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FGF14 (GAA•TTC) repeat expansion-related ataxia SCA27B is common in Northern Finland

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ABSTRACT

Introduction: An intronic repeat expansion $(GAA•TTC)_{exp}$ in the *FGF14* gene (*FGF14* $(GAA•TTC)_{exp}$) has recently been found to cause dominantly inherited ataxia SCA27B. The core phenotype consists of late-onset and slowly progressing ataxia with down-beat nystagmus and episodic features. Disease penetrance depends on the number of repeat units and ≥300 is widely used pathogenic threshold for complete penetrance. The Finnish population is genetically unique and SCA27B has not previously been reported in Finland.

Methods: We investigated *FGF14* $(GAA•TTC)_{exp}$ in a cohort of 96 Finnish patients with suspected hereditary ataxia or ataxia of unknown etiology, of whom 62 patients had no previous genetic diagnosis. We also assessed *FGF14* $(GAA•TTC)_{exp}$ in 561 controls in order to estimate its population prevalence in North Ostrobothnia.

Results: We found five patients with *FGF14* $(GAA•TTC)_{\geq 250}$ giving a frequency of 5.2 % in the ataxia cohort. One patient had a rare biallelic genotype. Four patients had the classical SCA27B phenotype with no atypical features. Two of the patients had a previous genetic diagnosis and digenic contribution could not be excluded. Moreover, we found one patient with suspected *FGF14* disease and with $(GAA•TTC)_{248}$, but the segregation analysis remained inconclusive. The $(GAA•TTC)_{\geq 250}$ frequency was 2.7 % in the general population. Population prevalence was 1.7 per 100 000 in North Ostrobothnia. The frequency of alleles harboring 200–249 repeats was 2.2 % in patients and 1.5 % in controls.

Conclusion: Our results suggest that screening of *FGF14* expansion should be carried out in Finnish patients with suspected hereditary ataxia or ataxia of unknown etiology.

1. Introduction

Hereditary ataxia is commonly caused by repeat expansions. Recent development in sequencing technology has enabled the detection of an increasing number of disease-causing repeat expansions in various neurological diseases. The dominantly inherited spinocerebellar ataxia (SCA) 27A has been shown to result from pathogenic point, frameshift, or structural variants in the *FGF14* gene [1], but it was not until 2023

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when an intronic trinucleotide repeat expansion $(GAA•TTC)_{exp}$ in *FGF14* was found to be a common cause of SCA27B [2,3]. The core features of SCA27B are late-onset cerebellar ataxia, down-beat nystagmus, early episodic nature, and slow progression [4–6]. Typical MRI findings include cerebellar atrophy and T2/FLAIR hyperintensity of the superior cerebellar peduncles [7]. The *FGF14* $(GAA•TTC)_{\geq 300}$ alleles are considered completely penetrant, while alleles containing 250–299 repeat units are associated with incomplete penetrance. The significance of alleles containing 200–249 repeat units is still unknown [2]. Indeed, a higher frequency of alleles with >180 repeat units has recently been reported in patients with ataxia [8]. Moreover, the expansion exhibits instability on intergenerational transmission with alleles $(GAA•TTC)_{\geq 100}$ expanding during maternal transmission or contracting during paternal transmission [2,9]. The frequency of SCA27B varies remarkably in different cohorts because of variable selection criteria and ethnicity of the patients and, in consequence, *FGF14* $(GAA•TTC)_{exp}$ has been reported to explain 3–60 % of late-onset ataxia cases [2,3,10–12].

Molecular epidemiology of ataxias in Finland differs significantly from that in other European populations [13]. The population-specific features include lack of SCA3, a low frequency of Friedreich's ataxia that is common elsewhere, and a high frequency of SCA8 and *POLG*-related ataxia, while SCA27B has not yet been reported. In this study, we investigated the frequency of SCA27B in Finnish patients with unspecified hereditary ataxia or ataxia of unknown etiology and report their *FGF14* $(GAA•TTC)_{exp}$ genotypes. In addition, we assessed the frequency of the expansion in a large sample of Finnish population controls.

2. Methods

A cohort of Finnish patients with ataxia has been described previously [13]. Briefly, adult patients who had visited Oulu University Hospital (OUH) between the years 1997 and 2019 and had a diagnosis of unspecified hereditary ataxia or unspecified ataxia were reviewed from the OUH database. The search yielded 408 patients. Eighteen patients were excluded based on age under 18 years and 36 patients were deceased. After exclusion of acquired and secondary ataxias, 125 patients were invited to the study. Five additional patients were referred to the study from the OUH neurology outpatient clinic. Moreover, 11 patients from an identical cohort identified in 1976–1994 were included in the cohort. A total of 96 patients participated and so far, genetic diagnosis has been established for 34 patients [13]. The controls consisted of 561 healthy (self-reported) anonymous blood donors from the Finnish Red Cross.

DNA was extracted with the Qiasymphony automated system using Qiagen DSP DNA Kit or manually using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Previously reported primers flanking the *FGF14* repeat locus were used [2]. XL-PCR was performed using PhireII Hot Start DNA polymerase (Thermo Fisher Scientific, Waltham, MA, U.S.A.) with standard conditions using 3 % DMSO as a PCR additive. Initial denaturation at 98 °C for 30 s was followed by 35 cycles of denaturation of 5 s, primer annealing at 59 °C for 5 s, and extension at 72 °C for 30 s. Final extension of 1 min was performed. PCR products were loaded on a 2 % agarose gel. A flanking sequence of 150 bp and 250 repeats yielded PCR product of 900 bp. All PCR-products of alleles ≥900 bp (≥250 repeats), 750–<900 bp (200–249 repeats) and 690-<750 bp (180–199 repeats) were purified from the agarose gel using GeneJET Gel Extraction kit with provided protocol (Thermo Fisher Scientific) and Sanger sequenced. In addition, a set of samples were further genotyped as described below to validate our sizing and sequencing methodology.

The *FGF14* repeat locus was genotyped by long-range PCR (LR-PCR) and repeat-primed PCRs (RP-PCR), as described previously [14]. Repeat sizes were first measured by capillary electrophoresis of fluorescent LR-PCR amplification products. Bidirectional repeat-primed PCRs targeting the 5′-end and the 3′-end of the locus were next performed to ascertain the presence of a $(GAA•TTC)_{exp}$. LR-PCR and RP-PCR products were analyzed on an ABI 3730xl DNA Analyzer with a 50-cm POP-7 capillary using the GeneScan 1200 Liz Dye Size Standard (Thermo Fisher Scientific) following the manufacturer's instructions. Results were analyzed using the GeneMapper software version 6 using the built-in micro-satellite default settings (Thermo Fisher Scientific). The presence of characteristic saw-toothed products indicated the presence of a $(GAA•TTC)_{exp}$ at the *FGF14* repeat locus. Chromatograms were inspected for the presence of interruptions. The reported repeat number refers to the number of pure GAA•TTC repeat units.

3. Ethics

The study protocol was approved by the Oulu University Hospital Ethics Committee (EETTMK:93/2010). All participants gave their written informed consent. Clinical examinations were done according to the WMA declaration of Helsinki (2013).

4. Results

We identified five patients with *FGF14* $(GAA•TTC)_{>250}$ (Table 1, Fig. 1). Patients P1, P2 and P5 harbored a heterozygous $(GAA•TTC)_{>300}$ and patient P3 had a biallelic $(GAA•TTC)_{300}$. Patient P4 had a heterozygous $(GAA•TTC)_{278}$ within the incomplete penetrance range. Patients P2 and P5 had a family history of ataxia and, in addition, patient P6 had a remarkable family history of ataxia. Patient P6 harbored $(GAA•TTC)_{248}$ and his affected mother had $(GAA•TTC)_{23_5}$, but his two affected brothers had <20 repeat units in both alleles suggesting another genetic cause in the family The frequency of *FGF14* $(GAA•TTC)_{\geq 250}$ was 5.2 % (5/96) in the ataxia patient cohort and 4.8 % among ataxia patients without genetic diagnosis (3/62). Patient P4 with $(GAA•TTC)_{278}$ had a previous diagnosis of *ATM*-related ataxia with two pathogenic variants p.His605fs and p.Gly2891Asp (refseq NM_001351834.2) and patient P5 had the homozygous pathogenic variant p.Trp748Ser in *POLG* (refseq NM_002693.3).

Fifteen control subjects harbored heterozygous *FGF14* $(GAA•TTC)_{\geq 250}$ giving a frequency of 2.7 % in the population controls. Population prevalence was estimated to be 1.7/100 000 in North Ostrobothnia (95 % confidence interval, 0.4–2.9/100 000). Eleven of the controls (2.0 %) had 250–299 repeat units, while four controls (0.7 %) had more than 300 repeat units. In addition, the PCR product of 9 controls was ≥900 bp, but sequencing revealed benign $(GAAGGA)_n$ or $(GAAGCA)_n$ expansions in *FGF14*. The allele frequency of $(GAA•TTC)_{200\text{-}249}$ was 2.2 % (4/184) in patients with ataxia and 1.5 % (17/1118) in controls (Exact test of population differentiation X^2, $p = 0.52$). The allele frequency of $(GAA•TTC)_{180\text{-}199}$ was 1.1 % in controls and 0.5 % in the patients.

5. Discussion

In this cohort of 96 patients with unspecified hereditary ataxia or ataxia of unknown etiology from Northern Finland [13], the proportion of patients with *FGF14* $(GAA•TTC)_{\geq 250}$ was 5.2 % while the proportion was 4.8 % in patients with other common genetic causes of ataxia excluded. The frequency shows that *FGF14* $(GAA•TTC)_{exp}$ should be included in the routine genetic testing as together with *RFC1*, *POLG*, and *ATXN8OS* they explain ~25 % of the hereditary ataxia in Northern Finland. Four out of the five patients with *FGF14* $(GAA•TTC)_{\geq 250}$ had a phenotype compatible with that previously reported for SCA27B with no atypical features as three of the five patients had episodic ataxia and nystagmus which are the core features of SCA27B. One patient had an early-onset ataxia with features of mitochondrial disease.

The frequency of SCA27B varies in different cohorts. Most of the reported cohorts exclude patients with other common genetic causes of ataxia and limit the testing to cases with onset after the age of 30 years and, therefore, the frequencies are higher compared to those calculated from unselected cohorts. A notably high *FGF14* $(GAA•TTC)_{exp}$ frequency

Table 1
Clinical features of the six Finnish patients examined for *FGF14* (GAA•TTC)$_{exp}$.

	P1	P2	P3	P4[a]	P5[a,b]	P6
Pure repeat units, N	326/9	372/8	300/300	278/15	330/15[c]	248/15
Gender	M	M	F	M	M	M
Age, years	75[d]	88	72[d]	86[d]	48[d]	27
Age at onset, years	64	71	63	70	24	18
First symptoms	Walking difficulties	Gait instability, dysarthria	Nystagmus	Decreased strength in lower limbs, clumsiness	Dysarthria	Dysarthria, gait instability
Dysarthria	No	Yes	Yes	Yes	Yes	Yes
Nystagmus	No	Vertical, horizontal	Vertical, horizontal	Vertical, horizontal	No	No
Episodic, triggers	No	Yes, exercise & heat	Yes, exercise	Yes, fatigue & exercise	No	Yes, alcohol
MRI/CT	Cerebellar atrophy, white matter atrophy	Normal	Cortical atrophy, ventricular enlargement	Cerebellar atrophy, cortical atrophy, hippocampus atrophy	Mild cortical cerebellar atrophy	Mild cerebral ventricular enlargement
Family history	Negative	Positive	Negative	Negative	Positive	Positive

[a] Previous genetic diagnosis.
[b] Other features: epilepsy, cognitive impairment, depression, polyneuropathy.
[c] Approximated size based on gel electrophoresis.
[d] Age at death.

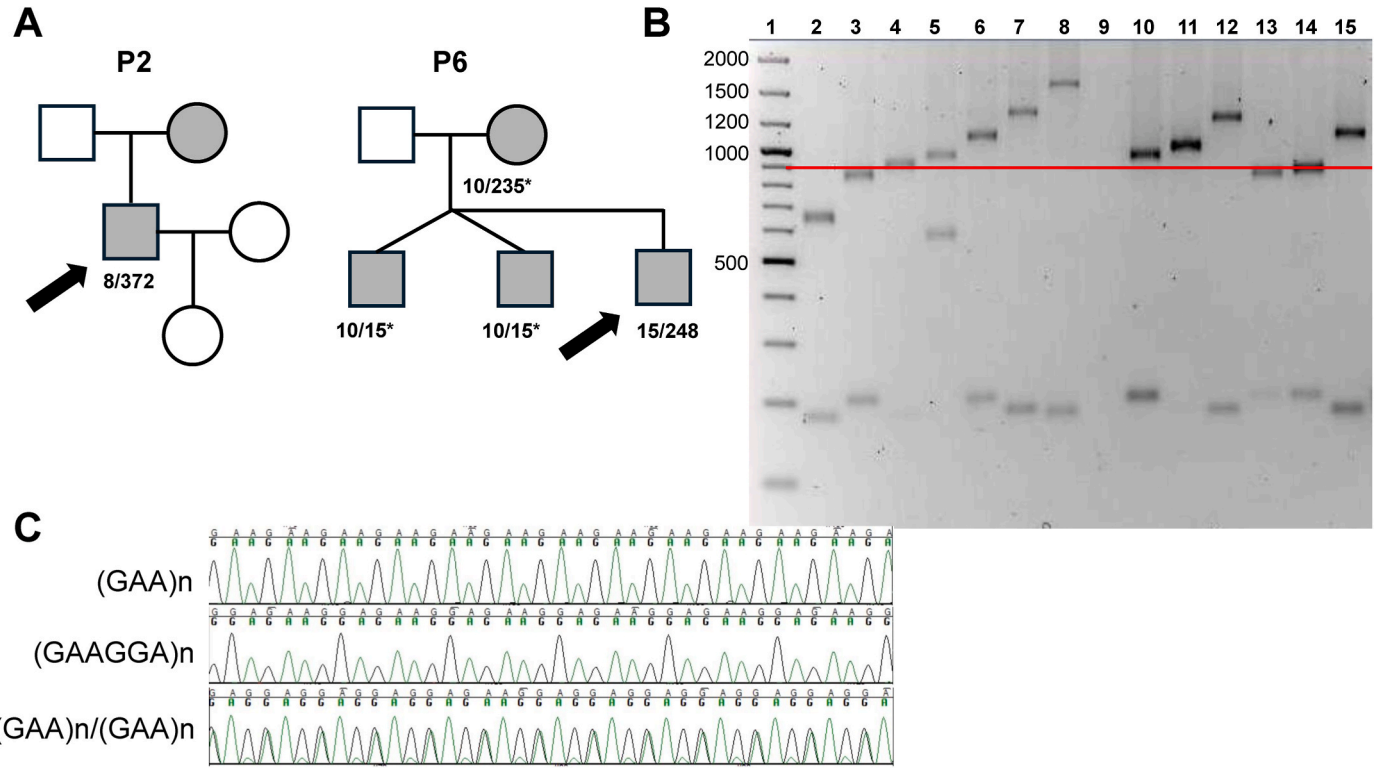

Fig. 1. *FGF14* (GAA•TTC)$_{exp}$ in patients with SCA27B. Family trees and molecular analyses. A) Family trees of patient P2 harboring heterozygous *FGF14* (GAA•TTC)$_{372}$ and P6 harboring heterozygous *FGF14* (GAA•TTC)$_{248}$. Genotypes are shown below the symbol. Arrow, proband; white symbol, healthy; grey symbol, patient with ataxia; asterix, approximated size based on gel electrophoresis. B) Example of agarose gel electrophoresis of XL-PCR products. Lane 1, Generuler 100 bp Plus marker; lanes 2–8, sizing controls, GAA•TTC repeat units (RU) in larger allele: 170, 247, 265, 280, 323, 396, 508; lane 9, no template control; lane 10, 278 RU (P4); lane 11, biallelic 300 RU (P3); lane 12, 372 RU (P2); lane 13, <250 RU; lane 14, 248 RU (P6); lane 15, 326 RU (P1). C) Examples of sequence chromatograms of expansions (GAA)n, (GAAGGA)n and biallelic (GAA)n.

of 28 % has been reported in Spanish patients with LOCA without previous genetic diagnosis [15], while in German, Italian and Serbian patients with common genetic causes excluded, the frequencies varied from 5.4 % to 18 % [2,3,16,17]. Furthermore, in Indian, Japanese and Australian patients, frequencies of 10 %, 3 % and 15 % have been reported [2,12]. In genetically unselected cohorts of Indian, American and Australian patients, the frequencies of 1.8 %, 7.5 % and 13.7 % have been reported [3,6,18]. The allele frequency of *FGF14* (GAA•TTC)$_{\geq 250}$ was 1.34 % in our 561 population controls while that of 0.98 % has been reported in German and French-Canadian population controls [2], 2.6 % in German and 0.47 % in Australian controls [3], and 1.36 % in French controls [9]. Our patients and two controls with *FGF14* (GAA•TTC)$_{\geq 250}$ were residents of North Ostrobothnia giving a population prevalence of 1.7/100 000 for the province.

The pathogenic threshold of the repeat number is still unsolved and factors associated with variable penetrance are currently unknown. Indeed, reduced penetrance of ataxia may occur even with larger alleles [19]. Previous studies have shown that alleles of 200–249 repeat units are enriched in patient cohorts suggesting that they may be considered pathogenic with incomplete penetrance in patients with compatible phenotype, in whom other genetic causes of ataxia have been excluded, and if familial segregation has been confirmed [12,20]. According to the recent report the pathogenic threshold may be as low as 180 repeat units [8]. In our study, the allele frequency of $(GAA•TTC)_{200\text{-}249}$ was only modestly increased in patients compared to that in controls and the frequency of alleles with 180–199 repeat units was, indeed, lower in patients than that of the controls. Intriguingly, patient P6 had $(GAA•TTC)_{exp}$ with 248 repeat units and a prominent family history of episodic ataxia. He had an early-onset episodic ataxia and the repeat number was 235 in his symptomatic mother. However, segregation analysis revealed that two affected brothers of the proband did not have *FGF14* $(GAA•TTC)_{exp}$ suggesting that there is another genetic cause involved. Despite extensive genetic testing of the family members, investigations have so far remained negative.

Four patients in our study had disease onset after the age of 60 years. This, along with their phenotype, was consistent with SCA27B [5–7]. Patient P4 with $(GAA•TTC)_{278}$ had previously been diagnosed with two pathogenic variants in the *ATM* gene [13], but compound heterozygosity had not been confirmed, because relatives were not available for investigation. He had a late-onset ataxia, which is compatible with SCA27B but uncommon in ataxia-telangiectasia caused by *ATM*. Patient P5 with homozygous p.Trp748Ser in *POLG* had an early-onset ataxia with epilepsy, cognitive impairment and polyneuropathy being thus compatible with POLG disease, but digenic phenotype cannot be excluded as he carried *FGF14* $(GAA•TTC)_{>300}$. Patient P5 had a disease onset at 24 years of age, which is early, but not exceptional, for SCA27B, since disease onset at age of 28 and 11 years has been reported [16,21]. Family history was positive in P2 and P5 but negative in the remaining patients. Indeed, a negative family history should not be an exclusion criterion for considering SCA27B, since up to half of all cases appear to be sporadic [22]. Furthermore, the sex-specific intergenerational instability of the expansion may result in misleading family trees.

The age at onset of SCA27B ranges from 50 to 70 years [5]. The available ages of the 15 controls carrying $\geq$250 repeat units varied between 26 and 51 years, being thus below the typical age at onset of SCA27B. Four controls carried a large expansion of >300 repeat units and the ages at the time of blood donation were available for two of them both being 26 years. The control subjects had reported themselves to be free of any neurological symptoms at the time of sample collection. Unfortunately, since the samples had been collected anonymously, we were unable to examine if they had developed any symptoms since.

Our study has limitations to be noted. Our patients were ascertained from a defined region in Finland, and the frequency data cannot be directly generalized to the national level because of significant regional genetic differences in the Finnish population. The controls were ascertained from several different regions within Finland, but the frequencies of *FGF14* expansion between control groups were identical suggesting that our frequency estimate should be a valid approximation. Furthermore, four of the five patients with SCA27B were deceased and therefore, clinical features have been gathered from patient charts and additional examinations related to the SCA27B could not be carried out.

In conclusion, the detection of *FGF14* $(GAA•TTC)_{exp}$ requires expansion-specific methodology which should be kept in mind when considering genetic testing. Long-read sequencing is superior for the analysis of *FGF14* $(GAA•TTC)_{exp}$ as well as for other disease-causing expansions, but very large expansions might be difficult to detect, and long-read sequencing is not yet available in common genetic testing. We showed that SCA27B is common in Northern Finland, but further studies are required to investigate nationwide frequency and population prevalence in Finland.

CRediT authorship contribution statement

Laura Kytövuori: Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **David Pellerin:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Mikko Kärppä:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Jussi O.T. Sipilä:** Writing – review & editing, Conceptualization. **Marie-Josée Dicaire:** Writing – review & editing, Validation, Methodology, Investigation. **Pablo Iruzubieta:** Writing – review & editing, Validation, Methodology, Investigation. **Bernard Brais:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **Kari Majamaa:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Data availability

All data are available in this article.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mikko Kärppä reports a relationship with Abbvie that includes: board membership. Mikko Kärppä reports a relationship with Lundbeck that includes: board membership. Mikko Kärppä reports a relationship with NordicInfu Care that includes: board membership. Mikko Kärppä reports a relationship with Teva that includes: board membership. Mikko Kärppä reports a relationship with Pfizer that includes: board membership. Jussi OT Sipilä reports a relationship with Lundbeck that includes: travel reimbursement. Jussi OT Sipilä reports a relationship with Sandoz that includes: board membership. Jussi OT Sipilä reports a relationship with Boehringer-Ingelheim that includes: board membership. Jussi OT Sipilä reports a relationship with Orion that includes: equity or stocks. Jussi OT Sipilä reports a relationship with Terveystalo that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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