Short report

Intronic FGF14 GAA repeat expansions are a common cause of ataxia syndromes with neuropathy and bilateral vestibulopathy

David Pellerin,1,2 Carlo Wilke,3,4 Andreas Traschütz,3,4 Sara Nagy,1,5 Riccardo Curra,1,6 Marie-Josée Dicaire,2 Hector García-Moreno,7,8 Mathieu Anheim,9,10 Thomas Wirth,9,10 Jennifer Faber,11,12 Dagmar Timmann,13 Christel Depienne,14 Dan Rujescu,15 José Gazulla,16 Mary M Reilly,1 Paola Giunti,7,8 Bernard Brais,2,17,18 Henry Houlden1,19 Ludger Schöls,4,19 Michael Struppa,20 Andrea Cortese1,20 Matthijs Synofzik3,4

ABSTRACT

Background Intronic GAA repeat expansions in the fibroblast growth factor 14 gene (FGF14) have recently been identified as a common cause of ataxia with potential phenotypic overlap with RFC1-related cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS). Our objective was to report on the frequency of intronic FGF14 GAA repeat expansions in patients with an unexplained CANVAS-like phenotype.

Methods We recruited 45 patients negative for biallelic RFC1 repeat expansions with a combination of cerebellar ataxia plus peripheral neuropathy and/or bilateral vestibulopathy (BVP), and genotyped the FGF14 repeat locus. Phenotypic features of GAA-FGF14-positive versus GAA-FGF14-negative patients were compared.

Results Frequency of FGF14 GAA repeat expansions was 38% (17/45) in the entire cohort, 38% (5/13) in the subgroup with cerebellar ataxia plus polyneuropathy, 43% (9/21) in the subgroup with cerebellar ataxia plus BVP and 27% (3/11) in patients with all three features. BVP was observed in 75% (12/16) of GAA-FGF14-positive patients. Polyneuropathy was at most mild and of mixed sensorimotor type in six of eight GAA-FGF14-positive patients. Family history of ataxia (59% vs 15%; p = 0.007) was significantly more frequent and permanent cerebellar dysarthria (12% vs 54%; p = 0.009) significantly less frequent in GAA-FGF14-positive than in GAA-FGF14-negative patients. Age at onset was inversely correlated to the size of the repeat expansion (Pearson’s r, −0.67; R2=0.45; p=0.0031).

Conclusions GAA-FGF14-related disease is a common cause of cerebellar ataxia with polyneuropathy and/or BVP, and should be included in the differential diagnosis of RFC1 CANVAS and disease spectrum.

INTRODUCTION

Dominantly inherited intronic GAA repeat expansions in the fibroblast growth factor 14 gene (FGF14) have recently been shown to be a common cause of hereditary ataxia (GAA-FGF14-related disease; spinocerebellar ataxia 27B (MIM: 620174)).1,2 Initial observations of cerebellar ataxia and bilateral vestibulopathy (BVP) in a subset of patients carrying an FGF14 GAA repeat expansion suggested partial phenotypic overlap between GAA-FGF14-related disease and cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS).1,2 Biallelic intronic pentanucleotide repeat expansions in the replication factor C subunit 1 gene (RFC1) are a frequent cause of CANVAS, accounting for 70% to 100% of cases in various series.3,4 Phenotypic analysis of RFC1-positive patients has shown that CANVAS is not a strictly delineated disease entity but rather a phenotypic cluster occurring along a continuum of variable involvement of the cerebellar, sensory and vestibular systems.5–8 While biallelic RFC1 repeat expansions are a frequent cause of CANVAS-spectrum disease, other causative genes are yet to be identified, especially in the subgroup of patients with partial features of CANVAS.1,9

Here, we studied the frequency of FGF14 GAA repeat expansions in patients with a combination of cerebellar ataxia plus peripheral neuropathy and/or BVP negative for biallelic RFC1 repeat expansions, and report on the phenotypic spectrum of GAA-FGF14-positive patients.

METHODS

Patient enrollment

Forty-five index patients with neurodegenerative ataxia for which an underlying genetic cause had not yet been identified were recruited from seven different centres in Europe (France: 1, Germany: 4, Spain: 1, UK: 1 centre). To be eligible for inclusion in the study, patients needed to have cerebellar ataxia plus polyneuropathy confirmed by nerve conduction studies (excluding focal entrapment neuropathies) and/or BVP evidenced by reduced bilateral vestibulo-ocular reflex by bedside head impulse test or video head impulse test (vHIT); and negative results on screening for biallelic RFC1 repeat...
expansions. The bedside head impulse test, performed by experienced neurologists with expertise in ataxia, was available in 38 of 45 (84%) patients, the vHIT was available in 21 of 45 (47%) patients and either test was available in 39 of 45 (87%) patients. Results of brain MRI and nerve conduction studies were available for review in 82% (37/45) and 80% (36/45) of patients, respectively. Deep phenotyping was performed through review of medical records and, when possible, patient re-evaluation using a standardised data sheet for both GAA-FGF14-positive and GAA-FGF14-negative patients.

Figure 1  Frequency of the FGF14 GAA repeat expansion, age at onset correlation and clinical features of GAA-FGF14-positive patients. (A) Percentage of patients who carried an FGF14 (GAA)≥250 repeat expansion in the subgroups with (1) cerebellar ataxia plus polyneuropathy (CA+PN) (5 of 13 patients), (2) cerebellar ataxia plus bilateral vestibulopathy (CA+BVP) (9 of 21) and (3) cerebellar ataxia plus polyneuropathy and bilateral vestibulopathy (CA+PN+BVP) (3 of 11). (B) Inverse correlation between size of the FGF14 repeat expansion and age at disease onset in 17 patients (Pearson's r, −0.67; R²=0.45; p=0.0031). The grey area displays the 95% CI. Simple linear regression fitting (slope, −0.079 and intercept, 89.84) suggests that age at onset decreases by about 3.96 years (95% CI: 1.56 to 6.37 years) for every increment of 50 GAA repeats above the pathogenic threshold of 250 repeat units. (C) Frequency of individual phenotypic features in 17 GAA-FGF14-positive patients. Numbers in brackets indicate the number of affected patients over the total number of patients assessed for this feature. FGF14, fibroblast growth factor 14 gene.
had large amplification products by PCR underwent bidi-electrophoresis of PCR amplification products. Patients who of fragment length analysis were confirmed by agarose gel

Of the 45 patients enrolled in this study, 17 (38%) carried a

RESULTS

Individual deidentified patient data may be shared at the request of any qualified investigator on reasonable request.

Data availability

Table 1 presents the baseline characteristics of the GAA-FGF14-positive and GAA-FGF14-negative cohorts. Comparison of all clinical features in the two cohorts revealed significantly less frequent permanent cerebellar dysarthria (2/17; 12%) vs 14/26; 54%; Fisher’s exact test p=0.009) and non-significantly more frequent episodic symptoms (10/17; 59% vs 7/26; 27%; Fisher’s exact test p=0.06) in GAA-FGF14-positive compared with GAA-FGF14-negative patients. Family history of ataxia, which was positive in 59% of GAA-FGF14-positive patients, was significantly more frequent in GAA-FGF14-positive compared with GAA-FGF14-negative patients (59% vs 15%; Fisher’s exact test, p=0.007).

**DISCUSSION**

Our study demonstrates that FGF14 GAA repeat expansions are common in patients negative for biallelic RFC1 repeat expansions presenting with a combination of cerebellar ataxia plus polyneuropathy and/or BVP. Compared with European cohorts of late-onset ataxia in which the frequency of GAA-FGF14 ataxia is 10–18%,1 2 the frequency of 38% observed in this cohort suggests that FGF14 repeat expansions are enriched in patients partially fulfilling criteria for CANVAS. These results may suggest a combined vulnerability of the cerebellar, peripheral nerve and vestibular systems in GAA-FGF14-related disease. Our study thus confirms and extends previous findings showing that BVP is part of the phenotypic spectrum of GAA-FGF14-related
Our estimate of the frequency of BVP in GAA-FGF14-related disease may even represent an underestimate, as only a relatively small proportion of patients underwent vHIT. Moreover, given the inclusion criteria of our study, the true prevalence of BVP in unselected cohorts of GAA-FGF14-positive patients fully assessed with vHIT remains to be established. Although the prevalence of vestibular impairment in spinocerebellar ataxias has not been well studied, this feature is not specific to GAA-FGF14-related disease, as it is found with variable frequency in other inherited ataxias such as RFC1-related disease (87–90%), 6,14 Friedrich ataxia (53–55%) 12,13 and spinocerebellar ataxia 3 (57–100%). 14–16

Despite phenotypic overlap between RFC1-related disease and GAA-FGF14-related disease, certain features may help differentiate these disorders. Chronic cough, a prevalent feature in RFC1-related disease, 5,6 was uncommon in our cohort. While motor neuropathy is typically absent or minimal in RFC1-positive patients, 17–19 it co-occurred with sensory neuropathy in six of eight GAA-FGF14 patients. Our findings also suggest that episodic symptoms—which were common in previously reported cohorts—are a frequent feature in GAA-FGF14-positive patients, which may help to discriminate these patients from RFC1-positive patients in whom episodic symptoms are rare. Finally, the pattern of inheritance, which is autosomal dominant in GAA-FGF14-related disease and autosomal recessive in RFC1-related disease, may help differentiating both disorders, although acknowledging that in comparison with other spinocerebellar ataxias 18 a substantial proportion of patients with GAA-FGF14-related disease present sporadically (15–50%, depending on cohorts) 17 or with seemingly recessive inheritance.

Limitations of this study include its small cohort size and the fact that only 29% (13/45) of patients underwent brain MRI, nerve conduction studies and vHIT. Since bedside head impulse test has a sensitivity of less than 70% for detecting vestibulopathy compared with vHIT, 18 a systematic assessment of the vestibular function in phenotypically unselected GAA-FGF14-positive cohorts using vHIT will be necessary to fully define the frequency of vestibular hypofunction in GAA-FGF14-related disease in future studies. Larger natural history studies are needed to fully define the phenotypic spectrum of GAA-FGF14-related disease (for first in-depth phenotype and progression study, see Wilke et al 20) and to assess its frequency in patients meeting the proposed diagnostic criteria for clinically definite CANVAS negative for biallelic RFC1 repeat expansions. Such studies will also be critical to evaluate the degree to which polyneuropathy is pathologically related to GAA-FGF14-related disease—a late-onset disorder—rather than an age-related process, given its high prevalence in the general elderly population. 21

In conclusion, we showed that FGF14 GAA repeat expansions are a common cause of cerebellar ataxia plus polyneuropathy and/or BVP in patients negative for biallelic RFC1 repeat expansions, thus expanding the phenotypic spectrum of this recently described disorder. Our results further suggest that GAA-FGF14-related disease should be included in the differential diagnosis of RFC1 CANVAS and disease spectrum.

Author affiliations
1Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, University College London, London, UK
2Department of Neurology and Neurosurgery, Montreal Neurological Hospital and Institute, McGill University, Montreal, QC, Canada
3Research Division Translational Genomics of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany
4German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
5Department of Neurology, University Hospital Basel, University of Basel, Basel, Switzerland
6Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
7Ataxia Centre, UCL Queen Square Institute of Neurology, University College London, London, UK
8National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK
9Service de Neurologie, Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre, Strasbourg, France
10Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, Strasbourg, France
11Department of Neurology, University Hospital Bonn, Bonn, Germany
12German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
13Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), Essen University Hospital, University of Duisburg-Essen, Essen, Germany
14Institute of Human Genetics, Essen University Hospital, University of Duisburg-Essen, Essen, Germany
15Department of Psychiatry and Psychotherapy, Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria
16Department of Neurology, Hospital Universitario Miguel Servet, Zaragoza, Spain
17Department of Human Genetics, McGill University, Montreal, QC, Canada
18Centre de Réadaptation Lucie Bruneau, Montreal, QC, Canada
19Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany
20Department of Neurology and German Center for Vertigo and Balance Disorders, LMU University Hospital, LMU Munich, Munich, Germany

Twitter Christel Depienne @ChristelDepiennn

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ORCID iDs
David Pellerin  http://orcid.org/0000-0002-5807-995X
Carlo Wilke  http://orcid.org/0000-0002-7230-8597
Jennifer Faber  http://orcid.org/0000-0003-3265-0262
Mary M Reilly  http://orcid.org/0000-0003-0686-905X
Henry Houlden  http://orcid.org/0000-0002-2866-7777
Andrea Cortese  http://orcid.org/0000-0002-2208-5311
Matthias Synofzik  http://orcid.org/0000-0002-2280-7273

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