	0.59
Motor impairment	7.1%	1	8.9%	2	1
Sensory impairment	40%	0	33.7%	2	0.84
Hypopallesthesia	40%	0	51%	9	0.60
Amyotrophy	7.7%	2	4.1%	6	0.47
Fasciculations	7.7%	2	2%	5	0.31
Dysautonomia	20%	0	58.6%	4	0.01*
Orthostatic hypotension	0%	0	25.8%	6	0.02*
Genitourinary impairment	20%	0	38.4%	4	0.27
Post-void residue	0%	5	9.8%	22	0.58
Diplopia	40%	0	2%	2	<0.01**
Oculomotor disorders	80%	0	49%	3	0.049*
Impaired smooth pursuit	33.3%	0	26.3%	2	0.52
Nystagmus	66.7%	0	19.2%	4	<0.01**
Square wave jerks	0%	0	1%	3	1

(Continues)

TABLE 1 Continued

Parameter	SCA27B group	Missing values	ILOCA group	Missing values	P-value
Hypometric saccades	6.7%	0	7.1%	4	1
Hypermetric saccades	40%	0	19%	3	0.09
Slow saccades	0%	0	7%	3	0.59
Vertical gaze palsy	0%	0	2%	3	1
Horizontal gaze palsy	0%	0	1%	3	1
Neuropsychological assessment, neuroimaging, and electromyography findings					
Altered neuropsychological assessment	33.3%	3	63.9%	20	0.056
Abnormal brain MRI	100%	1	91.8%	6	0.6
Cerebellar atrophy	64.3%	1	64.9%	6	1
Cerebellar vermian atrophy	64.3%	1	63.9%	6	1
Cerebellar hemispheric atrophy	50%	1	52.8%	6	1
Pons atrophy	14.3%	1	8.2%	6	0.61
Cervical medullar atrophy	0%	1	5.2%	6	1
Midbrain atrophy	7.1%	1	9.3%	6	1
Middle cerebellar peduncle atrophy	28.6%	1	8.2%	6	0.07
Middle cerebellar peduncle hypersignals	7.1%	1	2.1%	6	0.33
Corpus callosum splenium hypersignals	14.3%	1	15.5%	6	1
Pons hypersignals	7.1%	1	13.5%	6	1
Hemispheric white matter hypersignals	64.3%	1	55.7%	6	1
Hot cross bun sign	0%	1	3.1%	6	1
Bipallidal T2* hyposignals	21.4%	1	6.1%	6	0.13
Basal ganglia calcifications	0%	1	3.1%	6	1
Nigrostriatal dopaminergic denervation	26.7%	0	16.2%	4	0.297
Mean striatal/occipital ratio on ¹²³ I-ioflupane scintigraphy	2.8 ± 0.41	1	2.9 ± 0.42	19	0.18
Altered electroneuromyography	60%	0	33%	3	0.08
Sensory axonal neuropathy	13.3%	0	16%	3	1
Motor and sensory axonal neuropathy	46.7%	0	20.2%	9	0.045*
Motor and sensory demyelinating neuropathy	6.7%	0	0%	3	0.13

Note: Quantitative variables are expressed as mean ± standard deviation and proportions as percentages. GAA expansion size among SCA27B patients is given with median and range. P-values reflect the comparisons between the two groups. Bold type denotes statistical significance. * $P < 0.05$. ** $P < 0.01$.

Results

A total of 119 undiagnosed patients with SLOCA were selected for *FGF14* GAA expansion screening. The 118 patients that were successfully genotyped were included in the final analysis. Baseline clinical characteristics of the SCA27B and ILOCA groups are shown in Table 1. Overall, mean (standard deviation) duration of follow-up was 2 years (1.1) while mean number of visits was 3.6.² We identified 15 patients with SLOCA who carried a pathogenic *FGF14* (GAA)_{≥250} expansion,

representing a prevalence of 12.7% in our cohort (median size 346, range: from 281 to 525 GAA repeat units among SCA27B patients). Fig. 1A shows the distribution of *FGF14* GAA expansion size in SCA27B and ILOCA patients. We did not identify biallelic *FGF14* expansions carriers.

Discriminative features between SCA27B and ILOCA groups and their respective sensitivity and specificity are presented in Table 1 and in Data S1. At baseline, higher age-of-onset or age-at-inclusion, higher SDFS score, presence of vertigo, diplopia, oculomotor

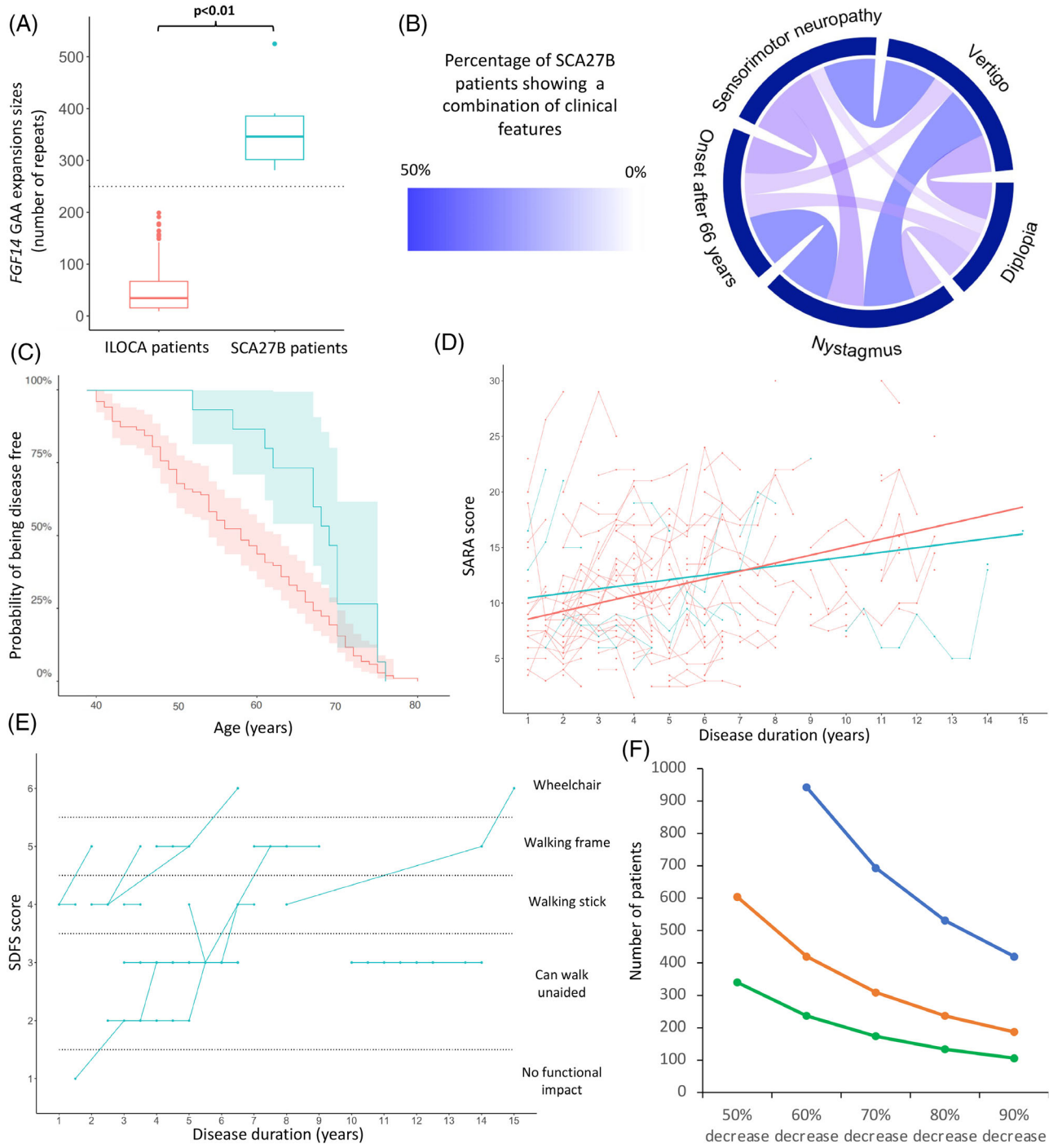


FIG. 1. (A) *FGF14* GAA expansions size range. Box plot showing the variability of GAA expansion size range among SCA27B patients and idiopathic late-onset cerebellar ataxia (ILOCA) patients. Middle line shows the median, extremity of the box the interquartile range, and upper and lower whiskers the range. Dashed line shows the pathogenicity cut-off of 250 repeats. Larger GAA expansions were noted in the SCA27B group ($P < 0.01$). (B) Phenotypic clusters in SCA27B. Size and color intensity of the links between two clinical features are correlated to the proportion of SCA27B patients presenting with the combination of the clinical characteristics. Phenotypic clusters between nystagmus and vertigo, vertigo and sensorimotor neuropathy, and onset after 66 years of age and nystagmus can be observed. (C) Survival until disease occurrence among ILOCA and SCA27B patients. y-axis: probability of being disease free; x-axis: age in years; blue curve: SCA27B patients' curve; red curve: ILOCA patients' curve. Shading represents the confidence interval associated with the curves in their respective colors. (D) Scale for the Assessment and Rating of Ataxia (SARA) score progression. y-axis: SARA score value; x-axis: time elapsed since disease onset; thin blue curve: individual SCA27B patients' scores; thin red curve: individual ILOCA patients' scores, bold blue curve: modeled progression of SARA score among SCA27B patients; bold red curve: modeled progression of SARA score among ILOCA patients. (E) Evolution of Spinocerebellar Degeneration Functional Scale (SDFS) among SCA27B patients. y-axis: SDFS score value, x-axis: time elapsed since disease onset. Each point represents an assessment; lines connect two assessments for each patient. (F) Sample size requirement for different treatment size effects and parallel-group interventional trials durations. y-axis: sample size requirement; x-axis: proportion of SARA score reduction achieved with the drug; blue curve: 2 years parallel-groups trial; orange curve: 3 years parallel-groups trial; green curve: 4 years parallel-groups trial. [Color figure can be viewed at wileyonlinelibrary.com]

disorders (especially nystagmus), absence of dysautonomia, absence of orthostatic hypotension, and presence of a mild sensorimotor axonal neuropathy were significantly associated with SCA27B. We found the highest specificity for diplopia (0.98), while the presence of oculomotor disorders and absence of orthostatic hypotension had the highest sensitivity (0.8 and 1, respectively). Deconstructing SCA27B into its constituent clinical features allowed identification of phenotypic clusters along a continuum of variable phenotypic combinations (Fig. 1B). We identified a unique SCA27B patient carrying 346 GAA repeat units expansion who showed CA combined with lower motor neuron disease. No difference was found in extrapyramidal or neuroimaging features, with most patients exhibiting mild or no cerebellar atrophy with inconstant pallidal iron deposits. No correlation between expansion size and clinical features was noted including age of onset (Pearson correlation coefficient 0.26, $P = 0.34$).

We subsequently modeled the disease age-of-onset in SCA27B and ILOCA patients. Kaplan–Meier curves depicting the probability of being disease-free are shown in Fig. 1C. Log-rank test confirmed that survival until disease onset was longer in SCA27B patients compared with ILOCA ($P = 0.02$).

Cross-sectional progression of ataxia based on progression of SARA scores among ILOCA and SCA27B patients is shown in Fig. 1D. Overall, modeling through LMEM did not identify an interaction between time and diagnostic group ($P = 0.23$). Ataxia progression was slow among the SCA27B group with a progression rate of 0.4 (standard error = 0.2) SARA points per year.

Evolution of SDFS score among SCA27B patients is shown in Fig. 1E. Specific analysis indicated dependence on walking aids (SDFS 4–5) in 50% of patients (6/12) within 5 years, and 73.3% within 10 years (11/15). Wheelchair dependence occurred in only 13.3% patients (2/15). Premature death not related to SCA27B occurred in two patients of the cohort at 78 years of age after 3 years of disease and at 79 years of age after 4 years of disease, respectively, because of a myeloproliferative syndrome and a bronchopulmonary cancer. Mortality did not differ significantly between the ILOCA and SCA27B groups (13.3% vs. 4.8%, $P = 0.22$).

Using the longitudinal progression estimate we calculated the preliminary sample sizes required to detect different treatment effects in parallel-group interventional trials. To detect a 50% reduction in SARA score progression with 80% power a total of 1357 patients would be required in a 2-year parallel-groups trial and 340 patients would be required in a 4-year parallel-groups trial. Evolution of sample sizes requirement depending on treatment effect and trials duration is shown in Fig. 1F.

Discussion

This study reports on *FGF14* GAA expansion screening in a deep-phenotyped and longitudinally followed French SLOCA cohort. Our study provides an estimation of the expansion prevalence among this group, determines discriminative clinical features of SCA27B, and based on an assessment of the natural history underlines its slow progression which will be a challenge for future treatment trials.

Our screening showed that *FGF14* GAA expansion is a major cause of SLOCA. We previously reported on the genetic findings in our SLOCA cohort⁷ and demonstrated that the most frequent genetic causes were *SPG7* and *RFC1* biallelic pathogenic variants, which were found in 3.3% and 2.4% of patients not fulfilling the diagnosis criteria for cerebellar MSA, respectively. In contrast, GAA expansions in *FGF14* accounted for 12.7% of undiagnosed CA patients in the present study, suggesting that SCA27B represents by far the most common genetic cause of SLOCA identified to date. These findings have important implications and support the use of *FGF14* GAA expansion screening as a first-tier diagnostic test among patients presenting with SLOCA.

We showed that among patients with undiagnosed SLOCA, presence of vertigo, diplopia, and oculomotor disorders including nystagmus were associated with SCA27B, which strengthens previous reports from the literature.^{1–3} We additionally identified new clinical markers, including age-of-onset, absence of dysautonomia including orthostatic hypotension, and higher baseline SDFS score compared with ILOCA patients. Parkinsonism or dopaminergic denervation were uncommon features in SCA27B. Considering the rarity of dysautonomia and orthostatic hypotension in this group, this suggests that the presentation of SCA27B and MSA-C, the most common cause of SLOCA,^{4,7} are not overlapping. No neuroimaging feature discriminated SCA27B, although most patients had mild or no cerebellar atrophy, while some cases showed pallidal iron deposits. We also identified clinical features suggestive of lower motor neuron disease in a single SCA27B patient. Conversely to the initial reports from the literature^{1,2} we found a higher prevalence of mild axonal sensorimotor neuropathy among SCA27B patients compared with non-expansion carriers, although this could be partly related to the significantly higher age at baseline among SCA27B patients, reflecting the higher prevalence of neuropathy in an elderly population.

We modeled a slow ataxia progression of 0.4 SARA points per year among SCA27B cases. Ataxia progression appears to be more than three times slower than *RFC1*-CA (1.3) and nearly two times slower than Friedreich ataxia (0.77) reported progression rates.^{14,15} This led to elevated sample size requirement to achieve an 80%

power to detect significant differences in prolonged parallel-groups interventional trials. These findings highlight the need for a surrogate endpoint to facilitate the demonstration of treatment effect in the shorter term, including neuroimaging or blood sample biomarkers.¹⁶

While based on a large undiagnosed SLOCA cohort, our study has some limitations. First, our study was monocentric. Second, we did not perform extended longitudinal blood or neuroimaging biomarker screening but rather focused on accessible clinical markers.

In conclusion, we have demonstrated that heterozygous *FGF14* GAA expansion is a major cause of SLOCA, with significant upcoming challenges in trial design for the identification of therapeutic agents. Further prospective studies aiming to longitudinally investigate clinical progression and identify imaging or blood sample biomarkers are warranted. ■

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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

No Correlation between Plasma GPNMB Levels and Multiple System Atrophy in Chinese Cohorts

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