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GAA-*FGF14*-Related Ataxia

Synonyms: Spinocerebellar Ataxia 27B (SCA27B), *FGF14* $(GAA)_n$-Mediated Ataxia, GAA-*FGF14* Ataxia, GAA-*FGF14* Disease, GAA-*FGF14*-Related Disease, SCA27B/ATX-*FGF14*

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Summary

Clinical characteristics

GAA-*FGF14*-related ataxia is a mid to late adult-onset slowly progressive cerebellar syndrome with predominant gait involvement. Median age at onset is 60 years (range: 21-87 years). Nearly 50% of individuals may first experience episodic manifestations including gait and limb ataxia, visual disturbances (diplopia, oscillopsia, and blurring), vertigo and/or dizziness, or dysarthria on average two to four years before the onset of progressive ataxia. Episodic symptoms may persist after the onset of progressive ataxia and may be triggered by alcohol intake and physical activity. Although some individuals eventually require assistance with mobility, use of a wheelchair is less necessary than in other common hereditary spinocerebellar ataxias (e.g., SCA1, SCA2, and SCA3). Dysarthria does not develop in all individuals and often remains mild to moderate. Cerebellar oculomotor signs, including downbeat nystagmus, horizontal gaze-evoked nystagmus, and impaired visual fixation suppression of the vestibuloocular reflex, are common. Unilateral or bilateral vestibular hypofunction and tremor of the upper limbs may occur. Age of onset and clinical presentation can vary within the same family.

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Diagnosis/testing

The diagnosis of GAA-*FGF14*-related ataxia is established in a symptomatic individual with a compatible phenotype by the identification of a heterozygous $(GAA)_{>300}$ repeat expansion in intron 1 of *FGF14* by molecular genetic testing. Due to reduced penetrance of *FGF14* $(GAA)_{250\text{-}300}$ repeat expansions, the diagnosis of GAA-*FGF14*-related ataxia can also be established in symptomatic individuals with a $(GAA)_{250\text{-}300}$ repeat expansion if their phenotype is compatible, other inherited causes of ataxia have been excluded, and, if possible, familial segregation with the disease is confirmed. Individuals whose phenotype differs significantly from GAA-*FGF14*-related ataxia should be screened for other causes of inherited ataxias.

Management

Treatment of manifestations: There is no cure for GAA-*FGF14*-related ataxia. The goals of treatment are to improve quality of life, maximize function, and reduce complications. This ideally involves multidisciplinary care by specialists in relevant fields, such as neurologists, ophthalmologists, orthoptists, physical therapists, occupational therapists, speech-language therapists, and psychologists. Preliminary studies have shown promising symptomatic benefits of 4-aminopyridine for ataxic symptoms and downbeat nystagmus.

Surveillance: To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, regularly scheduled follow up by the treating specialists is recommended.

Agents/circumstances to avoid: Inform affected individuals that alcohol intake and strenuous physical activity may precipitate episodes of ataxia and may exacerbate incoordination. Avoid medications with known toxicity to the cerebellum and the vestibular system.

Genetic counseling

GAA-*FGF14*-related ataxia is inherited in an autosomal dominant manner. Most individuals diagnosed with GAA-*FGF14*-related ataxia inherit an abnormal GAA repeat expansion from a parent who has a high normal-size or likely pathogenic or pathogenic GAA repeat expansion (a parent with an abnormal GAA repeat expansion may or may not have manifestations of GAA-*FGF14*-related ataxia). Each child of an individual with GAA-*FGF14*-related ataxia has a 50% chance of inheriting the GAA-*FGF14*-related allele. The likelihood that offspring who inherit the GAA-*FGF14*-related allele will have a GAA repeat size in the pathogenic, reduced penetrance, or non-pathogenic range is influenced by intergenerational instability; the size of the GAA repeat is more likely to expand upon maternal transmission and to contract upon paternal transmission. Once a GAA repeat expansion has been identified in an affected family member, predictive testing for at-risk relatives and prenatal and preimplantation genetic testing for GAA-*FGF14*-related ataxia are possible. However, accurate prediction of future possible clinical manifestations in a fetus found to have an *FGF14* GAA repeat expansion is not possible, and the current lack of knowledge regarding somatic instability of the repeat prenatally makes the interpretation of prenatal genetic test results challenging.

Diagnosis

Suggestive Findings

GAA-*FGF14*-related ataxia **should be suspected** in probands with the following clinical findings, imaging findings, and family history.

Clinical findings. Mid to late adult-onset (median age: 60 years; range: 21 to 87 years) of slowly progressive cerebellar ataxia.

Commonly associated neurologic findings include the following:

- Episodic ataxia, commonly triggered by exercise / physically demanding tasks or alcohol intake; may manifest with diplopia, vertigo, dysarthria, and ataxia
- Cerebellar oculomotor signs, such as saccadic pursuit, dysmetric saccades, rebound nystagmus, gaze-evoked nystagmus, impaired visual fixation suppression of the vestibuloocular reflex, and downbeat nystagmus. Note that early in the disease course, downbeat nystagmus may occur with other cerebellar oculomotor signs in the absence of other neurologic findings.
- Visual symptoms, such as diplopia, oscillopsia, and visual blurring
- Vertigo and/or dizziness
- Vestibular hypofunction that can present with dizziness and loss of balance
- Decreased vibration sense in distal lower extremities

Less commonly associated neurologic findings include the following:

- Mild spasticity
- Postural tremor
- Autonomic dysfunction, mostly urinary urgency
- Mild sensory or sensorimotor axonal polyneuropathy

Imaging findings. Brain MRI shows cerebellar atrophy in a substantial number of individuals, which is most pronounced in the vermis and is mostly mild to moderate [Pellerin et al 2023a, Wilke et al 2023].

Family history may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations) or the proband may represent a simplex case (i.e., the only family member known to be affected). Because reduced penetrance and intergenerational instability are observed in GAA-*FGF14*-related ataxia, absence of a known family history or seemingly autosomal recessive inheritance (e.g., affected males and females in a single generation) does not preclude the diagnosis [Pellerin et al 2023a, Wilke et al 2023].

Establishing the Diagnosis

The diagnosis of GAA-*FGF14*-related ataxia **is established** in a symptomatic individual with a compatible phenotype by the identification of a heterozygous $(GAA)_{>300}$ repeat expansion in intron 1 of *FGF14* by molecular genetic testing (see Table 1 and Table 9).

Due to reduced penetrance of *FGF14* $(GAA)_{250\text{-}300}$ repeat expansions, the diagnosis of GAA-*FGF14*-related ataxia can also be established in symptomatic individuals with a $(GAA)_{250\text{-}300}$ repeat expansion if their phenotype is compatible, other inherited causes of ataxia have been excluded, and, if possible, familial segregation with the disease has been confirmed.

Individuals whose phenotype differs significantly from GAA-*FGF14*-related ataxia should be screened for other causes of inherited ataxias.

Repeat sizes [Pellerin et al 2023a, Rafehi et al 2023, Méreaux et al 2024]

- **Normal.** Six to 249 GAA repeats
- **Likely pathogenic (reduced penetrance).** 250 to 300 GAA repeats
- **Pathogenic.** >300 GAA repeats

Note: (1) To date, pathogenic GAA repeat expansions in *FGF14* **cannot be reliably detected** by standard sequence-based multigene panels, exome sequencing, or short-read genome sequencing. (2) Non-GAA-pure repeat expansions in *FGF14* are likely *not* pathogenic for GAA-*FGF14*-related ataxia [Pellerin et al 2023b]. Therefore, the molecular diagnosis of GAA-*FGF14*-related ataxia relies on the accurate detection and establishment of both the size and purity of the GAA repeat expansion [Bonnet et al 2023, Hengel et al 2023, Pellerin et al 2023b] (see Tables 7 and 9).

Molecular genetic testing relies on targeted analysis to characterize the size and purity of *FGF14* GAA repeats [Bonnet et al 2023] (see Table 8).

Note (1) Short-read genome sequencing (GS)-based tools for the detection of triplet repeat expansions have been developed [Dolzhenko et al 2017, Dolzhenko et al 2019, Ibañez et al 2022]. However, short-read GS cannot accurately differentiate pathogenic from non-pathogenic *FGF14* alleles beyond approximately 50 triplets. As such, short-read GS must always be followed by suitable techniques such as long-range PCR and repeat-primed PCR to confirm a diagnosis of GAA-*FGF14*-related ataxia. (2) Long-read sequencing may be able to detect GAA repeat expansions [Pellerin et al 2023a, Rafehi et al 2023] (see Table 7).

Table 1. Molecular Genetic Testing Used in GAA-*FGF14*-Related Ataxia

Gene [1]	Method [2, 3]	Proportion of Probands with a Pathogenic Variant Detectable by Method
FGF14	Targeted analysis of GAA expansions [4]	100%

[1] See Table A. Genes and Databases for chromosome locus and protein name.
[2] See Table 8 for specific methods to characterize the number of GAA repeats in *FGF14*.
[3] To date, standard sequence-based multigene panels, exome sequencing, and short-read genome sequencing cannot reliably detect pathogenic repeat expansions in this gene.
[4] Bonnet et al [2023]

Clinical Characteristics

Clinical Description

To date, more than 400 individuals with GAA-*FGF14*-related ataxia have been identified [Ashton et al 2023, Bonnet et al 2023, Brais et al 2023, Hengel et al 2023, Iruzubieta et al 2023, Novis et al 2023, Pellerin et al 2023a, Rafehi et al 2023, Wilke et al 2023, Wirth et al 2023, Zeng et al 2023, Ando et al 2024, Borsche et al 2024, Méreaux et al 2024, Pellerin et al 2024b, Pellerin et al 2024c]. The following description of the phenotypic features associated with this condition is based on these reports (see Table 2).

Table 2. GAA-*FGF14*-Related Ataxia: Frequency of Select Features

Feature		% of Persons w/Feature	Comment
Ataxia	**Gait**	95%-100%	
	Upper limb	44%-71%	
Episodic symptoms		13%-80%	May be triggered by exercise / physically demanding tasks, alcohol intake, or caffeine
Cerebellar dysarthria		12%-74%	
Cerebellar oculomotor signs		80%-96%	Includes saccadic pursuit, dysmetric saccades, rebound nystagmus, gaze-evoked nystagmus, downbeat nystagmus, impaired visual fixation suppression of vestibuloocular reflex
Nystagmus	**Horizontal gaze-evoked**	33%-67%	
	Downbeat	10%-67%	May be episodic; at disease onset may occur w/other cerebellar oculomotor signs in absence of other neurologic findings
Diplopia, oscillopsia, visual blurring		40%-68%	
Decreased vibration sense in distal lower extremities		29%-57%	
Dysphagia		14%-35%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Vertigo or dizziness	21%-67%	
Postural tremor of upper limbs	10%-27%	
Vestibulopathy	10%-75%	
Spasticity	3%-21%	Generally mild

Based on Ashton et al [2023], Bonnet et al [2023], Iruzubieta et al [2023], Pellerin et al [2023a], Rafehi et al [2023], Wilke et al [2023], Wirth et al [2023], Méreaux et al [2024], Pellerin et al [2024c]

GAA-*FGF14*-related ataxia is a mid to late adult-onset slowly progressive cerebellar syndrome with predominant gait involvement. Age of onset and clinical presentation can vary within the same family.

The median age at onset is 60 years (range: 21 to 87 years) [Iruzubieta et al 2023, Pellerin et al 2023a, Rafehi et al 2023, Wilke et al 2023, Wirth et al 2023, Zeng et al 2023, Méreaux et al 2024]. While the most common manifestation at disease onset is an unsteady gait (80%), nearly 50% of individuals present initially with episodic manifestations, including ataxia, visual disturbances (diplopia, oscillopsia, visual blurring), vertigo, or dysarthria, on average two to four years before the onset of progressive ataxia [Ashton et al 2023, Bonnet et al 2023, Pellerin et al 2023a, Pellerin et al 2024c]. The frequency and duration of these episodes are highly variable: they may last from minutes to days and occur daily to monthly [Ashton et al 2023]. Alcohol intake and physical activity are common triggers [Bonnet et al 2023, Pellerin et al 2024c]. Caffeine has also been reported to trigger episodes [Ashton et al 2023].

Although some individuals eventually require assistance with mobility, the use of a wheelchair is uncommon even after protracted disease duration.

Dysarthria, which does not develop in all individuals (40%-60%), often remains mild to moderate [Iruzubieta et al 2023, Pellerin et al 2023a, Wilke et al 2023, Méreaux et al 2024, Pellerin et al 2024c]. Speech remains easy to understand in most individuals, although occasional words may be unintelligible.

Dysphagia develops in less than half of individuals. Although it may increase the risk of aspiration, dysphagia is very rarely severe enough to require enteral nutrition or cause cachexia.

Visual disturbances, such as diplopia, oscillopsia, or visual blurring, are common.

Cerebellar oculomotor signs, which may include horizontal gaze-evoked nystagmus, downbeat nystagmus, dysmetric saccades, saccadic pursuit, rebound nystagmus, and impaired visual fixation suppression of the vestibuloocular reflex, occur in almost all individuals. Horizontal gaze-evoked nystagmus and downbeat nystagmus are common. Downbeat nystagmus may present episodically or occur at disease onset with other cerebellar oculomotor signs in the absence of other neurologic findings [Pellerin et al 2024b].

Vertigo and/or dizziness may occur during episodes of ataxia or interictally. It may lead to gait unsteadiness.

Unilateral or bilateral vestibular hypofunction is common [Pellerin et al 2023a, Rafehi et al 2023, Wilke et al 2023, Pellerin et al 2024b, Pellerin et al 2024c]. Some individuals experience gait unsteadiness and dizziness due to vestibular hypofunction.

Postural or rest tremor of the upper limbs is observed in some patients [Pellerin et al 2023a, Wilke et al 2023, Wirth et al 2023, Méreaux et al 2024].

Afferent sensory deficit manifests as reduced vibration sense and hyporeflexia; however, sensory neuropathy is not commonly demonstrated on nerve conduction studies [Iruzubieta et al 2023, Pellerin et al 2023a, Rafehi et al 2023, Wilke et al 2023, Pellerin et al 2024c]. When peripheral neuropathy is present, nerve conduction studies are consistent with mild axonal sensory or sensorimotor polyneuropathy [Pellerin et al 2023a, Wirth et al 2023, Pellerin et al 2024c]. Whether the polyneuropathy is pathophysiologically related to GAA-*FGF14*-related ataxia or simply reflective of an age-related disease process remains to be established. Muscle stretch reflexes can be normal, decreased, or brisk.

Spasticity of the lower limbs is most often mild and is not a common manifestation.

Parkinsonism is uncommon (4%-12%) [Rafehi et al 2023, Wilke et al 2023, Pellerin et al 2024c].

Autonomic dysfunction is rare at disease onset but may develop later in the disease course. Urinary urgency and erectile dysfunction occur in 28%-57% of individuals and 13% of males, respectively. In comparison, population-based surveys in the United States have shown that the prevalence of urinary urge incontinence ranges from 1.7% to 36.4% of the general population [Milsom et al 2014], and cross-sectional studies have revealed a prevalence of erectile dysfunction of 18.4% of adult males ages 20 years or older [Selvin et al 2007].

Frank autonomic dysfunction manifested by orthostatic hypotension is rare in GAA-*FGF14*-related ataxia [Wilke et al 2023, Wirth et al 2023, Méreaux et al 2024, Pellerin et al 2024c].

Hearing loss, namely presbycusis, has been described in some individuals [Rafehi et al 2023].

Cognitive impairment is relatively infrequent, even in advanced stages of GAA-*FGF14*-related ataxia [Wilke et al 2023].

Of note, age-related mechanisms as well as other additional diseases (age related or not age related; acquired or inherited) can contribute to or aggravate the clinical features of GAA-*FGF14*-related ataxia [Wilke et al 2023, Pellerin et al 2024b].

The possibility of **concurrent medical illnesses,** which are common in the elderly, must be considered in late-onset diseases such as GAA-*FGF14*-related ataxia. It has been shown that these are frequent and add to the neurologic spectrum and disease burden of underlying hereditary late-onset ataxia [Wilke et al 2023, Pellerin et al 2024b].

Life span does not appear to be shortened in individuals with GAA-*FGF14*-related ataxia [Wirth et al 2023].

Genotype-Phenotype Correlations

Age of onset inversely correlates with the size of the GAA repeat expansion in some cohorts [Pellerin et al 2023a, Rafehi et al 2023, Pellerin et al 2024b, Pellerin et al 2024c] but not all [Bonnet et al 2023, Iruzubieta et al 2023, Wilke et al 2023, Méreaux et al 2024].

Of note, one study found no association between disease progression or severity and the length of the GAA repeat expansion [Wilke et al 2023]. Another study showed that the sum of the two allele sizes does not correlate better with age of onset [Pellerin et al 2023a].

Biallelic *FGF14* GAA repeat expansions have been reported in a number of individuals [Ashton et al 2023, Bonnet et al 2023, Brais et al 2023, Novis et al 2023, Pellerin et al 2023a, Zeng et al 2023, Pellerin et al 2024b]. Four of 12 individuals had disease onset in their twenties. In some – but not all – individuals with biallelic *FGF14* GAA repeat expansions, disease manifestations and progression appear to be more severe compared to individuals heterozygous for an *FGF14* GAA repeat expansion [Ashton et al 2023, Pellerin et al 2023a, Wilke et al 2023].

Penetrance

Reduced penetrance has been reported in persons heterozygous for 250-300 *FGF14* GAA repeats [Pellerin et al 2023a, Rafehi et al 2023]. It is likely that knowledge of GAA repeat length-related penetrance will evolve significantly as more data become available.

Intergenerational Instability

The *FGF14* GAA repeat is highly unstable and almost always changes in size upon parent-to-offspring transmission when the size of parent's GAA repeat expansion is greater than 75 repeats [Pellerin et al 2024b].

The size of the GAA repeat is more likely to expand with maternal transmission and to contract with paternal transmission [Pellerin et al 2023a, Pellerin et al 2024b].

The instability of the GAA repeat locus upon maternal transmission, which is at high risk of further expansion, partly accounts for the high incidence of simplex cases of GAA-*FGF14*-related ataxia (i.e., a single occurrence of a disorder in a family), whereby an unaffected mother transmits an expanded pathogenic allele to her offspring.

In contrast, contraction of the size of the GAA repeat upon male transmission may lead to transmission of reduced-penetrance alleles to the offspring, resulting in "generation skipping" of the disease [Pellerin et al 2023a]. This differential transmission dynamic also likely accounts for the reduced male transmission of the disease observed in two studies [Pellerin et al 2023a, Méreaux et al 2024].

The degree of intergenerational instability is proportional to the size of the GAA repeat of the transmitted allele and dependent on the purity of the repeat tract. GAA repeat expansions may be pure $(GAA)_n$ in sequence or may be interrupted with regions of non-GAA sequences. During intergenerational transmission, pure GAA repeats have been shown to be more unstable than non-GAA-pure repeats. Only pure GAA repeats are believed to be pathogenic, while non-GAA-pure repeats are believed to be not pathogenic for ataxia [Hengel et al 2023, Pellerin et al 2023b].

Nomenclature

Prior to establishing the molecular diagnosis, individuals with phenotypes consistent with GAA-*FGF14*-related ataxia may have been diagnosed with idiopathic late-onset cerebellar ataxia (ILOCA), sporadic adult-onset ataxia (SAOA), or autosomal dominant cerebellar ataxia type III (pure cerebellar ataxia).

The current alphanumeric designation for GAA-*FGF14*-related ataxia is SCA27B (OMIM 620174). To clarify the nomenclature and to distinguish GAA-*FGF14*-related ataxia from the allelic spinocerebellar ataxia (SCA27) associated with point, frameshift, or structural variants in *FGF14*, OMIM changed SCA27 to SCA27A and created a new designation, SCA27B, for GAA-*FGF14*-related ataxia.

Prevalence

The prevalence of GAA-*FGF14*-related ataxia is difficult to estimate given that only about 400 individuals have been reported to date. The prevalence of late-onset cerebellar ataxia of unknown cause is one to nine in 100,000 individuals (see Orphanet). GAA-*FGF14*-related ataxia has been identified in cohorts with adult-onset ataxia of previously unknown cause at rates ranging from 9% to 61%.

Excluding French Canadian cohorts, we have estimated the prevalence of GAA-*FGF14*-related ataxia to be in the range of 0.1 to three in 100,000 individuals of European ancestry [Pellerin, Danzi, Renaud, Houlden, Synofzik, Zuchner, & Brais, personal observation]. This prevalence, like that of spinocerebellar ataxia 1, 2, 3, and 6, has recently been validated by a systematic comparative study of consecutive patient cohorts in a single-center European study [Hengel et al 2023]. Although a large degree of uncertainty remains regarding the prevalence of

GAA-*FGF14*-related ataxia, to date it appears to be among the most common causes of inherited adult-onset ataxia as well as of autosomal dominant ataxia (of any age) [Hengel et al 2023]. However, GAA-*FGF14*-related ataxia may not be as common in East Asian populations, as it was not identified in 312 patients with suspected spinocerebellar degeneration of unknown cause from Hokkaido Island in northern Japan in one study [Mizushima et al 2024], and was identified in only 11 of 940 individuals (1.2%) from Japan with chronic progressive cerebellar ataxia in another study [Ando et al 2024].

It is important to note that although the frequency of *FGF14* alleles longer than 250 triplets is estimated to be about 1%-2% in the population [Pellerin et al 2023a, Rafehi et al 2023, Méreaux et al 2024, Pellerin et al 2024a], this does not reflect a prevalence of GAA-*FGF14*-related ataxia nearing 1-2 in 100 individuals. In fact, 88.9% of alleles longer than 250 triplets in 2,191 controls undergoing long-read sequencing were identified to be non-GAA-pure and seem to have no association with GAA-*FGF14*-related ataxia [Pellerin et al 2024a].

Geographic variation in prevalence. Rates of GAA-*FGF14*-related ataxia are reported to be as high as 60% in individuals of French Canadian descent with adult-onset ataxia of previously unknown cause [Pellerin et al 2023a], making GAA-*FGF14*-related ataxia one of the most common genetic causes of late-onset ataxia within the French Canadian population [Brais, personal observation]. The enrichment in this population is likely due to a founder effect, as such effects have been previously described in this population [Scriver 2001], and some French Canadian individuals with GAA-*FGF14*-related ataxia appear to share a common haplotype at the *FGF14* locus [Pellerin et al 2023a].

Genetically Related (Allelic) Disorders

Spinocerebellar ataxia type 27A (OMIM 193003). Heterozygous loss-of-function point, frameshift, or structural variants in *FGF14* are associated with early-onset, slowly progressive cerebellar ataxia with nystagmus, dysarthria, postural tremor, orofacial dyskinesia, psychiatric disturbances, and intellectual disability / cognitive impairment [van Swieten et al 2003, Brusse et al 2006, Miura et al 2019, Paucar et al 2020]. Tremor is the initial presenting feature in a substantial proportion of individuals with SCA27A. Affected individuals may also exhibit episodic ataxia (often triggered by febrile episodes), head tremor, parkinsonism, and developmental delay [Coebergh et al 2014, Choquet et al 2015, Amado et al 2017, Groth & Berman 2018, Schesny et al 2019, Piarroux et al 2020, Loeffler et al 2022]. SCA27A typically presents at an earlier age (mean age at onset of tremor: 12.1 years; mean age at onset of ataxia: 23.7 years) than GAA-*FGF14*-related ataxia and is more frequently associated with postural tremor and neuropsychiatric manifestations. Cerebellar atrophy is less common in SCA27A than in GAA-*FGF14*-related ataxia [Groth & Berman 2018].

Contiguous gene deletions in the 13q33 region involving *FGF14* and *ITGBL1* have also been associated with SCA27A (OMIM 193003) [Ceroni et al 2023].

Differential Diagnosis

GAA-*FGF14*-related ataxia has been reported in persons of multiple ancestral backgrounds and is among the most common causes of hereditary – in particular autosomal dominant – adult-onset ataxia [Hengel et al 2023, Novis et al 2023, Pellerin et al 2023a, Rafehi et al 2023, Zeng et al 2023]. In a single-center study, GAA-*FGF14*-related ataxia accounted for 16% of German individuals with autosomal dominant cerebellar ataxia [Hengel et al 2023].

The differential diagnosis of adult-onset ataxia is broad and encompasses acquired, hereditary, and neurodegenerative ataxias.

Hereditary adult-onset ataxias. The clinical features of GAA-*FGF14*-related ataxia, including oculomotor signs, are similar to those of other hereditary pure cerebellar ataxias, such as spinocerebellar ataxia type 6 (SCA6) and

SCA8. Disease progression in GAA-*FGF14*-related ataxia is generally slower than in other common genetic late-onset ataxias, such as SCA6 and *RFC1* CANVAS (*c*erebellar *a*taxia, *n*europathy, and *v*estibular *a*reflexia *s*yndrome) / spectrum disorder [Wilke et al 2023]. GAA-*FGF14*-related ataxia may be otherwise difficult to distinguish clinically from other hereditary adult-onset ataxias (see Hereditary Ataxia Overview) and other forms of episodic ataxia [Jen & Wan 2018, Hassan 2023].

Episodic ataxia type 2 (EA2) – caused by pathogenic missense, nonsense, splice site, or frameshift variants or exon/multiexon deletion in *CACNA1A* – has significant phenotypic overlap with GAA-*FGF14*-related ataxia [Baloh 2012]. Like individuals with GAA-*FGF14*-related ataxia, individuals with EA2 initially experience episodic ataxia with paroxysmal attacks of ataxia, dysarthria, diplopia, and vertigo. Episodes of ataxia, which may be triggered by exercise, emotional stress, and alcohol, may last for hours, and interictal gaze-evoked nystagmus and downbeat nystagmus are frequently observed [Jen et al 2004, Baloh 2012]. Individuals with EA2 may eventually develop a slowly progressive chronic cerebellar syndrome with cerebellar atrophy on MRI [Baloh 2012, Nachbauer et al 2014, Hassan 2023]. Unlike GAA-*FGF14*-related ataxia, onset of EA2 is typically in childhood or adolescence, although rare individuals manifesting in adulthood have been described [Imbrici et al 2005, Baloh 2012, Nachbauer et al 2014].

Genes of particular interest are summarized in Table 3.

Table 3. Selected Genes of Interest in the Differential Diagnosis of GAA-*FGF14*-Related Ataxia

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/GAA-*FGF14*-Related Ataxia	Distinguishing from GAA-*FGF14*-Related Ataxia
ATXN3	SCA3 (Machado-Joseph disease)	AD	• Adult-onset progressive cerebellar ataxia • Cerebellar dysarthria • Nystagmus • Vestibular hypofunction possible • Autonomic dysfunction	• Lid retraction • Dystonia / extrapyramidal syndrome • Peripheral amyotrophy • Muscle cramp & fasciculation • Generalized areflexia • Action-induced facial & lingual fasciculations • Parkinsonism • Progressive external ophthalmoplegia • Sleep disturbances • MRI: pontine atrophy
ATXN8OS/ ATXN8	SCA8	AD	• Adult-onset slowly progressive cerebellar ataxia (typical onset in 3rd-5th decade) • Cerebellar dysarthria • Nystagmus • Tremor	May present w/poor cough reflex, ophthalmoplegia, sensory neuropathy, cognitive impairment

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/GAA-*FGF14*-Related Ataxia	Distinguishing from GAA-*FGF14*-Related Ataxia
CACNA1A	SCA6	AD	• Adult-onset slowly progressive cerebellar ataxia • Cerebellar dysarthria • Nystagmus (horizontal gaze-evoked, downbeat) • Visual disturbances such as diplopia • Vestibular hypofunction possible • MRI: isolated cerebellar atrophy	• Less common episodic symptoms at disease onset (<15%) • In some, additional clinical signs incl dystonia, blepharospasm, extensor plantar responses
	Episodic ataxia type 2 (OMIM 108500)	AD	• Episodic ataxia w/paroxysmal attacks of ataxia, dysarthria, diplopia, vertigo • May be triggered by alcohol intake & physical activity • May eventually develop interictal progressive ataxia & downbeat nystagmus • MRI: cerebellar atrophy	• Typical onset in childhood / early adolescence (range: 2-32 yrs) • Attacks of ataxia may be assoc w/ dystonia, hemiplegia, & tonic upward gaze
FXN	Friedreich ataxia	AR	• Progressive cerebellar ataxia • Cerebellar dysarthria • Vestibular hypofunction possible • Autonomic dysfunction	• Typical onset <25 yrs (but late-onset presentation possible). • Sensory neuronopathy • Muscle weakness • Hypertrophic cardiomyopathy • Diabetes • Optic atrophy • Skeletal deformities (pes cavus, scoliosis)
KCNA1	Episodic ataxia type 1	AD	• Episodic ataxia w/paroxysmal attacks of ataxia, dysarthria, diplopia, vertigo • May be triggered by alcohol intake & physical activity	• Typical onset in childhood / early adolescence (range: 2-15 yrs) • Attacks of brief duration (seconds to minutes) • Attacks of ataxia may be assoc w/ choreoathetosis, carpal spasm, hyperthermia, & stiffening of body • Interictal myokymia • Neuromyotonia • Cognitive dysfunction • In some, seizures & skeletal deformities (scoliosis, high-arched palate)
RFC1	*RFC1* CANVAS / spectrum disorder	AR	• Adult-onset ataxia • Cerebellar dysarthria • Nystagmus (horizontal gaze-evoked, downbeat) • Vestibular hypofunction • Autonomic dysfunction	• Sensory neuronopathy • Frequent chronic cough • No episodic ataxia • Rare postural tremor

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/GAA-*FGF14*-Related Ataxia	Distinguishing from GAA-*FGF14*-Related Ataxia
SPTBN2	SCA5 (OMIM 600224)	AD	• Adult-onset slowly progressive cerebellar ataxia (mean onset in 3rd decade) • Cerebellar dysarthria • Nystagmus (gaze-evoked & downbeat) • In some, impaired vibration sense • MRI: isolated cerebellar atrophy	• In some, facial myokymia, horizontal gaze palsy • No episodic ataxia

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; SCA = spinocerebellar ataxia

Acquired causes of adult-onset ataxia to consider in the differential diagnosis of GAA-*FGF14*-related ataxia include vascular, toxic-metabolic, inflammatory, infectious, paraneoplastic, and neoplastic conditions [Coarelli et al 2023].

Multiple system atrophy, cerebellar type (MSA-C), a fatal sporadic progressive adult-onset (>30 years) neurodegenerative disorder, is an important differential diagnosis to consider in persons presenting with late-onset cerebellar ataxia. The following clinical characteristics can distinguish MSA-C from GAA-*FGF14*-related ataxia:

- MSA is a rapidly progressive disorder. Approximately 60% of affected individuals become wheelchair bound after five years, and the mean survival is six to ten years from symptom onset [Poewe et al 2022]. In comparison, disease progression in GAA-*FGF14*-related ataxia is slow, less than 15% of affected individuals become wheelchair bound despite prolonged disease course [Pellerin et al 2023a, Wilke et al 2023, Wirth et al 2023, Pellerin et al 2024b], and life expectancy does not appear to be shortened [Wirth et al 2023].
- Persons with MSA-C typically exhibit cerebellar features, extrapyramidal features, pyramidal features, rapid eye movement sleep behavior disorder, significant dysphagia, and debilitating autonomic failure [Fanciulli & Wenning 2015]. In comparison, multisystem involvement is not characteristic of GAA-*FGF14*-related ataxia, and when present, autonomic dysfunction is typically mild [Wilke et al 2023, Pellerin et al 2024c].
- In contrast to GAA-*FGF14*-related ataxia, episodic symptoms and vestibular hypofunction do not occur in MSA-C.
- Certain imaging findings favor a diagnosis of MSA-C: atrophy of the putamen, middle cerebellar peduncles, pons, and cerebellum; cruciform T_2-weighed hyperintensity in the pons ("hot cross bun" sign); increased diffusivity of the putamen and middle cerebellar peduncles [Wenning et al 2022].

Management

No clinical practice guidelines for GAA-*FGF14*-related ataxia have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with GAA-*FGF14*-related ataxia, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. GAA-*FGF14*-Related Ataxia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic assessment for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use clinical neurologic eval & standardized scale to establish baseline for ataxia, such as SARA. [1]
	Assessment for non-ataxia signs (reflexes, motor symptoms, tone, tremor, sensory symptoms, dysphagia, urinary dysfunction, cognitive impairment)	Use clinical neurologic eval & standardized scale to establish baseline for non-ataxia involvement, such as INAS. [2]
	Nerve conduction studies	Establish presence & severity of sensory or sensorimotor peripheral neuropathy.
	Vestibulopathy	Vestibular testing (video head impulse test) to assess vestibular hypofunction
	Clinical assessment of symptoms of autonomic dysfunction	• Assess for postural change in blood pressure to assess for orthostatic hypotension. • Consider autonomic testing in persons who are symptomatic.
	Brain MRI	Evaluate extent of atrophy of cerebellum & other structures.
ADL/Musculoskeletal	PT	• Assess need for balance exercises, gait training to maintain mobility, & exercises to help prevent falls & maintain function. • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs).
	OT	Assess need for adaptive devices to optimize ADL.
Cerebellar dysarthria	Speech-language pathologist eval	Assess need for: • Speech-language therapy; • Alternative means of communication.
Ophthalmologic involvement	Consultation w/ophthalmologist or orthoptist	• Assess nystagmus, saccades, & smooth pursuit & vertical & horizontal gaze limitation. • Consider referral for corrective measures incl prisms &/or surgery.
Dysphagia	Swallowing eval	• Consider video fluoroscopic swallowing study to assess risk of aspiration. • Referral to nutritionist & OT
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of GAA-*FGF14*-related ataxia to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADL = activities of daily living; INAS = Inventory of Non-Ataxia Signs; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia

1. Bürk & Sival [2018]

2. Jacobi et al [2013]

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for GAA-*FGF14*-related ataxia. The goals of treatment are to improve quality of life, maximize function, and reduce complications. This ideally involves multidisciplinary care by specialists in relevant fields, such as neurologists, ophthalmologists, orthoptists, physical therapists, occupational therapists, speech-language therapists, and psychologists (see Table 5).

Table 5. GAA-*FGF14*-Related Ataxia: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cerebellar ataxia	PT & OT	• PT to maintain mobility & function [1] • Self-directed exercise as prescribed by PT • OT to optimize ADL • Avoid alcohol intake & strenuous physical activity that may precipitate episodes of ataxia. • Consider adaptive devices to maintain/improve mobility (e.g., canes, walking sticks, walker). • Inpatient rehab w/PT & OT may improve ataxia & functional abilities in persons w/degenerative ataxias. [2] • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
	Pharmacologic treatment	4-aminopyridine may ↓ severity & frequency of episodes of ataxia & ataxic symptoms & downbeat nystagmus. [3]
Dysarthria	Speech-language therapy	Incl alternative means of communication as needed (e.g., writing pads & digital devices)
Ophthalmologic involvement	• Downbeat nystagmus may respond to 4-aminopyridine. [4] • Prisms may be used to obviate diplopia.	Neuro-ophthalmology consultation
Weight	Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ ambulation & mobility. • Feeding recommendations per nutritional therapy / OT

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Spasticity	Non-pharmacologic treatment	Stretching exercises
	Pharmacologic treatment	Consider drugs such as baclofen for treatment of severe spasticity (rarely required & should be used w/caution since it may ↑ risk of falls).
Hearing loss	Audiologist, ENT specialist	Consider hearing aids.
Autonomic dysfunction	Neurologist, neurorehabilitation specialist	Consider treatment for urinary urgency/frequency, erectile dysfunction.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	

ADL = activities of daily living; ENT = ears, nose, and throat; OT = occupational therapy; PT = physical therapy
1. Martineau et al [2014]
2. van de Warrenburg et al [2014], Zesiewicz et al [2018]
3. Seemann et al [2023], Wilke et al [2023], Pellerin et al [2024b]
4. Claassen et al [2013], Strupp et al [2017]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. GAA-*FGF14*-Related Ataxia: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cerebellar ataxia	• Neurologic eval to assess progression & need for pharmacotherapy • Monitor ataxia progression w/standardized scale (SARA). [1]	Annually; more often for acute exacerbation
	PT eval re mobility, need for durable equipment	Per treating PT
	OT eval re ADL, need for safety modifications	Per treating OT
Dysarthria	Eval re need for speech therapy or alternative communication method	Per symptom progression
Dysphagia	Assessment of nutrition, aspiration risk, & feeding methods	
Diplopia	Eval by ophthalmologist for prisms	
Hearing loss	Eval by audiologist for hearing aids	
Family/Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

OT = occupational therapy/therapist; PT = physical therapy/therapist; SARA = Scale for the Assessment and Rating of Ataxia
1. Bürk & Sival [2018]

Agents/Circumstances to Avoid

Inform affected individuals that alcohol intake and strenuous physical activity may precipitate episodes of ataxia and may exacerbate incoordination.

Avoid medications with known toxicity to the cerebellum and the vestibular system.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Although GAA-*FGF14*-related ataxia rarely manifests during child-bearing age, measures to support mobility should be taken in affected pregnant women.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GAA-*FGF14*-related ataxia is inherited in an autosomal dominant manner.

Note: Although GAA-*FGF14*-related ataxia is inherited in an autosomal dominant manner, the combined effects of intergenerational instability and reduced penetrance can result in the appearance of "generation skipping" of the disorder in family histories and seemingly autosomal recessive inheritance (e.g., multiple affected individuals in a single generation) [Pellerin et al 2023a].

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with GAA-*FGF14*-related ataxia inherited an abnormal GAA repeat expansion from a parent who has a likely pathogenic (reduced penetrance) or pathogenic GAA repeat expansion. A parent with an abnormal GAA repeat expansion in *FGF14* may or may not have manifestations of GAA-*FGF14*-related ataxia.
- Fifteen to 50% of individuals diagnosed with GAA-*FGF14*-related ataxia represent simplex cases (i.e., the only family member known to be affected) [Pellerin et al 2023a, Wilke et al 2023]. Note: Simplex cases may be observed with transmission of a GAA repeat (expanded to the pathogenic or likely pathogenic range in the proband) by an unaffected mother who has a GAA repeat that is either at the high end of normal size or in the reduced penetrance range.
- The *FGF14* GAA repeat is highly unstable and almost always changes in size upon parent-to-offspring transmission when the size of the parent's GAA repeat expansion is greater than 75 repeats [Pellerin et al 2024a] (see Clinical Characteristics, Intergenerational Instability). Because the size of the GAA repeat is more likely to expand with maternal transmission and to contract with paternal transmission, transmission of GAA-*FGF14*-related ataxia from an affected mother to offspring is more commonly seen than transmission from an affected father to offspring [Méreaux et al 2024, Pellerin et al 2024a].

- The family history of some individuals diagnosed with GAA-*FGF14*-related ataxia may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the heterozygous parent.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has an *FGF14* GAA expansion in the likely pathogenic or pathogenic range, the risk to the sibs of inheriting the GAA-*FGF14*-related parental allele is 50%. The likelihood that a sib who inherits the GAA-*FGF14*-related parental allele will have a GAA repeat size in the pathogenic, reduced penetrance, or non-pathogenic range is influenced by intergenerational instability (i.e., changes in repeat size upon parent-to-offspring transmission).
    - The size of the GAA repeat is more likely to expand with maternal transmission and to contract with paternal transmission.
    - The degree of intergenerational instability is proportional to the size of the GAA repeat of the transmitted allele and dependent on the purity of the repeat tract [Pellerin et al 2024a] (see Clinical Characteristics, Intergenerational Instability).
- Sibs who inherit an expansion of 250-300 GAA repeats may or may not develop GAA-*FGF14*-related ataxia. Reduced penetrance has been reported in individuals heterozygous for 250-300 GAA repeats [Pellerin et al 2023a, Rafehi et al 2023, Méreaux et al 2024]; however, GAA repeat length-related penetrance is not fully characterized at this time.
- Sibs who inherit an *FGF14* allele containing at least 300 GAA-pure repeats are expected to develop GAA-*FGF14*-related ataxia (see Clinical Characteristics, Penetrance). There is no known correlation between the penetrance of GAA-*FGF14*-related ataxia and the sex of the individual with the GAA repeat expansion. Age of onset and clinical presentation can vary within the same family.
- If the parents have not been tested for the *FGF14* GAA repeat expansion but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for GAA-*FGF14*-related ataxia because of the possibility of reduced or age-related penetrance in a heterozygous parent or the presence of a near-pathogenic GAA repeat size in the mother.

Offspring of a proband

- Each child of an individual with GAA-*FGF14*-related ataxia has a 50% chance of inheriting the GAA-*FGF14*-related allele. The likelihood that offspring who inherit the GAA-*FGF14*-related allele will have a GAA repeat size in the pathogenic, reduced penetrance, or non-pathogenic range is influenced by intergenerational instability.
- The size of the GAA repeat is more likely to expand in transmission to offspring if the proband is female and to contract in transmission if the proband is male (see Clinical Characteristics, Intergenerational Instability).

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an *FGF14* GAA repeat expansion, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once a pathogenic or likely pathogenic GAA repeat expansion in intron 1 of *FGF14* has been identified in an affected family member.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing. Of note:

  - It is difficult to predict the age of onset, severity, clinical features, and rate of progression in an asymptomatic individual with >300 GAA repeats. While age of onset was found to inversely correlate with the size of the GAA repeat expansion in some cohorts, some studies found no such association (see Clinical Characteristics, Genotype-Phenotype Correlations).
  - An asymptomatic individual with an expansion of 250-300 GAA repeats may or may not develop GAA-*FGF14*-related ataxia.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of GAA-*FGF14*-related ataxia, it is appropriate to consider testing of symptomatic individuals regardless of age, although GAA-*FGF14*-related ataxia has never been described in children and alternative genetic causes should also be explored and excluded in these individuals.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once a GAA repeat expansion in intron 1 of *FGF14* has been identified in an affected family member, prenatal and preimplantation genetic testing for GAA-*FGF14*-related ataxia are possible. However, accurate prediction of future possible clinical manifestations in a fetus found to have an *FGF14* GAA repeat expansion pathogenic variant is not possible. In addition, the current lack of knowledge regarding somatic instability of the repeat prenatally makes the interpretation of prenatal genetic test results challenging.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **SCA27B Ataxia Foundation**
  Phone: 615-900-0234
  Email: sca27b@gmail.com
  www.sca27b.org

- **Ataxia Canada**
  Canada
  Phone: 514-321-8684
  Email: ataxia@lacaf.org
  lacaf.org

- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GAA-FGF14-Related Ataxia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGF14	13q33.1	Fibroblast growth factor 14	FGF14 database	FGF14	FGF14

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for GAA-FGF14-Related Ataxia (View All in OMIM)

601515	FIBROBLAST GROWTH FACTOR 14; FGF14
620174	SPINOCEREBELLAR ATAXIA 27B, LATE-ONSET; SCA27B

Molecular Pathogenesis

FGF14 encodes fibroblast growth factor 14 (FGF14), which is primarily expressed in the brain, most abundantly in the cerebellum. FGF14 regulates spontaneous and evoked firing of Purkinje cells by interacting with and modulating the function of voltage-gated sodium channels at the axon initial segment [Lou et al 2005, Xiao et al 2013, Yan et al 2014, Bosch et al 2015, Di Re et al 2017].

FGF14 contains a variable GAA repeat in intron 1 of its major isoform. Expansion of the size of the GAA repeat is associated with disease (see Table 9).

Mechanism of disease causation. Likely loss of function via haploinsufficiency

Note: Expansion of non-GAA-pure repeats appears to be **not pathogenic** for ataxia, as it has been shown that non-GAA-pure repeat expansions do not segregate with disease in families with ataxia [Pellerin et al 2023a, Pellerin et al 2023b, Hengel et al 2023].

***FGF14*-specific laboratory technical considerations.** See Table 7.

Table 7. *FGF14*-Specific Laboratory Technical Considerations

Technical Consideration	Comment [Reference]
Sequence of repeat	• GAA (expanded pathogenic); however, interrupted repeats are also possible. • Expansions consisting of an alternative non-GAA motif, such as GAAGGA or $(GAA)_n$(GCA), are thought to be not pathogenic for ataxia. [1]
Methods to detect expanded allele (See Table 8 .)	Options: • Long-range PCR (LR-PCR) [2] • Repeat-primed PCR (RP-PCR) [2] • Long-read sequencing [3]
Somatic instability	There are currently no published data on somatic instability of the *FGF14* GAA repeat expansion.
Intergenerational instability	• GAA repeat expansions may be pure – $(GAA)_n$ – in sequence or may be interrupted with regions of non-GAA sequences. Pure GAA repeats have been shown to be more unstable than non-GAA-pure repeats during intergenerational transmission. [4] • The GAA repeat is more likely to expand when maternally transmitted. [5] • The GAA repeat is more likely to contract when paternally transmitted, and may result in smaller repeats that may fall into the decreased penetrance size range or non-pathogenic range. [5]

1. Pellerin et al [2023a], Hengel et al [2023], Pellerin et al [2024c]
2. Bonnet et al [2023], Pellerin et al [2023a]
3. Pellerin et al [2023a], Rafehi et al [2023]
4. Pellerin et al [2023b]
5. Pellerin et al [2023a], Pellerin et al [2023b]

Methods to characterize *FGF14* GAA repeats. Due to the technical challenges of detecting and sizing *FGF14* GAA repeat expansions, multiple methods may be needed to rule out or detect an expanded allele (see Table 8). Repeats in the normal range (6-249 GAA repeats) may be detected by traditional PCR. However, detection of apparent homozygosity for a normal GAA repeat does not rule out the presence of an expanded GAA repeat; thus, testing by repeat-primed PCR is required (see Table 8).

Table 8. Methods to Characterize *FGF14* GAA Repeats

Interpretation of GAA•TTC [1] Repeat Number	Expected Results by Method		
	Conventional flanking PCR	Repeat-primed PCR [2]	Expanded repeat analysis [3]
Normal: 6-249	Detectable [4]	See footnote 2.	Expansions can be detected and repeat size can be approximated. [5]
Likely pathogenic (reduced penetrance): 250-300 [6]	Detectable [4]	Although expansions may be detected, repeat size cannot be determined. [7, 8]	
Pathogenic: >300	Detectable	Although expansions can be detected, repeat size cannot be determined. [7]	

1. GAA and TTC refer to the reverse and forward sequences, respectively.
2. The design of a repeat-primed PCR (RP-PCR) assay may include conventional PCR primers to size normal repeats and detect expanded repeats in a single assay. The RP-PCR assay itself does not determine repeat size, even for alleles in the normal range.
3. Methods to detect and approximate the size of expanded repeats include long-range PCR sized by capillary electrophoresis or agarose gel electrophoresis [Bonnet et al 2023]. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/or patient due to competition by the normal allele during amplification.
4. Detection of an apparently homozygous repeat does not rule out the presence of an expanded GAA repeat; thus, testing by RP-PCR or expanded repeat analysis is required to detect a repeat expansion.
5. Long-read sequencing may be used to detect and measure the size of repeat expansions [Pellerin et al 2023a, Rafehi et al 2023].
6. Alleles in the 250-300 repeat range are likely to be pathogenic, albeit with reduced penetrance.
7. RP-PCR for the GAA repeat expansion has been described [Bonnet et al 2023, Pellerin et al 2023a].
8. Non-GAA-pure repeats do not show the characteristic stutter/sawtooth pattern that indicates an expanded GAA repeat [Bonnet et al 2023]. The sequence motif of the non-GAA-pure expansions can be determined by Sanger sequencing or long-read sequencing.

Table 9. *FGF14* Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Repeat Range [Reference]
$(GAA)_{50}$	$(GAA)_{6\text{-}249}$	--	Normal
	$(GAA)_{250\text{-}300}$		Reduced penetrance
	$(GAA)_{>300}$		Pathogenic

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

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Drs Pellerin, Danzi, Zuchner, Synofzik, and Brais are also interested in hearing from clinicians treating families affected by adult-onset ataxia in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Drs Pellerin, Danzi, Zuchner, or Brais to inquire about review of *FGF14* variants of uncertain significance.

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