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SHORT REPORT

The *FGF14* GAA repeat expansion in Greek patients with late-onset cerebellar ataxia and an overview of the SCA27B phenotype across populations

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Abstract

A pathogenic GAA repeat expansion in the first intron of the fibroblast growth factor 14 gene (*FGF14*) has been recently identified as the cause of spinocerebellar ataxia 27B (SCA27B). We herein screened 160 Greek index cases with late-onset cerebellar ataxia (LOCA) for *FGF14* repeat expansions using a combination of long-range PCR and bidirectional repeat-primed PCRs. We identified 19 index cases (12%) carrying a pathogenic *FGF14* GAA expansion, a diagnostic yield higher than that of previously screened repeat-expansion ataxias in Greek LOCA patients. The age at onset of SCA27B patients was 60.5 ± 12.3 years (range, 34–80). Episodic onset (37%), downbeat nystagmus (32%) and vertigo (26%) were significantly more frequent in *FGF14* expansion-positive cases compared to expansion-negative cases. Beyond typical cerebellar signs, SCA27B patients often displayed hyperreflexia (47%) and reduced vibration sense in the lower extremities (42%). The frequency and phenotypic profile of SCA27B in Greek patients was similar to most other

Georgia Karadima and Georgios Koutsis have equal contribution.

previously studied populations. We conclude that *FGF14* GAA repeat expansions are the commonest known genetic cause of LOCA in the Greek population and recommend prioritizing testing for *FGF14* expansions in the diagnostic algorithm of patients with LOCA.

KEYWORDS
ataxia, cerebellar ataxia, *FGF14*, Greek population, spinocerebellar ataxia 27B (SCA27B)

1 | INTRODUCTION

Late-onset cerebellar ataxia (LOCA) is a group of neurodegenerative disorders manifesting as a progressive cerebellar syndrome that usually develops after the age of 30 years.[1,2] Despite recent advances in our understanding of the genetic basis of LOCA, a genetic diagnosis is reached in less than 30% of patients.[3]

An intronic GAA repeat expansion in the fibroblast growth factor 14 gene (*FGF14*) has been recently shown to cause spinocerebellar ataxia 27B (SCA27B) (OMIM: 620174), accounting for 10 to 61% of unsolved cases in several LOCA cohorts.[4,5] Current data support a pathogenic threshold of $(GAA)_{\geq 250}$ repeats, although incomplete penetrance was observed in the $(GAA)_{250-300}$ range.[4,5] Core clinical features of SCA27B include slowly progressive cerebellar ataxia with frequent early episodic symptoms, vestibulocerebellar oculomotor signs, and dizziness/vertigo.[4,6]

Greek patients with LOCA have been screened for several repeat-expansion disorders, including common autosomal dominant spinocerebellar ataxias (SCA), cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) and fragile X-associated tremor ataxia syndrome (FXTAS).[7–9] In this study, we aimed to investigate the frequency and phenotypic profile of SCA27B in a cohort of Greek patients with unsolved LOCA and to present an overview of the SCA27B phenotype across countries and continents.

2 | PATIENTS AND METHODS

2.1 | Patients

From 1995 to 2022, 504 index cases with suspected hereditary ataxia were referred to the Neurogenetics Unit, 1st Department of Neurology, National and Kapodistrian University of Athens (NKUA) for molecular diagnosis. Among them, 160 patients with LOCA (age at onset >30 years), remaining undiagnosed following screening for SCA1,2,3,6,7, Friedreich ataxia (FRDA), FXTAS and CANVAS were included in this study (Suppl. Figure 1). This study was carried out in the Neurogenetics Unit, NKUA, Athens, Greece; the UCL Queen Square Institute of Neurology, London, UK; and the Montreal Neurological Hospital and Institute, McGill University, Montreal, Canada. Written informed consent was obtained from all patients. The study protocol was approved by the Eginitio Hospital Ethics Committee (Ethics ID: 345/21-05-2019).

2.2 | Methods

The experimental methodology was performed as described previously,[10] with a modification of the 5′ repeat-primed PCR (RP-PCR) for cases genotyped in Athens (Suppl. methods). Cases were first screened for GAA repeat expansions in *FGF14* with fluorescent long-range PCR (fLR-PCR). Agarose gel electrophoresis of the amplicons followed and repeat sizes were measured by capillary electrophoresis.[10] Cases with one normal allele or one normal allele and one expanded allele next underwent bidirectional RP-PCR targeting the 5′-end and 3′-end of the locus, in order to verify the GAA repeat expansion and also interrogate the sequence motif over the entire length of larger expansions.[10] We considered a threshold of $(GAA)_{\geq 250}$ repeats as pathogenic.[4,5] Capillary gel electrophoresis was performed on an ABI3500 genetic analyzer. Allele sizes were estimated using GeneMarker® v2.2.0 software (SoftGenetics). Statistical analyses were performed on SPSS version 20 (Chicago, IL, USA) and R (version 4.2.0).

3 | RESULTS

3.1 | Frequency and clinical characteristics of Greek patients with SCA27B

We identified 19 patients carrying a pathogenic *FGF14* GAA expansion (11.9%). Of these, 13 had the expansion in the full penetrance range (GAA ≥300) and 6 had the expansion in the reduced penetrance range (GAA 250–299). Representative results of gel and capillary electrophoresis, and a violin plot of the repeat distribution are shown in Suppl. Figure 2.

Table 1 shows demographic and clinical characteristics of the total cohort, as well as of expansion-positive and negative cases separately. The significance level has been Bonferroni adjusted to 0.0026 to account for multiple comparisons. The age at onset (AAO) of expansion-positive cases was 60.5 ± 12.3 years (range, 34–80), significantly different ($p = 0.001$) from expansion negative cases (52.3 ± 9.9 years). AAO refers to the age at which the first symptom was noted, irrespective of whether it be episodic or chronic. Expansion-positive cases had significantly more often episodic onset (36.8% vs. 5.7%; $p = 0.0003$), downbeat nystagmus (31.6% vs. 5.0%; $p = 0.001$) and vertigo (26.3% vs. 2.1%; $p = 0.001$) vs. expansion-negative cases. In cases with positive family history, the frequency of

TABLE 1 Demographic and clinical data of late-onset cerebellar ataxia cohort screened for *FGF14* GAA repeat expansions.

	Total LOCA cohort (%)	*FGF14* expansion-positive (%)	*FGF14* expansion-negative (%)	*p*-Value[a] (expansion-positive vs. expansion negative)[b]
N	160	19	141	–
Male sex	72 (45.0)	9 (47.4)	63 (44.7)	1.000
Age in years (range)	60.6 ± 10.6 (35–87)	67.9 ± 11.6 (40–87)	59.6 ± 10.1 (35–83)	**0.001**[c]
Age at onset in years (range)	53.2 ± 10.5 (31–80)	60.5 ± 12.3 (34–80)	52.3 ± 9.9 (31–78)	**0.001**[c]
Disease duration in years (range)	7.5 ± 6.5 (1–31)	7.5 ± 6.0 (1–24)	7.5 ± 6.6 (1–31)	0.978[c]
Familial cases	35 (21.9)	6 (31.6)	29 (20.6)	0.373
Episodic onset	15 (9.4)	7 (36.8)	8 (5.7)	**0.0003**
Gait ataxia	160 (100.0)	19 (100.0)	141 (100.0)	1.000
Appendicular ataxia	136 (85.0)	15 (78.9)	121 (85.8)	0.491
Nystagmus (all types)	72 (45.0)	10 (52.6)	62 (44.0)	0.624
Downbeat nystagmus	13 (8.1)	6 (31.6)	7 (5.0)	**0.001**
Dysarthria	128 (80.0)	15 (78.9)	113 (80.1)	1.000
Vertigo (episodic)	8 (5.0)	5 (26.3)	3 (2.1)	**0.001**
Hyperreflexia	61 (38.1)	9 (47.4)	52 (36.9)	0.452
Babinski sign	32 (20.0)	4 (21.1)	28 (19.9)	1.000
Reduced vibration sense	41 (25.6)	8 (42.1)	33 (23.4)	0.095
Postural tremor	14 (8.8)	1 (5.3)	13 (9.2)	1.000
Parkinsonism	15 (9.4)	0 (0.0)	15 (10.6)	1.000
Dysautonomia	10 (6.3)	0 (0.0)	10 (7.1)	0.609
Cerebellar atrophy on MRI	99/143 (69.2)	12/16 (75.0)	87/127 (68.5)	0.776

Note: Data are presented for the total cohort, as well as for expansion-positive and expansion-negative cases separately. Data are mean ± SD (range).
Abbreviation: LOCA, late-onset cerebellar ataxia.
[a]*p*-Value set at 0.0026 (Bonferroni adjusted value for multiple comparisons); significant differences shown in bold.
[b]Fisher's exact test, unless otherwise noted.
[c]Student *t*-test.

pathogenic expansions was 17.1% versus 10.4% in sporadic cases, which was not significantly different ($p = 0.373$, Fisher's exact test). Beyond typical cerebellar signs, SCA27B cases often displayed hyperreflexia (47.4%) and reduced vibration sense in the lower limbs (42.1%).

Table 2 displays clinical and genetic data of individual patients with SCA27B. Episodic onset, when present, was dominated by ataxia, vertigo or dysarthria. Cerebellar atrophy was present in 75.0% of cases (12/16). Vestibulocerebellar oculomotor signs were observed in 52.6% of cases. A mild axonal neuropathy was present in 12.5% of cases with NCS (2/16). The median expansion size was 370 GAA repeats (range, 262–568). There was no correlation between expansion size and AAO ($r = -0.087$; $p = 0.724$). Comparing clinical data between SCA27B cases with reduced penetrance expansions $(GAA)_{250-299}$ versus cases with full penetrance expansions $(GAA)_{\geq 300}$ revealed no significant differences (Suppl. Table 1).

3.2 | Frequency and clinical characteristics of SCA27B patients from different populations

Supplementary Table 2 presents inclusion criteria and frequency of *FGF14* GAA expansions from previous studies, comparing them to this study.[4–6,10–14] In most populations, the frequency of SCA27B ranged from 9% to 19%, a figure similar to present results. Compared to the Greek population, the frequency of the expansion was significantly higher in French Canadian and Spanish LOCA cases, as well as German cases with autosomal dominant cerebellar ataxia (ADCA).[4,12,14]

A comparison of clinical characteristics of 283 SCA27B cases published to date (Table 3) shows AAO ranging from 27 to 87 years, with 38% of cases reporting episodic onset.[4–6,10–14] Gait ataxia is virtually always present (97.2%), followed by appendicular ataxia (77.0%), nystagmus (60.5%), dysarthria (55.8%), and vertigo (34.8%). Several studies show a high frequency of reduced vibration sense (48.9%).[6,11,14] Dysautonomia has also been reported in some studies (27%), albeit absent from our cohort.[5,6,11,14] Hyperreflexia has been noted in three studies and appears frequent (42%).[5,14] Data are conflicting regarding the frequency of peripheral neuropathy, ranging from 0 to 60%.[5,11,14]

4 | DISCUSSION

We screened a cohort of 160 Greek index cases with LOCA for pathogenic *FGF14* GAA expansions and identified 19 positive cases. This

TABLE 2 Demographic, clinical and genetic data of individual *FGF14* expansion-positive Greek patients.

ID	ATX No	Sex	Age	AAO[a]	FH	Episodic onset	Gait ataxia	App. ataxia	Nyst. (all types)	DB nyst.	Dysarth.	Vert.	Hyper-reflexia	Babinski sign	Spasticity	Reduced vibration sense	Postural tremor	Parkins.	Auton. Dysf.	CA on MRI	Abn. NCS	Neurol. Comorb.	*FGF14*-repeat expansion
1	157	M	60	40	+	–	+	–	–	–	+	–	+	+	+	+	–	–	–	+	–	–	8/335
2	163	M	64	40 (59)	–	Vertigo	+	+	–	–	+	+	–	–	–	+	–	–	–	NR	–	–	9/449
3	277	F	72	68	–	–	+	+	+	+	–	–	–	–	–	–	–	–	–	NR	–	–	9/271
4	488	F	68	65	+	–	+	+	+	–	–	–	+	–	–	–	–	–	–	+	–	–	35/539
5	668	F	71	66	+	–	+	+	+	+	+	–	–	–	–	–	–	–	–	NR	NR	–	8/416
6	707	M	40	34	–	–	+	+	–	–	+	–	+	+	+	+	–	–	–	+	+	–	8/267
7	708	F	87	74 (76)	–	Ataxia	+	+	+	–	+	–	–	–	–	–	–	–	–	+	–	SVD	43/268
8	789	M	62	60	–	–	+	+	–	–	+	–	+	–	–	+	–	–	–	+	–	–	9/313
9	805	F	68	61	–	–	+	+	–	–	+	–	–	–	–	–	–	–	–	+	–	–	15/386
10	817	M	62	59 (62)	+	Vertigo	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	SVD	9/295
11	828	F	77	70	–	–	+	+	+	–	+	–	+	–	–	–	–	–	–	+	–	SVD	38/266
12	838	F	72	65 (69)	–	Vertigo, oscillopsia	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	SVD	93/364
13	847	F	69	65 (66)	–	Dysarthria	+	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	21/387
14	856	F	86	80 (84)	+	Vertigo	*	+	+	+	+	+	+	–	–	–	–	–	–	+	NR	–	9/393
15	907	M	52	51	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	+	NR	–	9/370
16	946	M	61	59	–	–	+	+	–	–	+	–	+	+	–	–	–	–	–	+	–	–	9/455
17	982	M	68	58 (65)	–	Dysarthria	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	–	9/262
18	992	F	57	51	+	–	+	+	–	–	–	–	–	–	–	–	+	–	–	+	–	–	76/568
19	1016	M	84	73	–	–	+	–	–	–	+	–	–	–	–	+	–	–	–	+	–	–	9/400

Abbreviations: AAO, age at onset; Abn, abnormal; Age and AAO in years; App, appendicular; ATX, ataxia; Auton Dysf, autonomic dysfunction; CA, cerebellar atrophy; DB, downbeat; Dysarth, dysarthria; F, Female; FH, family history; M, Male; MRI, brain magnetic resonance imaging; NCS, nerve conduction studies; Neurol. Comorb., neurological comorbities; NR, not recorded; Nyst, Nystagmus; Parkins, parkinsonism; SVD, small vessel disease on brain MRI (Fazekas grade 1, excepting ATX 708, which was grade 2); Vert; episodic vertigo.

[a]In cases with episodic onset, age at onset of chronic symptoms also noted in parenthesis.

TABLE 3 Comparison of clinical data of *FGF-14* expansion-positive cases from different populations.

	Present study	Pellerin et al.[4]	Rafehi et al.[5]	Wilke et al.[6]	Wirth et al.[11]	Hengel et al.[12]	Novis et al.[13]	Iruzubieta et al.[14]	Bonnet et al.[10]	All cases
N	19	122[a]	13	50	15	26	9	18	11	283
Male sex	9 (47.4)	62 (50.8)	8 (61.5)	25 (50.0)	11 (73.3)	–	4 (44.4)	12 (66.7)	4 (36.4)	135/257 (52.5)
Age in years (range)	67.9 ± 11.6 (40–87)	–	69 (54–81)	73[b] (42–87)	72.4 ± 6.3	–		76[b] (62–87)	–	40–87
Age at onset all types in years (range)	60.5 ± 12.3 (34–80)	–	61 (46–77)	61[b] (37–78)	67.5 ± 7.0	55.0[b] (1 case AAO 27)	59.0[b] (28–67)	63[b] (39–72)	–	28–80
Age at onset of episodic features in years (range)	–	55 ± 13 (30–87)	–	–	–	–	–	–	64 ± 9	–
Age at onset of progressive ataxia in years (range)	62.6 ± 11.9 (34–84)	59 ± 11 (30–88)	–	–	–	–	–	–	66 ± 10	–
Disease duration in years (range)	7.5 ± 6.0 (1–24)	–	8.5 (1–16)	9.7[b]	4.8 ± 3.9	–	12.0[b] (3–39)	14[b] (4–33)	–	–
Familial cases	6 (31.6)	82/118 (69.5)	–	22/43 (51.2)	0 (0.0)	26 (100.0)	–	7/17 (41.2)	7 (63.6)	124/208 (59.6)
Episodic onset	7 (36.8)	56/121 (46.3)	–	6/47 (12.8)	–	–	1 (11.1)	7 (38.9)	8 (72.7)	85/224 (37.9)
Gait ataxia	19 (100.0)	113/118 (95.8)	13 (100.0)	41/43 (95.3)	15 (100.0)	–	9 (100.0)	18 (100.0)	11 (100.0)	239/246 (97.2)
Appendicular ataxia	15 (78.9)	94/118 (79.7)	10 (76.9)	27/41 (65.9)	9/14 (64.3)	–	9 (100.0)	10 (54.4)	10 (90.9)	184/239 (77.0)
Nystagmus (all types)	10 (52.6)	65/119 (54.6)	12/12 (100.0)	–	10 (66.7)	–	7 (77.7)	–	8 (72.7)	112/185 (60.5)
Downbeat nystagmus	6 (31.6)	50/119 (42.0)	–	–	–	–	0 (0.0)	6/16 (37.5)	-	62/163 (38.0)
Dysarthria	15 (78.9)	63/118 (53.4)	7/11 (63.6)	25/42 (59.5)	6/14 (42.9)	–	0 (0.0)	12/18 (66.7)	7 (63.6)	135/242 (55.8)
Vertigo (episodic)	5 (26.3)	33/114 (28.9)	–		10/15 (66.7)	–	4 (44.4)	6/14 (42.8)	5/10 (50.0)	63/181 (34.8)
Hyperreflexia	9 (47.4)	–	5 (38.5)	–	–	–	–	7 (38.9)	–	21/50 (42.0)
Babinski sign	4 (21.1)	–	–	0/41 (0.0)	3/14 (21.4)	–	–	2/17 (11.8)	–	9/91 (9.9)
Reduced vibration sense	8 (42.1)	–	–	22/40 (55.0)	6 (40.0)	–	–	9 (50.0)	–	45/92 (48.9)
Postural tremor	1 (5.3)	18/114 (15.8)	–	–	–	–	1 (11.1)	1/16 (6.3)	–	21/158 (13.3)
Parkinsonism	0 (0.0)	–	0	–	2/14 (14.3)	–	–	2 (11.1)	–	4/64 (6.3)
Dysautonomia	0 (0.0)	–	5 (38.5)	14/36 (38.9)	3 (20.0)	–	–	5/16 (31.3)	–	27/99 (27.3)
Cerebellar atrophy on MRI	12/16 (75.0)	67/91 (73.6)	5 (38.5)	28/29 (97.0)	9/14 (64.3)	–	4/8 (50.0)	9/15 (60.0)	4/9 (44.4)	138/195 (70.8)
Neuropathy on NCS	2/9 (22.2)	–	0/8 (0.0)	–	9 (60.0)	–	–	1/8 (12.5)	–	12/40 (30.0)
GAA repeats long allele	370[b] (262–568)	–	310[b] (270–450)	349[b] (252–583)	346[b] (281–525)	–	333[b] (253–449)	350[b] (255–451)	370[b] (259–550)	–
GAA repeats short allele	9[b] (8–93)	–	–	16[b]	–	–	–	–		–

Note: Numbers are *N* (%); Age and age at onset data are mean ± SD or median (range).

Abbreviations: AAO, age at onset; MRI, brain magnetic resonance imaging; NCS, nerve conduction studies.

[a]One-hundred and twenty-eight patients reported in total, but clinical data presented for 122 of them.

[b]Median value.

corresponds to a frequency of 12% for SCA27B in our population. The frequency of SCA1,2,3,6 and 7 in Greek probands with suspected hereditary ataxia has been estimated at around 5%.[7] Additionally, screening Greek cases with LOCA for CANVAS and FXTAS, yielded frequencies of 6.5% and 2.2%, respectively.[8,9] Furthermore, the frequency of FRDA in a Greek ataxia cohort was 35%, but >90% of these patients had onset before 25 years.[15] Taken together, the above suggest that SCA27B is the most common known genetic cause of LOCA in the Greek population.

The frequency of SCA27B observed in Greek LOCA is similar to reports from most other populations, spanning a range of 9%–19%.[4–6,11,13] In most studies, only LOCA index cases previously screened for SCA1,2,3,6,7, FRDA, FXTAS and CANVAS were included, suggesting that the populations are comparable. SCA27B was more frequent in French Canadian and Spanish LOCA cohorts, indicating a possible founder effect in these populations.[4,14] SCA27B was also more common in a German study, which only included undiagnosed ADCA.[12] We presently also found a higher, albeit not significantly so, frequency of SCA27B in familial cases (17%).

Regarding the core phenotype of SCA27B, our study mostly confirms previous observations. The late, frequently episodic, onset, along with the presence of downbeat nystagmus and vertigo may help differentiate SCA27B from other hereditary ataxias.[4] Beyond the pancerebellar syndrome, the common presence of afferent sensory deficits and hyperreflexia suggest that SCA27B is often a spinocerebellar degenerative disorder.[4–6] We presently failed to confirm the relatively high frequency of dysautonomia found by some, though not all, researchers.[5,6,11,14] Given that we specifically asked for dysautonomic symptoms in most cases, we suspect that frank autonomic failure is likely to be rare in SCA27B. Finally, we confirmed the low frequency of abnormal NCS found in some studies.[5,11,14]

We did not observe any correlation between expansion size and AAO. This is in agreement with some studies,[6,11,14] but not others, which observed a negative correlation.[4,5,10] To further investigate this, we also searched for differences in clinical characteristics between SCA27B cases with incompletely penetrant $(GAA)_{250-299}$ expansions vs. cases with fully penetrant $(GAA)_{\geq 300}$ expansions, but observed no significant differences.

In accordance with previous publications, we only screened cases with onset above 30 years.[4,6,14] However, two recent studies with a lower or no AAO limit, reported two cases with onset at 27 and 28 years.[12,13] Moreover, two Chinese siblings (AAO 21 and 26 years)[16] and a pair of consanguineous Indian siblings (AAO 25 and 27)[17] were reported carrying biallelic *FGF14* GAA expansions. This suggests that the minimal AAO of SCA27B may be lower, and that cases with onset above 20 years should be included in future diagnostic algorithms.

This study has certain limitations that need to be briefly outlined. First, we had no quantitative data from ataxia scales, making it hard to document the severity of SCA27B. Second, no prospective data were available to allow assessment of the progression of SCA27B. Finally, we had no long-read sequencing data to validate our PCR results, although a recent study has provided extensive evidence supporting the techniques presently used.[10]

In conclusion, we identified SCA27B as the commonest known genetic cause of LOCA in the Greek population and recommend prioritizing testing for *FGF14* GAA expansions in the diagnostic algorithm of Greek patients with LOCA.

AUTHOR CONTRIBUTIONS

C. Kar carried out molecular genetic analysis, performed in silico evaluation of the results and wrote the manuscript. A.M., Z.K., K.A., D.P., M-J.D., P.I., and M.D. performed molecular genetic analysis and revised the manuscript. C. Kon, M.P., and L.S. examined patients and revised the manuscript. B.B. provided positive controls, participated in study design and revised the manuscript. S.Z. and H.H. participated in study design and revised the manuscript. G. Kou examined patients, performed data analysis, participated in writing the manuscript and, along with G. Kar, designed the study, supervised the project and critically revised the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14482.

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 INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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