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Friedreich Ataxia

Synonym: FRDA

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Summary

Clinical characteristics

Typical Friedreich ataxia (FRDA) is characterized by progressive ataxia with onset from early childhood to early adulthood with mean age at onset from 10 to 15 years (range: age two years to the eighth decade). Ataxia, manifesting initially as poor balance when walking, is typically followed by upper-limb ataxia, dysarthria, dysphagia, peripheral motor and sensory neuropathy, spasticity, autonomic disturbance, and often abnormal eye movements and optic atrophy. Hypertrophic cardiomyopathy is present in about two thirds of individuals; occasionally it is diagnosed prior to the onset of ataxia. Diabetes mellitus and impaired glucose tolerance can also occur.

Among individuals with FRDA, about 75% have "typical Friedreich ataxia" and about 25% of individuals with biallelic *FXN* full-penetrance GAA repeat expansions have "atypical Friedreich ataxia" that includes late-onset FRDA (LOFA) (i.e., onset after age 25 years), very late-onset FRDA (VLOFA) (i.e., onset after age 40 years), and FRDA with retained reflexes (FARR).

Diagnosis/testing

The diagnosis of Friedreich ataxia is established in a proband with suggestive findings and biallelic pathogenic variants in *FXN* identified by molecular genetic testing. The two classes of *FXN* pathogenic variants are (1) GAA repeat expansions and (2) *FXN* pathogenic sequence variants, including base substitutions and small indels or large deletions. Approximately 96% of individuals with FRDA have biallelic *FXN* GAA repeat expansions in intron 1; approximately 4% are compound heterozygotes for an *FXN* GAA repeat expansion and either an intragenic *FXN* pathogenic variant or a large deletion.

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Management

Targeted therapy: Omaveloxolone, an Nrf2 activator, has been shown to slow the progression of FRDA; it is approved in the United States and Europe for individuals age 16 years and older.

Supportive care: Multidisciplinary care by specialists in relevant fields, such as neurologists, ophthalmologists, orthoptists, physical therapists, occupational therapists, cardiologists, endocrinologists, speech and language therapists, and psychologists.

Surveillance: Routinely scheduled evaluations by the treating multidisciplinary specialists.

Agents/circumstances to avoid: Use and misuse of illegal and controlled drugs, as they may affect neuronal well-being and, thus, exacerbate disease manifestations; medications that are toxic or potentially toxic to people with neuropathy; circumstances that increase the risk of falling (e.g., rough surfaces).

Evaluation of relatives at risk: If at-risk minor and adult sibs of an individual with FRDA have not had testing for the *FXN* pathogenic variant(s) in their family, they should be offered echocardiography surveillance to determine if treatable cardiac manifestations of presymptomatic disease are present.

Pregnancy management: Worsening, improving, or unchanged manifestations during pregnancy were each reported with equal frequency by women with FRDA. Close cardiac monitoring and regular testing for diabetes mellitus during pregnancy is recommended in any woman with FRDA. If cesarean section is required, epidural or spinal anesthesia is recommended rather than general anesthesia if possible.

Genetic counseling

FRDA is inherited in an autosomal recessive manner. If both parents are heterozygous for a pathogenic variant in *FXN*, each sib of an affected individual has at conception a 25% chance of inheriting biallelic FRDA-related genetic alterations, a 50% chance of inheriting one FRDA-related genetic alteration, and a 25% chance of inheriting neither of the familial FRDA-related genetic alterations. Sibs who inherit biallelic *FXN* pathogenic variants will be affected. Once the FRDA-related genetic alterations have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus diagnostic criteria for Friedreich ataxia (FRDA) have been published.

Suggestive Findings

FRDA **should be suspected** in a proband with the following clinical features, brain imaging findings, and family history.

Clinical features

- **Neurologic manifestations,** typically, but not always, with onset before age 25 years:
  - Progressive ataxia
  - Dysarthria
  - Decreased/loss of position sense and/or vibration sense in the lower limbs
  - Pyramidal involvement resulting in weakness of the legs, extensor plantar responses
- **Musculoskeletal manifestations:**
  - Muscle weakness
  - Scoliosis
  - Pes cavus

- **Hypertrophic non-obstructive cardiomyopathy**
- **Endocrinologic manifestations**
  - Glucose intolerance
  - Diabetes mellitus
- **Optic atrophy and/or deafness**

Brain imaging. Brain MRI is often normal in the early stages of FRDA. With advanced disease, atrophy of the cervical spinal cord and cerebellum may be observed [Bhidayasiri et al 2005]. Atrophy of the superior cerebellar peduncle, the main outflow tract of the dentate nucleus, may also be seen [Akhlaghi et al 2011]. The size of the cervical spinal cord correlates with disease severity as measured by the Friedreich Ataxia Rating Scale [Chevis et al 2013].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Friedreich ataxia **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *FXN* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. (1) Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *FXN* variant of uncertain significance does not establish or rule out the diagnosis.

The two classes of *FXN* pathogenic variants are (1) GAA repeat expansions and (2) *FXN* pathogenic sequence variants, including base substitutions and small indels or large deletions.

Repeat Expansions

Approximately 96% of individuals with FRDA have biallelic *FXN* GAA repeat expansions in intron 1.

Repeat sizes [Campuzano et al 1996, Dürr et al 1996, Filla et al 1996, Cossée et al 1997, Epplen et al 1997, Montermini et al 1997a, Sharma et al 2004]:

- **Normal.** 5-33 GAA repeats. More than 80%-85% of alleles have fewer than 12 repeats (referred to as **short normal**) and approximately 15% have 12-33 repeats (**long normal**).
- **Intermediate.** 34-55 GAA repeats (also considered **mutable normal**). GAA repeats that range from 44 to 55 repeats are called **borderline.** The shortest repeat length associated with disease (i.e., the exact demarcation between normal and pathogenic alleles) has not been clearly determined. See Penetrance.
- **Pathogenic (full penetrance).** 56-1300 GAA repeats

FXN Pathogenic Sequence Variants or Deletions

Approximately 4% of individuals are compound heterozygotes for an *FXN* GAA repeat expansion and either an intragenic *FXN* pathogenic variant or a large deletion [Zühlke et al 2004, Anheim et al 2012, Hoffman-Zacharska et al 2016, Aguilera et al 2023]. Note: To date individuals from a consanguineous family have been identified to be homozygous for a pathogenic *FXN* sequence variant, the only published example for FRDA in which there is no *FXN* intron 1 GAA repeat expansion [Candayan et al 2020] (see Molecular Genetics).

Molecular genetic testing has traditionally relied on targeted analysis to characterize the number of *FXN* GAA repeats (see Table 9) and sequence analysis to detect single-nucleotide *FXN* pathogenic variants.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel** customized to identify nucleotide repeat expansions.

- **Single-gene testing**
  - Testing is targeted for the expanded *FXN* GAA repeat in intron 1.
  - If an apparently heterozygous *FXN* expanded GAA repeat allele in the full-penetrance or intermediate range is identified, sequence analysis of *FXN* is performed next, followed by either deletion/duplication analysis or CNV analysis for large *FXN* intragenic or whole-gene deletions, to determine if a second *FXN* pathogenic variant is present.
- **A multigene ataxia panel** that includes *FXN* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

  Note: The intronic pathogenic repeat expansion in *FXN* **cannot be detected by exome sequencing**. However, genome sequencing-based tools for the detection of nucleotide repeat expansions have been developed [Ibañez et al 2022]. Depending on the method and analytic tools used by the genetic testing laboratory, such testing may be able to detect an expanded GAA repeat; however, to date such testing is not available in most clinical testing laboratories.

Table 1. Molecular Genetic Testing Used in Friedreich Ataxia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
FXN	Targeted analysis for GAA repeat expansion [3]	96%
	Sequence analysis for sequence variants [4] or CNV analysis for a large *FXN* intragenic or whole-gene deletion [5]	4%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence-based multigene panels and exome sequencing cannot reliably detect pathogenic repeat expansions in this gene. However, pathogenic repeat expansions may be more reliably detected using customized tools and long-read sequencing.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

Friedreich ataxia (FRDA) is characterized by progressive ataxia with onset from early childhood to early adulthood with mean age at onset from 10 to 15 years (range: age two years to the eighth decade) [Delatycki et al 1999b]. Ataxia manifests initially as poor balance when walking, followed by slurred speech and upper-limb ataxia.

Among individuals with FRDA, about 75% have "typical Friedreich ataxia" and about 25% of individuals with biallelic *FXN* full-penetrance GAA repeat expansions have "atypical Friedreich ataxia" [Dürr et al 1996] including late-onset FRDA (LOFA) (i.e., onset after age 25 years), very late-onset FRDA (VLOFA) (i.e., onset after age 40 years), and FRDA with retained reflexes (FARR).

Typical Friedreich Ataxia

Gait ataxia, present in all individuals with FRDA [Delatycki et al 1999b], is caused by a combination of spinocerebellar degeneration and loss of joint position sense (proprioception). It is the earliest manifestation in most affected individuals. Poor balance is accentuated when visual input is eliminated, such as in darkness or when the eyes are closed (Romberg sign).

Within five years of onset of manifestations, most individuals exhibit "scanning" dysarthria, lower-extremity weakness, and diminished or absent joint position and vibration sense distally. These neurologic manifestations result from progressive degeneration of the dorsal root ganglia, posterior columns, corticospinal tracts, dorsal spinocerebellar tracts of the spinal cord, and cerebellum. Ankle and knee jerks are generally absent, and plantar responses are usually upgoing.

Dysarthria, present in 95% of individuals [Delatycki et al 1999b], is generally of three types: mild dysarthria, increased velopharyngeal involvement manifesting as hypernasality, and increased laryngeal dysfunction manifesting as increased strained-strangled vocal quality [Folker et al 2010]. Over time, dysarthria becomes worse with changes in speaking rate and utterance duration [Rosen et al 2012].

Mild dysphonia characterized by hoarseness (combined roughness and breathiness), increased strain, and altered pitch variability is also seen [Vogel et al 2017].

Dysphagia, manifesting as oropharyngeal incoordination, weakness, and spasticity, has been reported in 92% of individuals [Vogel et al 2014]. In one study, significant airway compromise was observed in 34% of individuals and silent aspiration in 26%. Severity of dysphagia correlates with disease duration and severity [Keage et al 2017].

Peripheral motor and sensory involvement results from a mixed axonal peripheral neuropathy. Nerve conduction studies generally show a motor nerve conduction velocity of greater than 40 m/s with reduced or absent sensory nerve action potentials with an absent H reflex. Central motor conduction time is abnormal after transcranial magnetic stimulation [Brighina et al 2005].

Muscle weakness, often present, is most prominent early in the disease course in the hip extensors and abductors. As disease advances, distal limb muscle weakness and wasting become evident. Although pes cavus is common (55%), it generally causes little problem.

Restless leg syndrome, an uncontrollable urge to move the legs usually because of an uncomfortable sensation, affected 32%-50% of individuals in two studies [Frauscher et al 2011, Synofzik et al 2011].

Spasticity was reported in 21% of individuals [Ribaï et al 2007]. Spasticity in the lower limbs can significantly affect foot plantar flexors and inverters more than dorsiflexors and everters, commonly resulting in equinovarus deformity late in the disease [Delatycki et al 2005].

Likewise, spasticity may result in contractures and significant morbidity, particularly in individuals who are non-ambulatory [Milne et al 2016]. Scoliosis, present in approximately two thirds of individuals when assessed clinically, is identified in 100% of individuals assessed radiographically. Milbrandt et al [2008] found that 49 of 77 individuals had scoliosis; ten were treated with a brace and 16 required spinal surgery.

Spastic bladder, reported in 41% of individuals, manifests as urinary frequency and urgency [Delatycki et al 1999a]. In 158 individuals with FRDA, 82% had lower urinary tract involvement that affected quality of life in

22% [Musegante et al 2013]; of the 28 who underwent urodynamic studies, all had normal serum creatinine concentration and four had upper urinary tract dilatation.

Autonomic disturbance becomes more common with disease progression. It is thought that the loss of unmyelinated fibers results in autonomic clinical features such as cold cyanosed feet. Formal cardiovascular autonomic function testing, however, has not shown involvement of the sudomotor and cardiovascular autonomic functions [Indelicato et al 2018].

Sleep-disordered breathing and sleep apnea are more prevalent in individuals with FRDA (21%) than in the general population (5%) [Corben et al 2013].

Ophthalmologic manifestations. Abnormal eye movements, the most frequent non-ataxia clinical features in FRDA, affect 91% of individuals [Reetz et al 2018]. Abnormal extraocular movements include irregular ocular pursuit, dysmetric saccades, saccadic latency, square wave jerks, ocular flutter, and marked reduction in vestibulo-ocular reflex gain and increased latency [Fahey et al 2008]. Generally, horizontal and vertical gaze palsy does not occur.

Optic nerve atrophy, often asymptomatic, occurs in approximately 25% of individuals. Dürr et al [1996] found reduced visual acuity in 13% of individuals studied. Although study of the anterior and posterior visual pathways by visual field testing and optical coherence tomography (OCT), pattern visual evoked potentials, and diffusion-weighted imaging revealed that all individuals studied had optic nerve abnormalities, only five of 26 (19%) had related symptoms [Fortuna et al 2009]. With disease progression, diminution of contrast acuity is typical [Seyer et al 2013].

Cardiomyopathy. Hypertrophic cardiomyopathy, defined as increased thickness of the interventricular septum, is present in about two thirds of individuals [Delatycki et al 1999a]. While manifestations of cardiomyopathy usually occur later in the disease course [Dutka et al 1999], in rare instances cardiomyopathy may precede the onset of ataxia [Alikaşifoglu et al 1999, Leonard & Forsyth 2001]. For example, Quercia et al [2010] reported sudden death in a young child with FRDA.

Echocardiographic evaluation may reveal left ventricular hypertrophy that is more commonly asymmetric than concentric [Dutka et al 2000, Bit-Avragim et al 2001, Koc et al 2005]. Electrocardiography, which is abnormal in the vast majority, most commonly shows T wave inversion, left axis deviation, and repolarization abnormalities [Dutka et al 1999].

When more subtle cardiac involvement is sought by methods such as tissue Doppler echocardiography, an even larger percentage of individuals have detectable abnormalities [Dutka et al 2000, Mottram et al 2011]. Two studies found that in 12% and 20% of individuals ejection fraction was reduced [Regner et al 2012a, Weidemann et al 2012]; longitudinal strain is commonly reduced [St John Sutton et al 2014].

Later in the disease course, the cardiomyopathy may become dilated with reduction in left ventricular wall thickness [Rajagopalan et al 2010] and progressive systolic dysfunction [Kipps et al 2009]. Symptoms often present when disease is moderately advanced include exertional dyspnea (40%), palpitations (11%), and anginal pain. Coronary artery disease should be considered when there is angina and/or sudden deterioration in cardiac function [Giugliano & Sethi 2007].

Although supraventricular ectopy is observed with disease duration, associated diminished cardiac function or cardiac hypertrophy are uncommon [Mejia et al 2021].

Arrhythmias (especially atrial fibrillation) and congestive heart failure, which are prevalent in later stages of the disease, are the most common cause of death [Tsou et al 2011]. Of note, the degree of neurologic impairment did not predict whether an affected individual would have stable or rapid progression of cardiomyopathy. However, in their longitudinal study, Pousset et al [2015] identified genotypes associated with a "low-risk group"

(approximately 80% of individuals) in whom ejection fraction declined slowly and remained in the normal range and a "high-risk group" (approximately 20% of individuals) in whom decline of the ejection fraction declined into the abnormal range and was associated with high mortality (see Genotype-Phenotype Correlations).

Diabetes mellitus occurs in up to 30% of individuals [Cnop et al 2013]; 65% of diabetic individuals use insulin [McCormick et al 2017a].

Impaired glucose tolerance is seen in up to an additional 49% of individuals with FRDA [Ristow 2004, Cnop et al 2012].

Individuals who are not diabetic demonstrate high insulin responsiveness to oral glucose testing and low insulin sensitivity [Isaacs et al 2016].

Diabetes is an independent predictor of reduced survival in FRDA [Indelicato et al 2024]. In one study, multivariable analysis identified diabetes, disability stage, and history of arrhythmogenic disorder as independent predictors of survival. Combining these predictors with left ventricular systolic dysfunction, the authors created a sum score of four points. In the absence of all predictors, 10-year survival in FRDA is 96.4%, which approaches that of the general European population. However, these rates progressively decrease until they reach 42.4% when three or four predictors are present [Indelicato et al 2024].

Hearing loss includes sensorineural hearing loss in 13% of individuals with FRDA [Dürr et al 1996] and/or auditory neuropathy causing difficulty hearing in the presence of background noise (even in the absence of electrophysiologic evidence of auditory pathway disorder) [Rance et al 2008].

Cognition. While cognition is generally not impaired in FRDA, motor and mental reaction times can be significantly slowed [Botez-Marquard & Botez 1993, Wollmann et al 2002, Corben et al 2006].

Motor planning is markedly impaired [Corben et al 2010, Corben et al 2011]. Motor overflow is also more prevalent in people with FRDA than in controls [Low et al 2013].

The intelligence profile of individuals with FRDA is characterized by concrete thinking, poor capacity in concept formation and visuospatial reasoning, and reduced speed of information processing [Mantovan et al 2006]. Additional issues include problems with attention and working memory [Klopper et al 2011] and impaired inhibition and cognitive flexibility based on the Haylings Sentence Completion Task [Corben et al 2017].

In a meta-analysis of 18 studies reporting neuropsychological test results, individuals with FRDA exhibited reduced performance in cognitive domains including attention, executive functions, language, memory, and visuospatial functions [Naeije et al 2022].

Neurobehavioral/psychiatric manifestations. Personality in individuals with FRDA is characterized by high persistence and low self-transcendence (defined as an individual's ability to look beyond the self to adopt a larger perspective that includes concern for others) when assessed by the Temperament and Character Inventory [Sayah et al 2018].

Bone mineral density. In at least one site assessed, six of 28 individuals had reduced bone mineral density for age [Eigentler et al 2014]. There was a negative correlation between disease severity and femoral neck bone density. Although females were more likely to have clinical fractures than males, no association was found between bone mineral density and fracture occurrence. In fact, all fractures occurred in those with a z score greater than -2.

Other. Inflammatory bowel disease and growth hormone deficiency are more common in individuals with FRDA than in the general population [Shinnick et al 2016].

Neuroimaging. Cerebral, cerebellar, and spinal cord involvement is seen on different MRI-based techniques. Volumetric MRI studies have shown widespread involvement of white and gray matter. A voxel-based morphometry study showed symmetric volume loss in the dorsal medulla, infer-medial portions of the cerebellar hemispheres, rostral vermis, and dentate region [Della Nave et al 2008]. No volume loss in cerebral hemispheres was observed. Lower fractional anisotropy, higher mean diffusivity, and increased radial diffusivity compared to controls have been found in the dentatorubral, dentatothalamic, and thalamocortical tracts [Akhlaghi et al 2014].

Reduced N-acetylaspartate in the cerebellum has been demonstrated by ^{1}H-MRS [Iltis et al 2010] and increased diffusion-weighted imaging may be present in some brain white matter tracts [Rizzo et al 2011].

Volume loss in the dentate nucleus region, brain stem, and superior and inferior cerebellar penduncles appear to be early features in FRDA [Harding et al 2021]. White matter abnormalities, especially in the corticospinal tracts, are intermediate features, whereas cerebellar and cerebral gray matter loss appear at a later stage.

Progression and prognosis. The rate of progression of FRDA is variable. The average time from onset of manifestations to wheelchair dependence is ten years [Dürr et al 1996, Delatycki et al 1999a]. Several studies found that progression is more rapid in those with earlier disease onset [Reetz et al 2015, Tai et al 2015, Patel et al 2016, Rummey et al 2022].

In a large study, Harding [1981] reported an average age at death of 37 years. Tsou et al [2011] reported, in a study of 61 individuals, mean age of death of 36.5 years and median age of 30 years. The most common causes of death were cardiac (38 individuals), non-cardiac (most commonly pneumonia) (17), and unknown cause (6). More recently, in a study in which individuals were followed between 2010 and 2022, death occurred on average at age 39 years. Deaths due to cardiovascular events, responsible for 29.5% of deaths, occurred earlier than deaths due to non-cardiac deaths [Indelicato et al 2024].

Survival into the sixth and seventh decades has been documented.

Atypical Friedreich Ataxia

Late-onset FRDA (LOFA) and very late-onset FRDA (VLOFA). In approximately 15% of individuals with FRDA, onset is later than age 25 years.

LOFA onset is defined as onset between age 26 and 39 years. VLOFA onset is defined as onset at age 40 years and older [Bidichandani et al 2000, Bhidayasiri et al 2005]. The oldest reported age of onset among individuals with biallelic full-penetrance GAA expansions is 80 years [Alvarez et al 2013].

It typically takes five years to make a diagnosis in LOFA, compared to the three years described for typical FRDA [Indelicato et al 2020].

In 44 individuals with LOFA and 30 individuals with VLOFA, milder clinical findings than those in typical FRDA included dysarthria, absent tendon reflexes, extensor plantar reflexes, weakness, amyotrophy, loss of proprioception, cerebellar atrophy, scoliosis, cardiomyopathy, and functional disability.

When compared to individuals with onset between ages zero and seven years, eight to 14 years, and 15 to 24 years, difficulties with upright stability progress much more slowly in individuals with onset after age 24 years [Rummey et al 2022].

When compared to typical FRDA, secondary skeletal involvement (e.g., scoliosis and pes cavus) is less frequent in LOFA [Martinez et al 2017].

FRDA with retained reflexes (FARR) accounts for approximately 12% of individuals who have biallelic full-penetrance GAA expansions [Coppola et al 1999].

Tendon reflexes may be retained for more than ten years after disease onset. Some individuals with FARR have brisk tendon reflexes that can be accompanied by clonus. Other typical manifestations are later age of onset and lower incidence of secondary skeletal involvement and cardiomyopathy.

Spastic paraparesis without ataxia. Individuals who have biallelic full-penetrance GAA repeats may on rare occasion present with spastic gait without gait or limb ataxia; they usually have hyperreflexia. Age of onset is on average 5.8 years later than those with typical FRDA. Ataxia develops with time [Montermini et al 1997c, Gates et al 1998, Castelnovo et al 2000, Lhatoo et al 2001, Badhwar et al 2004].

In Acadians (eastern Canada) with FRDA, age at disease onset and wheelchair dependence are on average 3.0 years later than that of individuals with typical FRDA; likewise, the incidence of cardiomyopathy is lower (48% vs 82%) [Montermini et al 1997b].

Other rare presentations of FRDA

- Chorea and pure sensory ataxia [Berciano et al 1997, Hanna et al 1998, Zhu et al 2002]
- Apparently isolated cardiomyopathy, with ataxia becoming evident later [Leonard & Forsyth 2001]
- Visual deficit with episodic blindness, optic atrophy, spastic paraparesis, and sensory neuropathy without ataxia [Diehl et al 2010]

Genotype-Phenotype Correlations

Despite some general genotype-phenotype correlations by class of *FXN* pathogenic variants, it is not possible to precisely predict the specific clinical outcome in any individual based on genotype.

Biallelic Pathogenic Expanded GAA Repeats

In the following discussion the definitions of the length of pathogenic expanded GAA repeats are the following:

- **GAA1 allele.** The shorter of the two expanded alleles. GAA1 allele length inversely correlates with age of disease onset and disease severity.
- **GAA2 allele.** The longer of the two expanded alleles. In general, the length of the GAA2 allele does not significantly contribute to the phenotype. However, the size of the GAA2 allele may have a genotype-phenotype correlation when both the GAA1 and the GAA2 allele are relatively short (<700 triplets), thus resulting in a milder phenotype.

Age of onset. GAA1 allele length inversely correlates with age of disease onset.

- GAA1 allele lengths of <300 triplets are generally associated with very late-onset FRDA (VLOFA) (i.e., onset after age 40 years) [Lecocq et al 2016].
- GAA1 allele lengths of <500 triplets are generally associated with late-onset FRDA (LOFA) (i.e., onset after age 25 years) [Filla et al 1996, Dürr et al 1996, Metz et al 2013, Reetz et al 2015, Lecocq et al 2016, Martinez et al 2017]. While a GAA1 allele length of <700 triplets is associated with a mean age of onset of 18 years, a GAA1 allele length of >700 is associated with a mean age of onset of 9.7 years [Metz et al 2013].

Disease severity and rate of progression. In general, longer GAA1 allele lengths correlate directly with disease severity (including presence and severity of scoliosis and cardiomyopathy) and inversely with rate of disease progression and age of death.

- Shorter GAA1 allele lengths inversely correlate with disease progression. For instance, time to loss of independent ambulation is about 8 years when GAA1 allele length is >780 triplets in contrast with about 14 years when GAA1 allele length is <520 triplets [Dürr et al 1996].
- GAA1 allele lengths are a significant determinant and predictor of the rate of neurologic progression, as determined in several large longitudinal cohorts using validated rating scales [Regner et al 2012b, Metz et

al 2013, Patel et al 2016, Reetz et al 2021]. Among individuals who are ambulatory, disease progression is more rapid when GAA1 allele length is >350 triplets [Reetz et al 2021]. While younger individuals with longer GAA1 alleles progress more rapidly, the predictive effect of GAA1 allele length plateaus at ~600 triplets, above which the correlation is insignificant [Metz et al 2013].

- GAA1 allele lengths also correlate inversely with disease duration and age of death [Tsou et al 2011]. Complications of cardiac disease comprise the most frequent cause of death (~60%). Although the determinants of severity of cardiac disease are not entirely clear, a longer GAA1 allele predisposes individuals to a "high-risk group" with earlier progressive deterioration of left ventricular ejection fraction and poor cardiac prognosis [Pousset et al 2015]. Prevalence of scoliosis is also increased in this group [Rodden et al 2022].

Interrupted GAA Repeats

In the full-penetrance range of GAA repeats (i.e., 56-1300 repeats), some alleles are interrupted by G and/or A nucleotides that disrupt the otherwise pure tract of tandem GAA repeats. These alleles are typically short (equivalent to 100-300 GAA repeats) and associated with LOFA/VLOFA. Stolle et al [2008] reported six people with such interrupted alleles (with conventional GAA2 alleles of >600 repeats) whose onset ranged from ages 34 to 75 years. It is not clear if the milder FRDA phenotype resulted from the interruptions per se, or because interrupted GAA alleles are often short, or both.

It is nevertheless clear that a sufficient length of tandem pure GAA repeats is required for pathogenicity, since an expanded allele with ~65 tandem repeats of the GAAGGA hexanucleotide (equivalent to ~130 GAA triplets) is non-pathogenic [Ohshima et al 1999, Santoro et al 2020]. Apparently, minor interruptions are quite prevalent at the ends of the repeat tract, and Nethisinghe et al [2021] found that 3' interruptions are associated with shorter GAA alleles on average and a later age of onset.

Compound Heterozygotes for a Full-Penetrance GAA Expansion and a Borderline "Mutable" Allele

Individuals with somatically unstable borderline alleles (44-55 GAA repeats) often have LOFA/VLOFA, mild and gradually progressive disease, and normal reflexes/hyperreflexia [Sharma et al 2004].

The remaining variability in individuals with FRDA may be caused by genetic background (e.g., Acadian individuals, the presence of the p.Cys282Tyr variant in *HFE* [Delatycki et al 2014]), somatic variability of the expanded *FXN* GAA repeat [Montermini et al 1997c, Sharma et al 2004, De Biase et al 2007], and other unidentified factors.

Compound Heterozygotes for an Expanded GAA Repeat and an *FXN* Pathogenic Variant or Gene Deletion

About 4% of individuals who have FRDA are compound heterozygotes for one expanded GAA repeat and an *FXN* pathogenic variant or gene deletion. Compound heterozygotes almost always have one *FXN* allele with an expanded GAA repeat. The phenotypic effect of this single expanded GAA repeat depends on its length (see Biallelic Pathogenic Expanded GAA Repeats) and purity (see Interrupted GAA Repeats). For example, if the expanded GAA allele length is <500 triplets, it is expected to result in a less severe FRDA phenotype even when coupled with a null variant.

Non-repeat *FXN* pathogenic alleles are broadly classified as "null" variants (i.e., with complete loss of function) or "partial loss-of-function" variants.

Null variants include large gene deletions (including one exon or multiple consecutive exons), frameshifts (including indels and splicing variants), nonsense variants, and some missense variants that are particularly destabilizing. Individuals with a typical expanded GAA repeat (>600 triplets) and a null variant result in a more

severe phenotype compared with individuals who have biallelic expanded GAA repeats, with earlier ages of onset, higher severity scores on neurologic rating scales, and rapid disease progression [Anheim et al 2012, Galea et al 2016, Shen et al 2024].

Partial loss-of-function variants include missense variants and some splicing variants. While the phenotypic effects of these partial loss-of-function variants are heterogeneous, individuals with a typical expanded GAA repeat (>600 triplets) and such a variant are clearly less severely affected than those who have null variants [Galea et al 2016, Shen et al 2024].

The p.Gly130Val missense variant (see Table 10), seen in multiple unrelated families, results in a milder form of FRDA involving less effect on the upper limbs, prolonged ambulation, and a lower incidence of cardiac disease and dysarthria [Shen et al 2024].

Penetrance

Penetrance is complete in individuals with either biallelic FXN pathogenic GAA repeat sizes or compound heterozygosity for a pathogenic GAA repeat and an *FXN* pathogenic sequence variant or deletion. However, onset can range from younger than age five years to older than age 50 years because of the wide variability of pathogenic (full-penetrance) repeat sizes and other unknown reasons. This variability in age-related penetrance can occasionally occur within the same sibship.

Because the GAA repeat size at the lower end of the pathogenic (full-penetrance) range has not been clearly defined, it is possible that reduced penetrance is associated with borderline alleles (44-55 repeats) and expanded alleles comprising fewer than 100 GAA repeats. Individuals who are compound heterozygous for a borderline allele and a full-penetrance allele (range 56-1300 repeats) may develop LOFA or VLOFA.

Germline Instability

FRDA is typically caused by inheritance of an expanded GAA repeat allele from both parents. Indeed, the prevalence of FRDA is maintained in susceptible populations by the approximate 1% frequency of asymptomatic heterozygous carriers for an expanded GAA repeat allele. Although documented, expansion from premutation to fully penetrant alleles is very rare.

Moreover, intergenerational transmission of expanded alleles can result in changes in repeat length. Pathogenic GAA repeats tend to contract through paternal transmission, and contract or expand with equal frequency via maternal transmission. However, these changes are generally small in magnitude and have minimal phenotypic consequences.

Anticipation

Anticipation (i.e., the tendency in certain genetic disorders for individuals in successive generations to present at an earlier age and/or with more severe manifestations) is not observed in FRDA because FRDA is an autosomal recessive disorder and typically affects only one generation.

Prevalence

The prevalence of FRDA is 0.50:100,000 based on clinical and molecular diagnosis and 1.79:100,000 based on clinical diagnosis alone in countries with predominant European ancestry [Buesch & Zhang 2022]. The carrier frequency is 1/60-1/100.

FRDA is the most common early-onset inherited ataxia in Europe, the Middle East, South Asia (Indian subcontinent), and North Africa.

FRDA has not been documented in Southeast Asians, in sub-Saharan Africans, or among Native Americans. A lower-than-average prevalence of FRDA is noted in Mexico.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline *FXN* pathogenic variants.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Friedreich Ataxia

Gene(s)	Disorder	MOI	Selected Features / Comment
Peripheral neuropathy			
>80 genes incl: *GDAP1* *GJB1* *HINT1* *MFN2* *MPZ* *PMP22* *SH3TC2* *SORD*	Charcot-Marie-Tooth (CMT) hereditary neuropathy	AD AR XL	Some persons w/CMT present in childhood w/clumsiness, areflexia, & minimal distal muscle weakness. In children w/FRDA who have not developed dysarthria or extensor plantar responses, the diagnosis of CMT may be difficult to exclude solely on clinical findings.
TDP1	Spinocerebellar ataxia w/axonal neuropathy type 1	AR	Characterized by ataxia, axonal sensorimotor polyneuropathy, distal muscular atrophy, pes cavus, & steppage gait, signs that may collectively mimic FRDA.
Ataxia			
APTX	Ataxia w/oculomotor apraxia type 1 (AOA1) (OMIM 208920)	AR	Characterized by childhood onset of slowly progressive cerebellar ataxia followed by oculomotor apraxia & a severe primary axonal sensorimotor peripheral neuropathy. The initial manifestation is progressive gait imbalance in childhood (age 2-10 yrs) that may be assoc w/chorea. All affected persons initially have generalized areflexia that is followed later by peripheral neuropathy. The clinical phenotype may be highly variable; however, presence of chorea, severe sensorimotor neuropathy, oculomotor anomalies, & cerebellar atrophy on MRI & absence of Babinski sign can help to distinguish AOA1 from FRDA. [1]
MTTP	Abetalipoproteinemia	AR	Abetalipoproteinemia & other fat malabsorptive conditions should be considered in persons w/FRDA phenotype w/o GAA expansions. [2] If untreated, neuromuscular manifestations of abetalipoproteinemia secondary to the deficiency of vitamin E typically begin in the 1st or 2nd decade of life. Eventually, an FRDA-like ataxia, w/broad base & high-stepping gait, can develop in early adulthood in untreated individuals. **Most complications can be prevented through institution of a low-fat diet w/supplementation of fat-soluble vitamins (A, D, E, & K).**
PNPT1	Spinocerebellar ataxia type 25 (SCA25) (OMIM 608703)	AD	Ataxia w/sensory neuropathy. May present with FRDA-like phenotype. [3]
SETX	Ataxia w/oculomotor apraxia type 2	AR	Characterized by ataxia w/onset between ages 10 & 22 yrs, cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia, choreiform or dystonic movement, & elevated serum AFP concentration.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Selected Features / Comment
TTPA	Ataxia w/vitamin E deficiency (AVED)	AR	Most persons w/AVED fulfill the diagnostic criteria for FRDA, although titubation & hyperkinesia are more frequently seen in AVED than in FRDA. [4] The prevalence of cardiomyopathy is much less in those w/ AVED compared to those w/FRDA. Plasma concentration of vitamin E & lipid-adjusted vitamin E may also differentiate AVED & FRDA. Lifelong targeted therapy w/high-dose oral vitamin E supplementation initiated in presymptomatic persons (e.g., younger sibs of an index case) prevents manifestations of AVED. **Vitamin E supplementation early in disease course of a symptomatic person may to some extent reverse ataxia & mental deterioration.**
Other early-onset ataxias that may be distinguishable based on characteristic clinical features (See Hereditary Ataxia Overview.)			
ABCB7	X-linked sideroblastic anemia & ataxia (OMIM 301310)	XL	
ATM	Ataxia-telangiectasia	AR	Classic ataxia-telangiectasia is characterized by childhood onset of progressive neurologic manifestations (initially cerebellar ataxia, followed typically by extrapyramidal involvement & peripheral sensorimotor neuropathy), immunodeficiency, pulmonary disease, & ↑ risk of malignancy.
HEXA	Late-onset Tay-Sachs disease (TSD) (See *HEXA* Disorders.)	AR	Late-onset TSD presents in older teens or young adults w/slowly progressive spectrum of neurologic symptoms incl lower-extremity weakness w/muscle atrophy, dysarthria, incoordination, tremor, mild spasticity &/or dystonia, & psychiatric manifestations incl acute psychosis.
OPA1	Behr syndrome (See Mitochondrial DNA Maintenance Defects Overview.)	AR	Characterized by spasticity, ataxia, optic atrophy, & intellectual disability
SIL1	Marinesco-Sjögren syndrome	AR	Characterized by cerebellar ataxia w/cerebellar atrophy, dysarthria, nystagmus, early-onset (not necessarily congenital) cataracts, myopathy, muscle weakness, & hypotonia
TIMM8A	Deafness-dystonia-optic neuronopathy (DDON) syndrome	XL	Males w/DDON syndrome have prelingual or postlingual sensorineural hearing impairment in early childhood, slowly progressive dystonia or ataxia in their teens, slowly progressive ↓ visual acuity from optic atrophy beginning at age ~20 yrs, & dementia beginning at age ~40 yrs.
mtDNA genes	Ataxias assoc w/pathogenic variants in mtDNA (See Primary Mitochondrial Disorders Overview.)	Mat	Mitochondrial disorders may present at any age. Common clinical features incl ptosis, external ophthalmoplegia, proximal myopathy & exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, & diabetes mellitus. CNS findings are often fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, & spasticity. Chorea & dementia may also be prominent features.
Spasticity			
>80 genes incl: *ATL1* *CYP7B1* *KIF1A* *REEP1* *SPAST* *SPG7* *SPG11*	Hereditary spastic paraplegia (HSP)	AD AR XL Mat	FRDA is rare among persons w/uncomplicated (isolated) autosomal recessive spastic paraplegia. [5]

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Selected Features / Comment
SACS	Autosomal recessive spastic ataxia of Charlevoix-Saguenay	AR	May present w/early-onset ataxia & areflexia, Babinski sign, loss of vibratory sensation, & pes cavus w/o spasticity [6]
Other			
HTT	Huntington disease	AR	Rarely, FRDA can present as a phenocopy of Huntington disease. [7]

AD = autosomal dominant; AFP = alpha-fetoprotein; AR = autosomal recessive; CNS = central nervous system; FRDA = Friedreich ataxia; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA; XL = X-linked

1. Le Ber et al [2003]
2. Cavalier et al [1998], Hammans & Kennedy [1998]
3. SCA4 (OMIM 600223), an autosomal dominant ataxia of unknown genetic cause, may also present with an FRDA-like phenotype.
4. Cavalier et al [1998]
5. Wilkinson et al [2001], Badhwar et al [2004]
6. Shimazaki et al [2005]
7. Wild et al [2008]

Multisystem atrophy. Very late-onset FRDA (VLOFA) (i.e., age of onset >40 years) may mimic multiple-system atrophy of the cerebellar type [Berciano et al 2005].

Management

Guidelines have been published to assist with management of Friedreich ataxia (FRDA) [Corben et al 2022] (full text) (see also frdaguidelines.org).

Evaluations Following Initial Diagnosis

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

Table 4. Friedreich Ataxia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Clinical neurologic eval	Assess for gait & postural ataxia/balance, dysarthria, lower extremity weakness, mixed axonal peripheral neuropathy, tone abnormalities, autonomic disturbances.
Musculoskeletal/ADL	Orthopedic eval	Assess for significant scoliosis, foot deformity.
	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., orthotics, canes, walkers, motorized chairs).
	OT	Assess need for adaptive devices to optimize ADL.
Dysarthria	Speech-language pathologist eval	Assess need for: • Speech-language therapy; • Alternative means of communication.
Dysphagia	Swallowing eval	• Consider video fluoroscopic swallowing study to assess risk of aspiration. • Refer to nutritionist & OT if risk of aspiration is ↑.
Cardiac	Cardiology eval	Echocardiogram & EKG recommended for baseline assessment for cardiomyopathy.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genitourinary	Urology eval	Assess for symptoms of bladder dysfunction.
Sleep	Sleep specialist eval	Assess for obstructive sleep apnea &/or sleep disordered breathing.
Endocrine	Endocrinology eval	Assess for evidence of diabetes mellitus.
Ophthalmologic	Ophthalmology eval	• Assess for nystagmus, saccades & smooth pursuit, & vertical & horizontal gaze limitation. • Evaluate for optic atrophy. • Consider referral for corrective measures incl prisms &/or surgery.
Audiologic	Consultation w/audiologist or hearing assessment for sensorineural hearing loss &/or auditory neuropathy	
Neurobehavioral/ psychiatric manifestations	Mental health specialist eval	Assessment for depression & anxiety &, less commonly, psychosis
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of FRDA to facilitate medical & personal decision making
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; FRDA = Friedreich ataxia; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

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

Treatment of Manifestations

There is no cure for FRDA.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Omaveloxolone is approved in the United States and Europe for individuals age 16 years and older. It has been shown to slow progression of FRDA. Omaveloxolone is generally well tolerated. The main side effects noted are alteration in liver function that is generally of short duration and increase in serum lipids that sometimes requires therapy.

Table 5. Friedreich Ataxia: Targeted Treatment of Manifestations

Treatment Class	Mechanism of Action	Specific Drug	Dose	Comments
Nrf2 activator	Unknown	Omaveloxolone	150 mg daily	Intriguingly, persons w/o pes cavus showed greater improvement during part 1 of the Phase II omaveloxolone clinical trial when compared to persons w/pes cavus [Lynch et al 2019]. The mechanism underlying this observation remains unknown.

Nrf2 = nuclear factor erythroid 2-related factor 2

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields, such as neurologists, ophthalmologists, orthoptists, physical therapists, occupational therapists, cardiologists, endocrinologists, speech-language therapists, and psychologists (see Table 6).

Table 6. Friedreich Ataxia: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Ataxia	PT & OT	• PT to maintain mobility & function [1] • Self-directed exercise as prescribed by PT; completion of exercise program 3 or more days per week [2] • OT to optimize ADL • Adaptive devices to maintain/improve mobility (e.g., orthotics, canes, walking sticks, walkers, wheelchairs) • Inpatient rehab w/PT/OT may improve ataxia & functional abilities, which has been shown to improve physical function as measured by the Functional Independence Measure. [1] • OT & home adaptations to ensure safe environment & prevent falls (e.g., grab bars, raised toilet seats) • Avoid excessive alcohol intake.
Spasticity	• Non-pharmacologic treatment • Pharmacologic treatment	• PT & stretching exercises, standing frames & splints • Consider drugs such as baclofen & botulinum toxin for treatment of severe spasticity. Intrathecal baclofen can be beneficial when oral administration is unsuccessful or side effects are excessive. [3] • Active treatment is recommended to prevent permanent contractures & need for surgery.
Neuropathic pain	Pharmacologic treatment	Consider gabapentin, pregabalin, lamotrigine, amitriptyline, or duloxetine.
Scoliosis	Orthopedic interventions (operative & non-operative) [4]	Early treatment of scoliosis w/PT, brace, &/or botulinum toxin, &/or surgery to prevent cardiopulmonary complications
Foot deformities		Consider orthotics & surgery.
Dysarthria	Speech-language therapy	• Intensive behavioral therapy can improve speech. • Consider alternative means of communication as needed (e.g., writing pads & digital devices). [5]
Dysphagia	Gastroenterology	Mgmt may incl dietary modification &, in late stages of disease, use of nasogastric or gastrostomy feeding.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cardiac	Treatment of cardiac disease to ↓ morbidity & mortality	• Treatment options incl antiarrhythmic agents, anti-cardiac failure medication, anticoagulants, &/or pacemaker/implantable cardioverter defibrillator. [6] • Cardiac transplantation can be considered, particularly when cardiac disease is severe in those w/mild neurologic manifestations. [7]
Genitourinary	Treatment of bladder dysfunction	Antispasmodic agents, w/some persons requiring botulinum toxin for bladder & some requiring intermittent or permanent catheterization
Sleep	Treatment of sleep apnea by continuous positive airway pressure	Early treatment of sleep apnea w/non-invasive nocturnal ventilation to prevent neurologic & cardiopulmonary complications when untreated [8]
Endocrine	Treatment of diabetes mellitus	Treatment options incl diet &, if necessary, oral hypoglycemic agents &/or insulin [9]
	Treatment of osteoporosis	• Treat vitamin D deficiency. • Bisphosphonate therapy for proven osteoporosis [10]
Hearing loss	Treatment by audiologist, ENT specialist	Hearing aids, microphone, & receiver as needed [11]
Vision	Treatment by ophthalmologist, optometrist	Standard mgmt for refractive errors & strabismus
	Treatment by local low vision services	For those w/severe vision loss (e.g., optic neuropathy)
Sexual function	By neurologist, primary care practitioner	Consider phosphodiesterase-5 inhibitor for erectile dysfunction. [12]
Psychological	By mental health professional	Psychological (counseling &/or pharmacologic) support for affected persons & family
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.	Ongoing assessment of need for palliative care involvement &/or home nursing

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy
1. Milne et al [2012]
2. Milne et al [2018]
3. Berntsson et al [2013]
4. Delatycki et al [2005], Milbrandt et al [2008]
5. Vogel et al [2022]
6. Lynch et al [2012]
7. Sedlak et al [2004], Yoon et al [2012], McCormick et al [2017b]
8. Corben et al [2013]
9. Tamaroff et al [2022]
10. Eigentler et al [2014]
11. Rance et al [2010], Genetic Hearing Loss Overview
12. Corben et al [2021]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Friedreich Ataxia: Recommended Surveillance

System/Concern	Evaluation	Frequency
Ataxia	• Neurology eval to assess progression & need for pharmacotherapy • Monitor ataxia progression w/standardized scale (SARA).	At a minimum annually
	PT eval re mobility, need for durable equipment	Per treating PT
	OT eval re ADL, need for safety modifications	Per treating OT
Cardiac	Cardiology eval to assess for progression of cardiomyopathy	• In those w/known cardiomyopathy: per treating cardiologist • If EKG & echocardiogram performed at time of initial diagnosis are normal, repeat annually
Endocrine	Endocrinology eval to monitor for diabetes mellitus	• Per treating endocrinologist • Annual fasting blood glucose & hemoglobin A1c w/oral glucose tolerance test if impaired glucose/hemoglobin A1c. [1]
Hearing	Eval by audiologist, incl testing of hearing in presence of background noise, as it is more often abnormal than an audiogram assessed in a quiet environment [2]	Hearing assessment every 2-3 yrs or more often if there are concerns about hearing
Sleep	Eval by sleep specialist	• Annual assessment for sleep apnea by history of screening scale (e.g., Epworth Sleepiness Scale) • Sleep study to evaluate for obstructive sleep apnea if concerns on clinical history or screening scale
Osteoporosis	Eval by endocrinologist	Annual vitamin D measurement, DXA scan
Psychological	Eval by clinicians	Inquire re psychological well-being at each visit
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

ADL= activities of daily living; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia

1. Tamaroff et al [2022]

2. Rance et al [2008]

Agents/Circumstances to Avoid

Avoid the following:

- Use and misuse of illegal and controlled drugs, as they may affect neuronal well-being and, thus, exacerbate disease manifestations
- Circumstances that increase the risk of falling (e.g., rough surfaces)
- Medications that are toxic or potentially toxic to persons with FRDA. See the Charcot-Marie-Tooth Association website for an up-to-date list of medications that are potentially toxic to persons with CMT or a related neuropathy.

Alcohol, which can exacerbate ataxia, should be consumed in moderation.

Evaluation of Relatives at Risk

At-risk minor and adult sibs of an individual with FRDA should be offered echocardiography surveillance to determine if treatable cardiac manifestations of presymptomatic disease are present.

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

Pregnancy Management

A study of 65 pregnancies in 31 women with FRDA found no increase in the rate of spontaneous miscarriage, preeclampsia, prematurity, or cesarean section delivery [Friedman et al 2010]. Worsening, improving, or unchanged manifestations during pregnancy were each reported with equal frequency by women with FRDA.

Women with reduced cardiac ejection fraction are advised to seek counseling about potential morbidity and mortality during pregnancy [Corben et al 2022].

Close cardiac monitoring and regular testing for diabetes mellitus during pregnancy is recommended in any woman with FRDA [Peterson et al 2024].

If cesarean section is required, it is recommended that it be done under epidural or spinal anesthesia rather than general anesthesia if possible [Corben et al 2022].

Therapies Under Investigation

A pipeline of therapies under investigation can be found at FARA: Drug Development Pipeline.

Table 8. Friedreich Ataxia: Therapies Under Investigation

Treatment Approach	Comment	Specific Drug(s)	Current Status
↑ frataxin	↑ levels of frataxin, the protein deficient in FRDA	Nomlabofusp [1]	Phase II
		DT-216P2	Phase I
↑ mitochondrial function & ↓ oxidative stress	Deficiency of frataxin results in abnormal accumulation of intramitochondrial iron, defective mitochondrial respiration, & overproduction of oxygen free radicals w/evidence of oxidant-induced intracellular damage. Antioxidant therapy by free radical scavengers is a potential treatment for slowing the progression of FRDA.	Vatiquinone [2]	Placebo-controlled study complete; open-label study ongoing
		Nicotinamide riboside	Phase II
		Elamipretide	Phase I/II
Gene therapy	Use of viral vectors to deliver wild type *FXN*	LX2006 (AAV vector delivering *FXN* to heart)	Phase I/II
Modulation of frataxin-controlled pathways	Act on frataxin-controlled pathways to ↑ mitochondrial function	Leriglitazone [3]	Phase II complete
		Dimethyl fumarate [4]	Phase II
Rehabilitation		Rehabilitation [5]	Completed, results pending

AAV = adeno-associated virus; FRDA = Friedreich ataxia
1. Clayton et al [2024]
2. Ma et al [2023]
3. Pandolfo et al [2022]
4. Pane et al [2023]
5. Milne et al [2020]

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.

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

Friedreich ataxia (FRDA) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an FRDA-related genetic alteration (i.e., a pathogenic [full-penetrance] *FXN* GAA repeat expansion in intron 1, an intragenic *FXN* pathogenic variant or deletion, or an intermediate (mutable normal) GAA repeat expansion *).

  * Mutable normal GAA repeat expansions are rare. Although the exact prevalence is unknown, mutable normal GAA repeat expansions are far less commonly identified in carriers than pathogenic GAA repeat expansions. Consequently, expansion of mutable normal alleles as a means of transmitting FRDA is very unusual.

- Molecular genetic testing is recommended for the parents of the proband to evaluate the genetic status of the parents and inform recurrence risk assessment.

- Individuals who are heterozygous (carriers) for one FRDA-related genetic alteration are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are heterozygous for an *FXN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic FRDA-related genetic alterations, a 50% chance of inheriting one FRDA-related genetic alteration, and a 25% chance of inheriting neither of the familial FRDA-related genetic alterations.
  - Sibs who inherit biallelic *FXN* pathogenic variants will be affected. Variability in age of onset can occur among sibs (see Penetrance).
  - Sibs who inherit one FRDA-related genetic alteration (i.e., carriers) are asymptomatic and are not at risk of developing the disorder.
- If one parent is known to be heterozygous for a pathogenic full-penetrance GAA repeat expansion (or an intragenic *FXN* pathogenic variant or deletion) and the other parent is heterozygous for an intermediate (mutable normal) allele, sibs have a less-than-25% chance of being affected.
- Because of the wide range in age of onset that can occur within sibships and intergenerational instability of the GAA repeat expansion (sibs can have markedly different *FXN* GAA repeat sizes as pathogenic GAA repeat expansions tend to contract through paternal transmission and contract or expand with equal frequency on maternal transmission), an adult, apparently asymptomatic sib should still be considered at risk for FRDA unless molecular genetic testing has demonstrated that the sib did not inherit biallelic FRDA-related genetic alterations.

Offspring of a proband

- All offspring will inherit an FRDA-related genetic alteration from the affected parent. The risk to offspring of being affected with FRDA depends on the genetic status of the proband's reproductive partner (see Prevalence). If the reproductive partner of the proband:
  - Is not a carrier of an FRDA-related genetic alteration, offspring will be obligate heterozygotes (carriers) for an FRDA-related genetic alteration;

- Is a carrier of an *FXN* pathogenic (full-penetrance) GAA repeat expansion or an intragenic *FXN* pathogenic variant or deletion, offspring have a 50% chance of being affected;
- Is a carrier for an intermediate (mutable normal) GAA repeat expansion, the risk to each offspring of developing FRDA is less than 50%.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the FRDA-related genetic alterations in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk sibs for the purpose of early diagnosis and treatment.

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

- Predictive molecular genetic testing for at-risk sibs is possible once a molecular diagnosis of FRDA has been established (i.e., once biallelic *FXN* pathogenic variants have 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.

Predictive testing in minors (i.e., testing of asymptomatic at-risk sibs younger than age 18 years). Testing of minor sibs is neither recommended nor proscribed against [Corben et al 2022]. Parents requesting predictive testing should be made aware of the issues raised by presymptomatic testing for a disorder that may have onset in adulthood [Lowe et al 2015].

If predictive genetic testing is not performed, echocardiography should be offered to at-risk minor and adult sibs to determine if treatable cardiac manifestations of presymptomatic disease are present. At-risk sibs and the parents of at-risk minor sibs should be informed that identification of findings typical of FRDA on echocardiogram suggests that the sib has FRDA and the absence of abnormal findings on echocardiogram does not rule out the possibility that the sib has FRDA.

In a family with an established diagnosis of FRDA, it is appropriate to consider testing of symptomatic individuals regardless of age.

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, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with FRDA (see Prevalence).

Prenatal Testing and Preimplantation Genetic Testing

Once the FRDA-related genetic alterations have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

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.

- **FARA**
  Friedreich's Ataxia Research Alliance
  Phone: 484-879-6160
  Fax: 484-872-1402
  Email: info@CureFA.org
  CureFA.org
- **FARA (Australasia)**
  Friedreich Ataxia Research Association
  Australia
  Email: info@fara.org.au
  fara.org.au
- **MedlinePlus**
  Friedreich Ataxia
- **NCBI Genes and Disease**
  Friedreich's ataxia
- **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
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain

Phone: 601 037 982
Email: info@fedaes.org
fedaes.org

- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry
- **EFACTS Patient Registry**
  European Friedreich's Ataxia Consortium for Translational Studies
  EFACTS Patient Registry
- **Friedreich's Ataxia Global Patient Registry**
  Friedreich's Ataxia Research Alliance
  Email: info@CureFA.org
  Patient Registry

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. Friedreich Ataxia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FXN	9q21.11	Frataxin, mitochondrial	FXN database	FXN	FXN

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 Friedreich Ataxia (View All in OMIM)

229300	FRIEDREICH ATAXIA; FRDA
606829	FRATAXIN; FXN

Molecular Pathogenesis

Friedreich ataxia (FRDA) is caused by deficiency of the nuclear-encoded mitochondrial protein frataxin, encoded by *FXN*. Frataxin is an iron-binding protein required for: (1) the synthesis of iron-sulfur clusters and, thus, activity of enzymes in respiratory chain complexes I-III; (2) metabolism (aconitase); and (3) many other proteins involved in DNA, RNA, and protein synthesis [Monfort et al 2022].

The tissues primarily affected in FRDA are known to express high levels of frataxin. Deficiency of *FXN* mRNA (and thus deficiency of frataxin) cause secondary deficiency of iron-sulfur cluster-containing enzymes, mislocalization of cellular iron, and increased sensitivity to oxidative stress, all of which result in impaired mitochondrial respiratory function and increased oxidative stress, the molecular basis of FRDA [Delatycki & Bidichandani 2019].

The three types of inactivating *FXN* pathogenic variants are: (1) most commonly, a pathogenic (full-penetrance) GAA repeat expansion; (2) less commonly, nonsense or frameshift variants resulting in aberrant or premature termination of translation, and loss-of-function missense and splicing variants; and (3) rarely, a large *FXN* intragenic deletion or whole-gene deletion [Zühlke et al 2004, Anheim et al 2012, Hoffman-Zacharska et al 2016, Aguilera et al 2023].

The pathogenic expanded GAA repeat (fully penetrant alleles; see Table 9) results in transcriptional silencing of *FXN* by at least two mechanisms that are not mutually exclusive:

- Epigenetic silencing via repressive chromatin formation in the sequence flanking the expanded GAA repeat that interferes with both transcriptional initiation and elongation [Herman et al 2006, Kumari et al 2011, Evans-Galea et al 2012, Chutake et al 2014a, Chutake et al 2014b, Li et al 2015]
- Formation of one or more abnormal DNA and/or DNA/RNA structures that interferes with transcriptional elongation [Bidichandani et al 1998, Ohshima et al 1998, Grabczyk & Usdin 2000, Sakamoto et al 2001, Groh et al 2014, Matos-Rodrigues et al 2022]

Mechanism of disease causation. All four of the following classes of *FXN* pathogenic variants result either in deficiency of frataxin levels or in deficiency of frataxin function: (1) expanded pathogenic GAA repeats; (2) nonsense or frameshift variants resulting in aberrant or premature termination of translation; (3) loss-of-function missense variants; (4) large rearrangements including whole-exon/whole-gene deletions.

In about 96% of individuals with FRDA, the expanded GAA repeat is biallelic; in about 4%, one allele is the expanded GAA repeat and the second allele is one of the other classes of pathogenic variants. Of note, the single report of biallelic *FXN* missense variants was in a consanguineous family in which three sibs with a CMT-like phenotype were homozygous for the p.Arg165Cys variant [Candayan et al 2020].

Table 9. *FXN*-Specific Laboratory Technical Considerations

Technical Consideration	Comment [Reference]
Sequence of repeat	GAA (expanded pathogenic); however, interrupted repeats are also possible. Such "interrupted *FXN* alleles" differ in length and types of nucleotides in the interruption. Interrupted alleles may be associated with late-onset FRDA (LOFA) or very late-onset FRDA (VLOFA) [Stolle et al 2008] (see Genotype-Phenotype Correlations). Standard molecular genetic testing does not determine presence or absence of nucleotide interruptions of the GAA tract [Nethisinghe et al 2021].
Length of repeat	The exact demarcation between normal and full-penetrance GAA alleles remains poorly defined. While the risk for phenotypic expression with borderline alleles is increased, it is not possible to offer precise risk advice. Therefore, the interpretation of test results in an individual who is compound heterozygous for a large full-penetrance GAA expanded allele and a second allele of fewer than 100 GAA repeats is uncertain.
Methods to detect expanded allele (See Table 10 .)	Options: • Long-range PCR (LR-PCR) • Repeat-primed PCR (RP-PCR) • Long-read sequencing Note: Standard molecular genetic testing does not determine the presence or absence of nucleotide interruptions of the GAA tract. Recent advances in long-read sequencing enable detection of expanded interrupted GAA tracts [Uppili et al 2023]; however, to date such testing is not conducted by most diagnostic laboratories.
Somatic instability	Sharma et al [2004] showed that somatic instability of the borderline allele (see Table 10) was required for clinical expression of the FRDA phenotype; therefore, alleles with fewer than 37 GAA repeats are unlikely to cause disease. Although the exact frequency of borderline alleles has not been formally determined, they account for fewer than 1% of *FXN* alleles.
Germline instability	Germline transmission of expanded alleles is frequently associated with their instability. Maternal transmission leads to both expansions and contractions; paternal transmission preferentially leads to contractions [Campuzano et al 1996, Montermini et al 1997a].
Interpretation considerations	The interpretation of the pathogenicity of expanded alleles may be complicated by the possibility that the size of the expanded GAA repeat in leukocytes may not necessarily be the same as that in pathologically relevant tissues such as the dorsal root ganglia and heart. Large differences in allele lengths were noted between different tissues in autopsy studies [De Biase et al 2007, Long et al 2017].

Table 10. *FXN* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Repeat Range [Reference]	Comment
NM_000144.5 NP_000135.2	$(GAA)_5$-$(GAA)_{33}$	Normal	More than 80%-85% of alleles have <12 repeats (referred to as **short normal**); 15% have 12-33 repeats (**long normal**).
	$(GAA)_{34}$-$(GAA)_{55}$	Intermediate (also considered **mutable normal**) [1]	GAA repeats ranging from 44 to 65 are called **borderline**. [2, 3]
	$(GAA)_{56}$-$(GAA)_{1300}$	Full penetrance	
	c.389G>T	p.Gly130Val	Missense pathogenic variant reported to be assoc w/higher levels of partially processed frataxin that may contribute to milder clinical phenotypes [Clark et al 2017, Shen et al 2024] (see Genotype-Phenotype Correlation).

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.
1. Although the exact frequency of mutable normal alleles has not been formally determined, they likely account for fewer than 1% of *FXN* alleles.
2. The shortest repeat length associated with disease (i.e., the exact demarcation between normal and full-penetrance alleles) has not been clearly determined (see Penetrance). Therefore, the interpretation of test results in an individual who is compound heterozygous with a pathogenic full-penetrance GAA allele and a second allele of fewer than 100 GAA repeats may be difficult.
3. An affected individual with an allele of 56 GAA repeats has been reported by Tai et al [2015], which makes the upper limit of the mutable normal reference range less definitive.
4. Shen et al [2024]

Chapter Notes

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- 3 April 2002 (me) Comprehensive update posted live
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- 20 September 1998 (sb) Original submission

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