BRIEF REPORT

GAA-*FGF14* Expansions and *CACNA1A* Variants: Phenotypic Overlap and Diagnostic Implications

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ABSTRACT: Background: An intronic (GAA)•(TTC) repeat expansion in *FGF14* was recently identified as the cause of spinocerebellar ataxia 27B (SCA27B), a disorder presenting with both chronic cerebellar ataxia and episodic symptoms. The phenotype of SCA27B overlaps with that of *CACNA1A* spectrum disorders.
Objective: The objective of this work was to investigate the prevalence of GAA-*FGF14* repeat expansions in patients with ataxia so far considered to be related to underlying *CACNA1A* variants.
Methods: This is a cross-sectional multicenter study.
Results: GAA-*FGF14* testing showed pathogenic expansions (≥250 repeats) in 6/67 (9%) patients carrying *CACNA1A* variants. All patients with a pathogenic GAA-*FGF14* expansion had a disease onset >40 years and carried variants of uncertain significance (VUSs) in *CACNA1A*. Genetic reevaluation led to the reclassification of *CACNA1A* VUSs as likely benign in four of six patients, who were ultimately diagnosed with SCA27B.
Conclusions: Late-onset ataxia cases previously considered as *CACNA1A*-related disorder should be reevaluated and tested for SCA27B, particularly if related to a VUS in *CACNA1A*. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: CACNA1A; episodic ataxia; GAA-FGF14 ataxia; SCA27B; spinocerebellar ataxia 27B

Introduction

The recent identification of deep intronic (GAA)•(TTC) repeat expansions in the fibroblast growth factor 14 (*FGF14*) gene in unsolved cases of adult-onset cerebellar ataxia was a major breakthrough in the field of inherited movement disorders.[1–3] *FGF14* is predominantly expressed in cerebellar neurons and encodes an intracellular protein that regulates the activity of voltage-gated sodium channels at the axon initial

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segment, thereby influencing the firing of cerebellar Purkinje cells.[4,5] GAA-*FGF14*–related ataxia, also known as spinocerebellar ataxia 27B (SCA27B), is an autosomal dominant disorder presenting with mild, slowly progressive, chronic cerebellar dysfunction often with superimposed episodic features.[1,6,7] According to current evidence, a threshold of at least 250 uninterrupted repeat units, $(GAA)_{\geq 250}$, is considered pathogenic.[1] Alleles with more than 300 repeats are highly penetrant, whereas those with 250 to 300 repeats are incompletely penetrant.[1,8] Alleles with 200 to 249 repeats are in a gray zone, with controversial evidence about their pathogenicity.[8–11] Furthermore, a recent study suggested an enrichment of even shorter expansions (180–249 repeats) in patients with ataxia.[12]

Cumulative reports from large cohorts worldwide[1,2,13,14] suggest that GAA-*FGF14*–related ataxia may be one of the most common inherited ataxias as the genetic testing becomes widely available.[15,16] They also highlight that in the context of large-scale, phenotype-agnostic screening, GAA-*FGF14* expansions often cooccur with other pathogenic variants.[8,13,17,18] This raises the question whether these cases have a dual genetic cause (as recently suggested in Beijer and colleagues[18]), or whether GAA-*FGF14* expansions may act as a disease modifier (as recently suggested in multiple system atrophy[19]).

Of particular clinical relevance, the phenotype of SCA27B may largely overlap with that of adult patients with *CACNA1A* spectrum disorders.[20,21] *CACNA1A* is a bicistronic gene that encodes both the pore-forming subunit of the neuronal P/Q Ca^{2+} channel and the transcription factor α1ACT, which drives maturation of the Purkinje cells in early development.[22,23] Single-nucleotide variants and small deletions in *CACNA1A* are associated with dominantly inherited phenotypes sharing a common denominator of chronic cerebellar signs and paroxysmal features. Expansion of a CAG repeat in exon 47 of the gene causes a late-onset, progressive disorder, spinocerebellar ataxia type 6 (SCA6), which may also present with episodic features at disease onset.[24] *CACNA1A*-associated disease was the most frequent monogenic etiology in a large global cohort of patients with cerebellar ataxias caused by nonexpansion variants.[25] In this large *CACNA1A* cohort, clinical features were variable, and age at onset ranged from the first to the seventh decade of life.[25] Both GAA-*FGF14*– and *CACNA1A*-related disorders may respond to two therapeutics that reduce the burden of episodic symptoms, acetazolamide and 4-aminopyridine.[6,7,9,21] In murine models, both loss-of-function variants in *CACNA1A* and *FGF14* disrupt the pacemaking function of the Purkinje cell and trigger paroxysmal motor symptoms.[26,27]

These observations prompted us to investigate (1) whether there are patients with a suggestive phenotype so far considered related to *CACNA1A* variants, which is in fact more likely due to a GAA-*FGF14* repeat expansion; and (ii) whether there are patients with a dual molecular diagnosis, that is, a clearly pathogenic allele in both *CACNA1A* and *FGF14*, indicating the presence of two independent but potentially additive genetic conditions.

Subjects and Methods

Patients with ataxia previously classified as having probable *CACNA1A* disease were recruited in an international collaboration involving three centers (Innsbruck, Austria; Tübingen, Germany; and Montreal, QC, Canada). All patients underwent an in-depth diagnostic including either short-read–based whole-exome sequencing or ataxia panel, as well as testing for repeat expansion disorders (Friedreich's ataxia, spinocerebellar ataxia types 1, 2, 3, 6, 7, and 17), whenever appropriate. The diagnosis of probable *CACNA1A* disease was based on the presence of a suggestive phenotype (episodic ataxia, chronic ataxia isolated or in combination with episodic features/developmental delay/hemiplegic migraine[28]) and detection of a Class III-V variant in *CACNA1A*, according to the American College of Medical Genetics and Genomics (ACMG) criteria,[29] along with exclusion of alternative molecular diagnoses. Class III variants are equivalent to "variant of uncertain significance" (VUS). Class IV and V variants (corresponding to "likely pathogenic" and "pathogenic" variants) are collectively referred to as "pathogenic" in the manuscript. Testing for GAA-*FGF14*–related ataxia was performed according to an established protocol at the Montreal Neurological Institute using long-range polymerase chain reaction (PCR), bidirectional repeat-primed PCR, and Sanger sequencing (for details, see Bonnet et al[30]).

The study was approved by local institutional review boards. Each patient provided written informed consent for study participation and publication.

Results

We collected a multicenter cohort of 67 adult patients with ataxia so far considered related to *CACNA1A* variants (n = 42 Tübingen, n = 20 Innsbruck, n = 5 Montreal). The most frequent main phenotype was episodic ataxia (n = 34, 51%), followed by chronic ataxia without apparent episodic features (n = 25, 37%). Developmental delay and hemiplegic migraine were the main features in four and five patients, respectively. Overall, 65/67 (97%) patients showed chronic cerebellar signs, whereas the remaining 2/67 had episodic ataxia with no cerebellar signs in the intervals.

CACNA1A variants were classified as pathogenic in 50 patients (75%; including five CAG expansions) and as VUSs in 17 patients (25%).

Diagnostic testing for GAA-*FGF14* expansions showed an enrichment of $(GAA)_{\geq 250}$ expansions in our cohort (6/67, 9% vs. 7/802, 0.87% in controls from the same ethnic background obtained from Mohren et al[12]; $P < 0.0002$ by Fisher's exact test). The clinical characteristics of the six patients (three sib pairs) with both a *CACNA1A* variant and an *FGF14* $(GAA)_{\geq 250}$ expansion are shown in Table 1 and Supporting Information Table S1. These patients invariably experienced disease onset later than 40 years of age, and all reported episodic symptoms [100% vs. 46% of patients without $(GAA)_{\geq 250}$ expansions; $P < 0.02$]. Brain magnetic resonance imaging showed only mild cerebellar atrophy, which was more pronounced, or limited, to the vermis (Fig. 1). The superior cerebellar peduncle sign was detected in only one case (patient 2T in Table 1).[31] All six patients carried *CACNA1A* variants that were classified as VUSs and were absent from population databases at the time of initial molecular assignment (see also Table 1). Both the $(GAA)_{\geq 250}$ expansion and the previously identified *CACNA1A* VUS segregated with the disease in the three sib pairs. In all three families, a history of autosomal dominant inheritance was reported (see Fig. 1). However, parental DNA was not available for segregation analysis. After *FGF14* testing, we reanalyzed these *CACNA1A* variants. We found that the *CACNA1A* variants p.Asp2172Tyr and p.Gln58ArgfsTer95 are now reported in gnomAD v4.1 with an allele frequency of 0.000008570 (12/1,400,290 chromosomes) and 0.00000979 (39/398,478 chromosomes), respectively. Although these variants are still rare, (1) their current frequency is greater than that expected for a highly penetrant condition such as *CACNA1A*-related disorders; and (2) they are now found along with an alternate molecular basis for disease, meeting the ACMG criteria BS1 and BP5. This led us to reclassify them as likely benign. Consequently, we reclassified four of six patients (sib pairs 2T-3T and I1-I2; see Table 1) as having SCA27B, without concomitant *CACNA1A* disease. The sib pair 2T-3T reported a history typical for episodic ataxia, with phasic worsening triggered by alcohol and physical exertion. Chronic cerebellar signs were mild and slowly progressive. In the sib pair I1-I2, the older sibling (I1) was homozygous for $(GAA)_{264}$ expansions, whereas the younger sibling (I2) carried a $(GAA)_{277}$ expansion and a $(GAA)_{219}$ expansion. They showed a strikingly different disease course. Patient 1I (initially reported in Ashton et al[6]) experienced an onset with both episodic features, including migraines, and chronic cerebellar symptoms. His chronic ataxia progressed rapidly, as reflected by a score of 29 points in the Scale for the Assessment and Rating of Ataxia 10 years after onset (Supporting Information Video S1). Cooccurring diseases that could account for this rapid progression were carefully excluded in repeated workups, and we ultimately attributed such an aggressive disease course to the additive effect of biallelic $(GAA)_{\geq 250}$ expansions. Patient 2I described an onset with isolated episodic features (oscillopsia), and at the last neurological examination, 7 years after onset, he had only very mild chronic cerebellar signs. In the other sib pair with $(GAA)_{\geq 250}$ expansions (3I-4I), the previously identified *CACNA1A* variant is still classified as VUS.

Intermediate GAA expansion ranging from 180 to 249 repeats was detected in five patients (7%; see also Table 1). The frequency of these expansions in our cohort did not differ from that of control subjects ($P = 0.1$ by Fisher's exact test, control subjects from Mohren et al[12]). One patient with a $(GAA)_{219}$ expansion also carried a $(GAA)_{277}$ on the other allele (patient 2I, described earlier and in Table 1). The other four patients with $(GAA)_{180–249}$ expansions carried established pathogenic *CACNA1A* variants. Three of them (5I, 6I, 7I) presented with childhood-onset disease with episodic features. Family studies in patient 7I showed that the $(GAA)_{181}$ expansion did not segregate with the disease phenotype.

Discussion

The recent description of GAA-*FGF14* repeat expansions in unsolved cases of ataxia sparked great interest. Several reports highlighted its high frequency in different populations[2,8,13,14,32] and its cooccurrence with other pathogenic variants.[8,13,17,18] The core phenotype of GAA-*FGF14*–related ataxia is a late onset, usually slowly progressive chronic ataxia, often heralded or accompanied by episodic features.[16] Several features of GAA-*FGF14*–related ataxia overlap with the phenotype of another recurrent etiology of hereditary ataxia: *CACNA1A* disease spectrum.[25] For these reasons, we investigated to what extent GAA-*FGF14* repeat expansions are detected in ataxia cases previously considered related to *CACNA1A* variants. We collected a large, multicenter cohort of cases previously considered likely to have *CACNA1A*-related disease based on consistent clinical features and the detection of either a VUS or a pathogenic variant in the gene. *CACNA1A* is listed among the genes most intolerant to genetic variation[33] and is at the same time highly polymorphic, thus setting inherent challenges in the interpretation of variants in the context of clinical diagnostics.[34] Therefore, patients with VUSs absent from population databases who showed a clinical phenotype fitting that of *CACNA1A* disease were included following an in-depth diagnostic excluding known alternative molecular causes at the time of referral. In this phenotypically well-defined

TABLE 1 *Detailed clinical and genetic data of patients with pathogenic (≥250 repeats) and intermediate (180–249 repeats) GAA-FGF14 expansions*

Patient data			*FGF14* genotype		*CACNA1A* genotype					Clinical features					
ID	Sex	Family no.	Repeat size: shorter allele	Repeat size: longer allele	Transcript	Protein	Variant classification[a]	ACMG criteria[a]	CADD Score	Age at onset (y)	Episodic features	Down-beat nystagmus[b]	Age at last follow-up (y)	SARA at last follow-up	SARA progression rate[c]
1I	Male	1	264	264	c.6514G>T	p.Asp2172Tyr	VUS	PM1-2	23.6	50	Yes	Yes	60	29	2.9
2I	Male	1	219	277	c.6514G>T	p.Asp2172Tyr				47	Yes	Yes	54	3	0.4
2T	Female	2	14	339	c.172del	p.Gln58ArgfsTer95	VUS	PM2, PP3	33	72	Yes	No	73	4	4.0
3T	Female	2	14	370	c.172del	p.Gln58ArgfsTer95				40	Yes	No	70	3.5	0.3
3I	Female	3	16	375	c.716T>C	p.Ile239Thr	VUS	PM1-2, PP3	28	65	Yes	No	73	6.5	0.8
4I	Male	3	8	362	c.716T>C	p.Ile239Thr				61	Yes	Yes	74	6.5	0.5
1T	Female	5	15	232	c.1745G>A	p.Arg582Gln	Pathogenic	PM1-2, PP3, PP5	33	33	No	No	45	8.5	0.7
5I	Male	6	10	199	c.3089 + 2T>C		Pathogenic	PVS1, PM2, PP1	n.a.	1	Yes	No	48	2	0.1
6I	Male	7	15	185	c.3603dup	p.Lys1202GlufsTer14	Pathogenic	PVS1, PM1-2	n.a.	7	Yes	Yes	55	7	0.3
7I	Female	8	10	181	c.3457C>T	p.Gln1153Ter	Pathogenic	PVS1, PM2, PP1	38	3	Yes	No	65	9.5	0.2

Abbreviations: ACMG, American College of Medical Genetics and Genomics; CADD, Combined Annotation Dependent Depletion; SARA, Scale for the Assessment and Rating of Ataxia; VUS, variant of uncertain significance; n.a., not available.

[a]We herein report the first CACNA1A variant classification, along with the supporting ACMG criteria at the time of the initial molecular assignment and the CADD scores. The reference sequence for *CACNA1A* is NM_001127222.2/ENST00000360228.11, except for the variant c.172del, which is found only in the first exon of the transcript ENST00000664864.1 (see https://gtexportal.org/home/gene/CACNA1A). For this reason and because it does not affect the open reading frame of other major transcripts expressed in the cerebellum, the PVS1 criterion was not fulfilled.

[b]We report the detection of down-beat nystagmus at neurological examination. However, it may occur only during episodic exacerbations and thus escape clinical observation.

[c]The rate of progression was estimated by dividing the most recent SARA score by the duration of the disease.

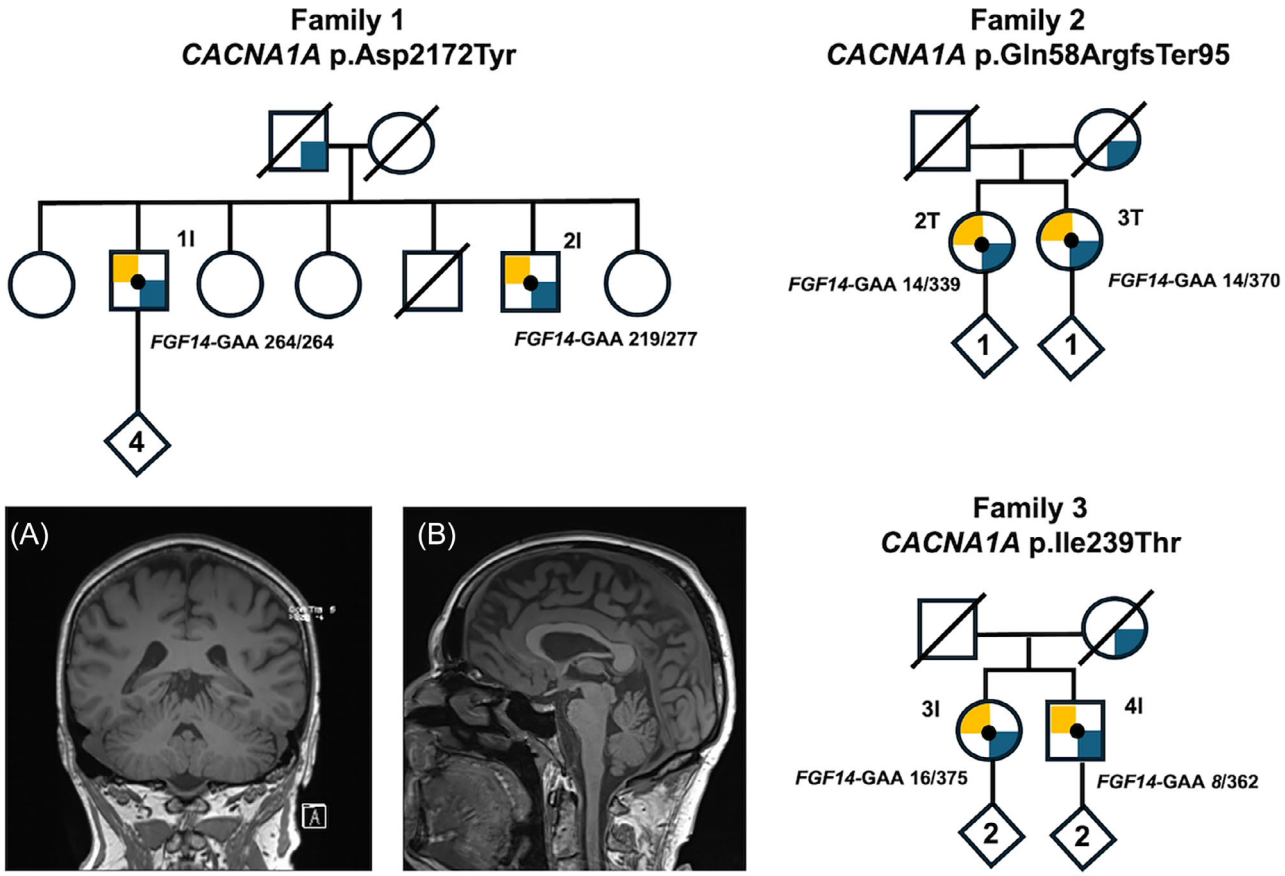

FIG. 1. Family trees and magnetic resonance imaging findings of patients with both a *CACNA1A* variant and a *FGF14* $(GAA)_{\geq 250}$ expansion. The blue quadrant represents chronic cerebellar ataxia, and the yellow quadrant represents episodic ataxia. The black dot indicates a carrier of the *CACNA1A* variant. Genetic testing was performed only in the subjects labeled with a patient ID. (**A**, **B**) The patient's T1-weighted coronal and sagittal brain magnetic resonance imaging scans, acquired at the most recent follow-up, 10 years after onset. Despite the patient's clinical progression (Scale for the Assessment and Rating of Ataxia score of 29/40 points), only mild cerebellar atrophy affecting the upper vermis is evident. [Color figure can be viewed at wileyonlinelibrary.com]

cohort, we observed an enrichment of pathogenic GAA-*FGF14* repeat expansions (≥250 repeats), which were detected in 6/67 patients. Notably, all patients with a pathogenic GAA-*FGF14* expansion carried *CACNA1A* variants, which were classified as VUSs. These *CACNA1A* VUSs were absent from population datasets at the time of first molecular assignment and segregated with the disease in all sib pairs. Patients carrying pathogenic GAA-*FGF14* repeat expansions invariably had a late onset of disease (>40 years of age). Otherwise, their phenotype with mild chronic cerebellar ataxia and episodic features was not distinguishable from that associated with the *CACNA1A* disorder known as "episodic ataxia type 2." The few other known alternative genetic etiologies for this phenotype had been ruled out during the initial diagnostic workup. These considerations motivated the diagnosis of a probable *CACNA1A*-related disorder at that time. GAA-*FGF14* testing prompted a genetic reevaluation, which led to the reclassification of two of three *CACNA1A* VUSs as likely benign variants. The reclassification was primarily driven by the observation that these variants have a high allele frequency in the latest update of the population database gnomAD (November 2024), which contains fivefold more genomic information compared with previous releases.[35] Thus, in four of six patients with VUSs in *CACNA1A*, SCA27B became a more plausible diagnosis a posteriori. In two other patients with a $(GAA)_{\geq 250}$ expansion, the *CACNA1A* variant is still classified as a VUS.

Recent work has suggested a possible pathogenic role for intermediate GAA-*FGF14* expansions (180–249 repeats).[9,12] We detected $(GAA)_{180–249}$ expansions in 5/67 patients. Four of them carried established pathogenic *CACNA1A* variants. They invariably had a disease onset <40 years, mostly in childhood. A $(GAA)_{181}$ expansion did not segregate with the disease in one family. The fifth patient had a *CACNA1A* VUS and a compound genotype for an intermediate allele and a pathogenic GAA expansion. He had a mild, late-onset phenotype consistent with that of classical SCA27B, in contrast with his brother, who was

homozygous for $(GAA)_{264}$ expansions and exhibited an unusually rapid disease progression. Altogether these findings would argue against a major pathogenic effect of $(GAA)_{180–249}$ expansions. Intermediate expansions may still exert a modifier/weaker pathogenic effect, which is consistent with their enrichment in patients with idiopathic down-beat nystagmus,[9] an endophenotype of SCA27B. To date, a small number of cases with biallelic $(GAA)_{\geq 250}$ expansion have been described (reviewed in Pellerin et al[10]). The associated clinical presentation was reported to be either similar to that of heterozygous patients[7,8] or more severe, with earlier onset/faster progression.[36,37]

By reassessing *CACNA1A* variants in patients who tested positive for GAA-*FGF14* expansion, we were able to reclassify two of three *CACNA1A* VUSs as likely benign. However, the clinical variability and the large number of single-nucleotide polymorphisms in *CACNA1A* still pose a hurdle in the neurogenetic assignment.[34] Although functional studies and accurate family segregation studies can aid in solving this issue, they are not always readily available. Furthermore, segregation studies in late-onset disorders may be hindered by the lack of available parental DNA and by non-informative family histories because of recall biases. Our findings, together with cumulative literature, indicate that an early onset of the disease is a clinical clue highly suggestive of *CACNA1A* disease as opposed to a late onset (>40 years of age) in patients with SCA27B. This emphasizes the importance of an accurate clinical history focused on early manifestations (specific episodic symptoms in childhood, developmental issues), also in the genotype-first era.[38] With respect to clinical practice, our findings support a thorough reevaluation of patients with late-onset ataxia previously considered as a possible *CACNA1A* spectrum disorder based on their clinical phenotype and the detection of a *CACNA1A* VUS. ■

Author Roles: E.I.: conception of the project, data collection and analysis, and writing of the first draft. Z.F.: data collection and analysis and draft editing. D.P.: conception of the project and data collection and analysis. W.N.: data collection and analysis and draft editing. S.Z.: data collection and analysis and draft editing. A.T.: data collection and analysis and draft editing. M.A.: data collection and analysis and draft editing. L.S.: data collection and analysis and draft editing. T.H.: data collection and analysis and draft editing. B.B.: data collection and analysis and draft editing. S.B.: data collection and analysis and draft editing. M.S.: conception of the project, data collection and analysis, and draft editing.

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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.