



Friedreich Ataxia

Synonym: FRDA

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Summary

Clinical characteristics

Friedreich ataxia (FRDA) is characterized by slowly progressive ataxia with onset usually before age 25 years (mean age at onset: 10-15 yrs). FRDA is typically associated with dysarthria, muscle weakness, spasticity particularly in the lower limbs, scoliosis, bladder dysfunction, absent lower-limb reflexes, and loss of position and vibration sense. Approximately two thirds of individuals with FRDA have cardiomyopathy, up to 30% have diabetes mellitus, and approximately 25% have an "atypical" presentation with later onset or retained tendon reflexes.

Diagnosis/testing

The diagnosis of FRDA is established in a proband by detection of biallelic pathogenic variants in *FXN*. The most common type of variant, which is observed on both alleles in approximately 96% of individuals with FRDA, is an abnormally expanded GAA repeat in intron 1 of *FXN*. The remaining individuals with FRDA are compound heterozygotes for an abnormally expanded GAA repeat in the disease-causing range on one allele and another intragenic pathogenic variant on the other allele.

Management

Treatment of manifestations: Clinical management guidelines have been published. Prostheses; walking aids and wheelchairs for mobility; speech, occupational, and physical therapy; pharmacologic agents for spasticity; orthopedic interventions for scoliosis and foot deformities; hearing devices for auditory involvement; dietary modifications and placement of a nasogastric tube or gastrostomy for dysphagia; antiarrhythmic agents, anti-cardiac failure medications, anticoagulants, and pacemaker for cardiac disease; dietary modification, oral hypoglycemic agents or insulin for diabetes mellitus; antispasmodics for bladder dysfunction; continuous positive pressure for obstructive sleep apnea; psychological support, both pharmacologic and counseling.

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Prevention of secondary manifestations: Active management of spasticity to prevent permanent contractures; aggressive treatment of scoliosis to prevent cardiopulmonary complications; treatment of diabetes to avoid complications related to inadequate treatment; treatment of cardiac complications to avoid arrhythmias; treatment of sleep apnea to prevent neurologic and cardiopulmonary complications of untreated sleep apnea.

Surveillance: At least annual assessment of overall status; examination for complications including spasticity, scoliosis, and foot deformity; annual EKG, echocardiogram, and fasting blood sugar to monitor for diabetes mellitus; hearing assessment every two to three years; a low threshold for sleep study to investigate for obstructive sleep apnea.

Agents/circumstances to avoid: Environments that place an individual at risk for falls such as rough surfaces for ambulant individuals; excessive use of alcohol, which can increase ataxia; medications (e.g., isoniazid, nitrofurantoin) that are known to cause nerve damage.

Therapies under investigation: Idebenone, histone deacetylase inhibitors, EPI-743, PPAR gamma agonists, nicotinamide, resveratrol, thiamine.

Genetic counseling

FRDA is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of having no pathogenic variant. Carrier testing of at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if both *FXN* pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Friedrich ataxia (FRDA) **should be suspected** in individuals with a combination of the following clinical features and family history:

Clinical features

- **Neurologic findings**, typically with onset before age 25 years^{*}
 - Progressive ataxia of gait and limbs
 - Dysarthria
 - Decrease in/loss of position sense and/or vibration sense in lower limbs
 - Pyramidal weakness of the legs, extensor plantar responses

^{*}Note: In atypical cases, onset may be delayed; see Atypical Presentations, **Late-onset FRDA and very late-onset FRDA**.

- **Musculoskeletal features**
 - Muscle weakness
 - Scoliosis
 - Pes cavus
- **Hypertrophic non-obstructive cardiomyopathy**
- **Endocrinologic features**
 - Glucose intolerance
 - Diabetes mellitus

- **Optic atrophy and/or deafness**

Family history consistent with autosomal recessive inheritance

Note: Absence of a family history of autosomal recessive inheritance does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Friedreich ataxia **is established** in a proband by detection of biallelic pathogenic variants in *FXN* (see Table 1).

Allele sizes. Four classes of alleles are recognized for the GAA repeat sequence in intron 1 of *FXN* [Cossée et al 1997, Montermini et al 1997a, Sharma et al 2004]; note that an affected individual with a 56 GAA repeat allele has been reported by Tai et al [2015], which makes the upper limit of the mutable normal reference range less definitive.

- **Normal alleles.** 5-33 GAA repeats. More than 80%-85% of alleles contain fewer than 12 repeats (referred to as short normal) and approximately 15% have 12-33 repeats (long normal). Normal alleles with more than 27 GAA repeats are rare.
- **Mutable normal (premutation) alleles.** 34-65 GAA repeats. Although the exact frequency of these alleles has not been formally determined, they likely account for fewer than 1% of *FXN* alleles.
- **Full-penetrance (disease-causing expanded) alleles.** 66 to approximately 1,300 GAA repeats. The majority of expanded alleles contain between 600 and 1,200 GAA repeats [Campuzano et al 1996, Dürr et al 1996, Filla et al 1996, Epplen et al 1997].
- **Borderline alleles.** 44-66 GAA repeats. 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).

Rare alleles of variant structure. In contrast to the alleles discussed above in which the GAA trinucleotides are perfect repeats, in rare pathogenic alleles the GAA repeats are not in perfect tandem order but rather are interrupted by other nucleotides. Such "interrupted *FXN* alleles" differ in length and types of nucleotides in the interruption, but they are typically close to the 3' end of the GAA repeat tract (see Molecular Genetics).

Note: (1) Molecular genetic testing does not determine presence or absence of nucleotide interruptions of the GAA tract. (2) These rare interrupted alleles may be associated with LOFA or VLOFA [Stolle et al 2008] (see Genotype-Phenotype Correlations).

Interpretation of test results. The exact demarcation between normal and full-penetrance alleles remains poorly defined. While the risk for phenotypic expression with borderline alleles is increased, it is not possible to offer precise risks. Therefore, the interpretation of test results in an individual with a large GAA expanded allele of full penetrance and a second allele of fewer than 100 GAA repeats may be difficult.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**.

Single-gene testing

- Testing is targeted for the abnormally expanded GAA repeat in intron 1 of *FXN*.
- If only one abnormally expanded allele is identified, sequence analysis of *FXN* is performed next, followed by deletion/duplication analysis if no pathogenic inactivating variant is found on sequencing.

A multigene panel that includes *FXN* and other genes of interest (see Differential Diagnosis) may also be considered. While this is not recommended as a first-line strategy in typical cases, it may help identify some affected individuals with atypical presentations. To date, next-generation sequencing strategies cannot identify expanded repeats and therefore will not diagnose the majority of individuals with FRDA. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) 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](#).

Table 1. Molecular Genetic Testing Used in Friedreich Ataxia (FRDA)

Gene ¹	Method	Proportion of Probands with Pathogenic Variants ² Detectable by Method
<i>FXN</i>	Targeted analysis for GAA repeat expansion	96% ³
	Sequence analysis ^{4, 5}	4% ³
	Gene-targeted deletion/duplication analysis ⁶	See footnote 7.
Unknown ⁸	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Approximately 96% of individuals with FRDA have an abnormally expanded GAA repeat in intron 1 of *FXN* on both alleles [Campuzano et al 1996, Monrós et al 1997, Galea et al 2016]. The remainder of individuals with FRDA have an abnormally expanded GAA repeat in the disease-causing range in one *FXN* allele and another intragenic pathogenic variant in the other allele.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

5. Sequence analysis of exons and flanking regions will identify *FXN* pathogenic variants located outside the GAA repeat region. Nonsense, missense, frameshift, and splicing defect variants have been identified (see Molecular Genetics).

6. 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.

7. Rare affected individuals have one allele with either a large intragenic deletion or whole-gene deletion of *FXN* and the second allele with a full-penetrance expanded GAA repeat [Zühlke et al 2004, Anheim et al 2012, Hoffman-Zacharska et al 2016]. See Molecular Genetics.

8. Among individuals who satisfy the clinical diagnostic criteria for FRDA and who have normal vitamin E levels, fewer than 1% have no GAA expansion in either allele of *FXN*. It is possible that these individuals have pathogenic variants at a locus distinct from *FXN* [Dürr et al 1996, McCabe et al 2000, Christodoulou et al 2001, Marzouki et al 2001]. However, no other loci have been convincingly linked to the FRDA phenotype.

Clinical Characteristics

Clinical Description

Typical Friedreich ataxia is observed in about 75% of affected individuals and atypical presentations (with later onset or retained tendon reflexes) are observed in about 25%.

Typical Friedreich Ataxia

Neurologic manifestations. Individuals with typical Friedreich ataxia (FRDA) develop progressive ataxia with onset from early childhood through to early adulthood, starting with poor balance when walking, followed by

slurred speech and upper-limb ataxia. The mean age at onset of symptoms is ten to 15 years [Delatycki et al 1999b]; onset can be as early as age two years and as late as the eighth decade. Gait ataxia, caused by a combination of spinocerebellar degeneration and loss of joint-position sense (proprioception), is the earliest symptom in the vast majority. The poor balance is accentuated when visual input is eliminated, such as in darkness or when the eyes are closed (Romberg sign). Ankle and knee jerks are generally absent, and plantar responses are up-going.

Within five years of symptom onset, most individuals with FRDA exhibit "scanning" dysarthria, lower-extremity weakness, and diminished or absent joint-position and vibration sense distally – neurologic manifestations that result from progressive degeneration of the dorsal root ganglia, posterior columns, corticospinal tracts, dorsal spinocerebellar tracts of the spinal cord, and cerebellum. Involvement of peripheral sensory and motor neurons results in a mixed axonal peripheral neuropathy.

Muscle weakness is often present and is most prominent in hip extensors and abductors; as disease advances, distal limb muscle weakness and wasting become evident.

Spasticity in the lower limbs is common and can be significant, affecting foot plantar flexors and inverters to a greater extent than dorsiflexors and everters. Thus, in the late stages of disease, equinovarus deformity is commonly seen [Delatycki et al 2005] and may result in contractures – more commonly in nonambulatory affected individuals [Milne et al 2016] – and significant morbidity. Pes cavus is common (55%) but generally causes little problem for affected individuals. Restless leg syndrome is common in individuals with Friedreich ataxia, affecting 32%-50% of individuals in two studies [Frauscher et al 2011].

Scoliosis is present in approximately two thirds of individuals with FRDA when assessed clinically and 100% when assessed radiographically. A study found that 49 of 77 individuals with FRDA had scoliosis; ten were treated with a brace and 16 required spinal surgery [Milbrandt et al 2008].

Autonomic disturbance becomes more common with disease progression. The most common manifestations are cold, cyanosed feet; bradycardia is less common.

Electrodiagnostic findings. Nerve conduction studies generally show a motor nerve conduction velocity of greater than 40 m/s with reduced or absent sensory nerve action potential with an absent H reflex.

Central motor conduction time is abnormal after transcranial magnetic stimulation [Brighina et al 2005].

Speech. Dysarthria, present in the majority of individuals with FRDA, is generally of three types: mild dysarthria, increased velopharyngeal involvement manifest as hypernasality, and increased laryngeal dysfunction manifest as increased strained-strangled vocal quality [Folker et al 2010]. Dysarthria becomes worse as the disease progresses with the main changes seen over time being 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].

Swallowing. Dysphagia is common in FRDA with 92% of individuals reporting issues with swallowing [Vogel et al 2014]. Dysphagia in FRDA relates to oropharyngeal incoordination, weakness, and spasticity.

Hypertrophic cardiomyopathy, defined as increased thickness of the interventricular septum, is present in about two thirds of individuals with FRDA [Delatycki et al 1999a]. 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]. 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]. Between 12% and 20% of individuals have reduced ejection fraction [Regner et al 2012a, Weidemann et al 2012] and longitudinal strain is commonly reduced [St John Sutton et al 2014].

Later in the disease course, the cardiomyopathy may become dilated. Progressive systolic dysfunction is common [Kipps et al 2009] and reduction in left ventricular wall thickness is often seen as the disease progresses [Rajagopalan et al 2010]. A longitudinal study identified two groups; a "low risk" group (approximately 80%) with normal ejection fraction that declined slowly and remained in the normal range and a "high risk" group (approximately 20%) in whom ejection fraction declined into the abnormal range and was associated with high mortality [Pousset et al 2015]. Those in the "high risk" group had longer GAA expansions on the shorter allele. The degree of neurologic impairment did not predict whether an affected individual would have stable or rapid progression of cardiomyopathy.

Electrocardiography (EKG) is abnormal in the vast majority, with T wave inversion, left axis deviation, and repolarization abnormalities being most commonly seen [Dutka et al 1999].

Symptoms related to cardiomyopathy usually occur in the later stages of the disease [Dutka et al 1999] but in rare instances may precede ataxia [Alikasifoglu et al 1999, Leonard & Forsyth 2001]. Quercia et al [2010] established the diagnosis of FRDA in a young child evaluated for sudden death. Subjective symptoms of exertional dyspnea (40%), palpitations (11%), and anginal pain may be present in moderately advanced disease. Arrhythmias (especially atrial fibrillation) and congestive heart failure frequently occur in the later stages of the disease and are the most common cause of mortality [Tsou et al 2011]. Coronary artery disease may occur and should be considered if there is angina and/or sudden deterioration in cardiac function [Giugliano & Sethi 2007].

Urinary issues. Bladder symptoms including urinary frequency and urgency were reported by 41% of individuals in one study [Delatycki et al 1999a]. A study of 158 individuals with FRDA revealed lower urinary tract symptoms in 82% with impact on quality of life in 22% of those [Musegante et al 2013]. Of 28 who underwent urodynamic studies, all had normal serum creatinine and four had upper urinary tract dilatation.

Sleep-disordered breathing. Sleep-disordered breathing and sleep apnea are more prevalent in those with FRDA than in the healthy population. There is a minimum prevalence of 21% of obstructive sleep apnea compared to an incidence of about 5% in the general population [Corben et al 2013].

Diabetes mellitus occurs in up to 30% of individuals with FRDA [Cnop et al 2013]. Impaired glucose tolerance is seen in up to an additional 49% [Ristow 2004, Cnop et al 2012]. Non-diabetic individuals with FRDA demonstrate high insulin responsiveness to oral glucose testing and low insulin sensitivity [Isaacs et al 2016].

Ophthalmic manifestations. Optic nerve atrophy, often asymptomatic, occurs in approximately 25% of individuals with FRDA. Reduced visual acuity was found in 13% in one study [Dürr et al 1996]. Study of the anterior and posterior visual pathways in FRDA by visual field testing and optical coherence tomography, pattern visual evoked potentials, and diffusion-weighted imaging revealed that all individuals studied had optic nerve abnormalities, but only 5/26 (19%) had related symptoms [Fortuna et al 2009]. Progressive diminution of contrast acuity is typical with disease progression [Seyer et al 2013].

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]. Horizontal and vertical gaze palsy does not occur.

Hearing loss. Sensorineural hearing loss occurs in 13% of individuals with FRDA [Dürr et al 1996]. Auditory neuropathy may occur and difficulty hearing in background noise is common [Rance et al 2008].

Cognitive skills. While cognition is generally not impaired in FRDA, motor and mental reaction times can be significantly slowed [Wollmann et al 2002, Corben et al 2006]. Motor planning is markedly impaired [Corben et al 2010, Corben et al 2011]. The intelligence profile of individuals with FRDA is characterized by concrete thinking and poor capacity in concept formation and visuospatial reasoning with reduced speed of information processing [Mantovan et al 2006]. Problems with attention and working memory have also been demonstrated

[Klopper et al 2011]. Motor overflow is also more prevalent in FRDA than in controls [Low et al 2013]. Those with earlier onset and larger *FXN* intron 1 GAA repeats tend to have more severe cognitive difficulties than those with later onset and smaller GAA repeats [Nachbauer et al 2014]. Impairment of inhibition and cognitive flexibility was identified in individuals with FRDA on the Haylings Sentence Completion Task [Corben et al 2017].

Bone mineral density. A study of 28 individuals with FRDA identified that six (21.4%) had reduced bone mineral density for age in at least one site assessed [Eigentler et al 2014]. There was a negative correlation between disease severity and femoral neck bone density. Females were more likely to have clinical fractures than males but no association was found between bone mineral density and fracture occurrence. In fact, all fractures occurred in those with a Z-score better than -2.

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

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

In a large study conducted in the early 1980s, the average age at death was 37 years [Harding 1981]. In a more recent study, the mean and median age of death was 36.5 years and 30 years, respectively [Tsou et al 2011]. Survival into the sixth and seventh decades has been documented. The most common cause of death was cardiac (38/61), with the remainder (17/61) being non-cardiac (most commonly pneumonia) or unknown cause (6/61) [Tsou et al 2011].

Pregnancy. 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 symptoms during pregnancy were each reported by approximately one third of women with FRDA.

Neuroimaging. 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]. Cervical spinal cord size correlates with disease severity as measured by the Friedreich Ataxia Rating Scale [Chevis et al 2013].

A voxel-based morphometry study showed a symmetric volume loss in the dorsal medulla, infero-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 in individuals with FRDA [Akhlaghi et al 2014].

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

Atypical Presentations

Approximately 25% of individuals homozygous for full-penetrance GAA expansions in *FXN* have atypical findings [Dürr et al 1996] that include the following.

Late-onset FRDA (LOFA) and very late-onset FRDA (VLOFA). In approximately 15% of individuals with FRDA, onset is later than age 25 years. In individuals with LOFA, the age of onset is 26-39 years; and, in VLOFA, onset is after age 40 years [Bidichandani et al 2000, Bhidayasiri et al 2005]. The oldest reported age of onset among individuals homozygous for the GAA expansion is 80 years [Alvarez et al 2013].

A study of 44 individuals with LOFA and 30 individuals with VLOFA found that dysarthria, absent tendon reflexes, extensor plantar reflexes, weakness, amyotrophy, ganglionopathy, cerebellar atrophy, scoliosis, cardiomyopathy, and functional disability were milder, and GAA expansion on the smaller allele shorter, than in individuals with typical-onset FRDA [Lecocq et al 2016]. Another study of 18 individuals with LOFA reported similar findings [Martinez et al 2017].

- **FRDA with retained reflexes (FARR)** accounts for approximately 12% of individuals who are homozygous for the GAA expansion [Coppola et al 1999]. Some individuals with FARR show brisk tendon reflexes that can be accompanied by clonus. Tendon reflexes may be retained for more than ten years after the onset of the disease. FARR usually has a later age of onset and lower incidence of secondary skeletal involvement and cardiomyopathy [Coppola et al 1999].
- **FRDA in Acadians.** Montermini et al [1997b] showed that Acadians with FRDA have a later age of onset (on average 3.0 years later than those with typical FRDA) and of wheelchair confinement, and a much lower incidence of cardiomyopathy (48% vs 82%).

Spastic paraparesis without ataxia. Individuals who have biallelic full-penetrance GAA expansions may rarely present with spastic gait disturbance without gait or limb ataxia. These individuals usually have hyperreflexia and a later age of onset (on average 5.8 years later than those with typical FRDA); they develop ataxia with time [Montermini et al 1997b, Gates et al 1998, Castelnovo et al 2000, Lhatoo et al 2001, Badhwar et al 2004].

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 only becoming evident some time later [Leonard & Forsyth 2001]

Genotype-Phenotype Correlations

Despite the general genotype-phenotype correlations described below, it is not possible to precisely predict the specific clinical outcome in any individual based on genotype. 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 heterogeneity of the expanded GAA repeat [Montermini et al 1997b, Sharma et al 2004, De Biase et al 2007], and other unidentified factors.

Biallelic Pathogenic GAA Repeat Expansions

GAA repeat size. The age of onset, presence of leg muscle weakness/wasting, duration until wheelchair use, and prevalence of cardiomyopathy, pes cavus, and scoliosis have all shown statistically significant inverse correlations with the size of the expanded GAA repeat [Dürr et al 1996, Filla et al 1996, Monrós et al 1997, Montermini et al 1997b]. The size of the shorter of the two expanded pathogenic GAA repeat alleles shows better correlation than the larger repeat allele and accounts for approximately 50% of the variation in age of onset [Filla et al 1996].

La Pean et al [2008] found that age at diagnosis is a better predictor of disease severity – including disease progression and association with scoliosis and cardiomyopathy. This suggests that factors other than the repeat length (e.g., other genetic, epigenetic, and environmental variables) play a role in determining the severity of disease.

A longitudinal natural history study using a large heterogeneous cohort stratified by the size of the shorter of the two expanded alleles showed that individuals with fewer than 300 GAA repeats progressed more slowly compared to individuals with longer repeat sizes [Regner et al 2012b]. Similarly, Metz et al [2013] found that the rate of disease progression as a function of the length of the shorter of the two expanded alleles was most prominent with alleles containing fewer than 600 GAA repeats.

Late-onset FRDA (LOFA) and very late-onset FRDA (VLOFA)

- **Individuals with LOFA** (i.e., age of onset >25 years) frequently exhibit fewer than 500 GAA repeats in at least one of the expanded alleles [Bhidayasiri et al 2005].
- **Individuals with VLOFA** (i.e., age of onset >40 years) usually have fewer than 300 GAA repeats in at least one of the expanded alleles [Bidichandani et al 2000, Berciano et al 2005]. However, Bidichandani et al [2000] reported an individual with VLOFA who had biallelic expansions with greater than 800 GAA repeats on each allele, underscoring the inability to predict the clinical outcome in each individual.

In the full penetrance range, there are uncommon *FXN* alleles that are interrupted by other nucleotides thereby disrupting a section of the long tract of tandem GAA repeats (see Molecular Genetics). Counting only the number of GAA repeats in the uninterrupted section, such alleles tend to be shorter in length (equivalent in length to alleles of 100-300 GAA repeats), and are often associated with LOFA/VLOFA. Stolle et al [2008] reported six people with such interrupted alleles (with a conventional expanded GAA repeat variant containing >600 repeats in the other *FXN* allele) whose onset ranged from age 34 to 75 years. It is not clear if the milder FRDA phenotype results from the interruptions per se, or the fact that interrupted alleles are often short, or both.

FRDA in Acadians. Despite the milder phenotype in this population, no significant differences were found either in the size of the GAA expansions or in the pathogenic sequence variants of *FXN* compared to individuals with typical FRDA [Montermini et al 1997b]. This finding supports the existence of other genetic modifiers of disease severity.

Spastic paraparesis without ataxia may be seen in those with smaller expanded alleles [Berciano et al 2002], or in association with the p.Gly130Val missense variant [McCabe et al 2002].

Cardiomyopathy is more frequently seen in individuals with a higher number of GAA repeats [Dürr et al 1996, Filla et al 1996, Monrós et al 1997]:

- Isnard et al [1997] found echocardiographic evidence of left ventricular hypertrophy in 81% of those with FRDA with GAA repeat lengths greater than 770 repeats and in only 14% of those with repeat lengths of fewer than 770 repeats.
- Significant correlation is seen between the size of the GAA expansion and various diastolic parameters [Mottram et al 2011] as well as the thickness of the interventricular septum and left ventricular wall [Isnard et al 1997, Dutka et al 1999, Bit-Avragim et al 2001]. Pousset et al [2015] found that longer GAA expansions on the shorter allele were associated with greater progression to low ejection fraction and poorer resultant survival.
- Montermini et al [1997b] and Delatycki et al [1999b] showed that the presence of cardiomyopathy correlated with disease severity as defined by age of onset.
- Cuda et al [2002] described an individual with particularly severe early childhood-onset cardiac hypertrophy that preceded the onset of ataxia; the individual had biallelic large GAA expansions and additionally had a pathogenic variant in *TNNT2*, the gene encoding cardiac troponin T.

Diabetes mellitus or abnormal glucose tolerance does not show a clear-cut correlation with the size of the GAA expansion. Filla et al [1996] found that individuals with diabetes mellitus tend to have larger repeat lengths; in a larger cohort, however, Dürr et al [1996] did not find significant correlation either with the size of the GAA expansion or with disease duration. Despite the lack of correlation with the GAA expansion size, Delatycki et al [1999b] found a correlation between the incidence of diabetes mellitus and earlier age at onset. A study of glucose metabolism in individuals with FRDA identified a correlation between longer GAA repeat length on the shorter allele and higher serum glucose and hemoglobin A1C concentrations [Greeley et al 2014].

Compound Heterozygotes for a GAA Expansion and an Intragenic Inactivating Pathogenic Variant or Deletion

A study of 111 compound heterozygotes identified three subgroups based on the pathogenic non-expansion variant: (1) null variant (no frataxin produced), (2) moderate/strong impact on frataxin function and (3) minimal impact of frataxin function [Galea et al 2016]. Compared to those with biallelic GAA expansions, subgroup 1 had earlier onset and higher incidence of diabetes whilst those with biallelic GAA expansions had a higher rate of cardiomyopathy than any of the three compound heterozygous subgroups. Another study found an almost tenfold increase in diabetes in compound heterozygotes compared to those with biallelic GAA repeats [Greeley et al 2014].

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

Individuals with somatically unstable, borderline alleles often have LOFA/VLOFA, mild and gradually progressive disease, and normal reflexes/hyperreflexia [Sharma et al 2004].

Penetrance

Penetrance is complete in those with biallelic full-penetrance GAA repeat expansions and in compound heterozygotes for a full-penetrance GAA expansion in one allele and a *FXN* pathogenic variant in the other allele. However, because of wide variability in the size of pathogenic expanded alleles, and for other unknown reasons, onset can range from before age five years to after age 50 years. This variability in age-dependent penetrance can occasionally occur within the same sibship.

The allele size at the lower end of the pathogenic allele range has not been clearly defined in FRDA. It is possible that incomplete penetrance is associated with borderline alleles and expanded alleles containing fewer than 100 GAA repeats. Individuals with a borderline allele and a full-penetrance allele may develop LOFA/VLOFA. Sharma et al [2004] showed that somatic instability of the borderline allele was required for clinical expression of the FRDA phenotype; and, 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.

Anticipation

Friedreich ataxia (FRDA) is inherited in an autosomal recessive manner; therefore, anticipation is not observed because the disease is typically not observed in more than one generation.

Prevalence

The prevalence of FRDA is 2:100,000-4:100,000. The carrier frequency is 1:60-1:100.

FRDA is the most common 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 the typical and atypical clinical presentations of FRDA discussed in this *GeneReview* are known to be associated with pathogenic variants in *FXN*.

Differential Diagnosis

Peripheral neuropathy

- Friedreich ataxia (FRDA) may be confused with Charcot-Marie-Tooth type 1 (CMT1), a demyelinating peripheral neuropathy, and Charcot-Marie-Tooth type 2 (CMT2), an axonal (non-demyelinating) peripheral neuropathy. Some individuals with CMT present in childhood with clumsiness, areflexia, and minimal distal muscle weakness. In children with FRDA who have not developed dysarthria or extensor plantar responses, the diagnosis of CMT may be difficult to exclude solely on clinical findings. Inheritance of CMT can be autosomal dominant, autosomal recessive, or X-linked. See [CMT Overview](#).
- [Spinocerebellar ataxia with axonal neuropathy](#) (SCAN1) is characterized by ataxia, axonal sensorimotor polyneuropathy, distal muscular atrophy, pes cavus, and steppage gait – signs that may collectively mimic FRDA. SCAN1 is caused by biallelic pathogenic variants in *TDPI*, the gene encoding tyrosyl-DNA phosphodiesterase 1, a topoisomerase I-dependent DNA damage repair enzyme [El-Khamisy et al 2005]. Inheritance is autosomal recessive.

Ataxia

- [Ataxia with vitamin E deficiency](#) (AVED) (caused by biallelic pathogenic variants in *TTPA*, encoding alpha-tocopherol transfer protein), abetalipoproteinemia, or other fat malabsorptive conditions should be considered in individuals with the FRDA phenotype without GAA expansions [Cavalier et al 1998, Hammans & Kennedy 1998]. Most individuals with AVED fulfill the diagnostic criteria for FRDA, although titubation and hyperkinesia are more frequently seen in AVED than in FRDA [Cavalier et al 1998]. The prevalence of cardiomyopathy is much less in those with AVED compared to those with FRDA. It is important to differentiate FRDA from AVED because, unlike FRDA, AVED can be effectively treated with continuous lifelong vitamin E supplementation. Serum concentration of vitamin E and lipid-adjusted vitamin E may also be used to differentiate AVED from FRDA [Feki et al 2002]. Inheritance of *TTPA*-related AVED is autosomal recessive.
- [Ataxia with oculomotor apraxia type 1](#) (AOA1) (oculomotor apraxia and hypoalbuminemia; early-onset cerebellar ataxia with hypoalbuminemia) is characterized by childhood onset of slowly progressive cerebellar ataxia followed by oculomotor apraxia and a severe axonal sensorimotor peripheral neuropathy. The initial manifestation is progressive gait imbalance in childhood (age 2-10 years) that may be associated with chorea. All affected individuals initially have generalized areflexia that is followed later by a peripheral neuropathy. Cognitive impairment may be noted. The clinical phenotype of AOA1 may be highly variable; however, presence of chorea, severe sensorimotor neuropathy, oculomotor anomalies, and cerebellar atrophy on MRI and absence of the Babinski sign can help to distinguish AOA1 from FRDA [Le Ber et al 2003]. AOA1 is associated with biallelic pathogenic variants in *APTX* [Moreira et al 2001]. Inheritance is autosomal recessive. Because of its phenotypic similarities, this condition was initially called FRDA2 when the locus was mapped and before the gene was known [Christodoulou et al 2001].

AOA1 is the most common recessively inherited ataxia in Japan; in Portugal, it is second to FRDA. AOA1 has also been reported with variable frequencies in France, Germany, Italy, Taiwan, Tunisia, and Australia [Le Ber et al 2005].
- [Ataxia with oculomotor apraxia type 2](#) (AOA2) is characterized by ataxia with onset between age ten and 22 years, cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia, choreiform or dystonic movement, and elevated alpha-fetoprotein (AFP) levels [Le Ber et al 2004]. It is caused by biallelic pathogenic variants in *SETX*, the gene encoding probable helicase senataxin [Moreira et al 2004]. Inheritance is autosomal recessive. Among Europeans, AOA2 is the most common non-FRDA autosomal recessive cerebellar ataxia.

Other early-onset ataxias may be distinguishable by virtue of their characteristic clinical features (see also [Ataxia Overview](#)):

- [Ataxia-telangiectasia](#)
- Ataxias associated with pathogenic variants in mitochondrial DNA (see [Mitochondrial Disorders Overview](#))
- Behr syndrome (spasticity, ataxia, optic atrophy, and intellectual disability) (OMIM [210000](#))
- X-linked sideroblastic anemia and ataxia (OMIM [301310](#))
- [Marinesco-Sjögren syndrome](#) (cerebellar ataxia, cataracts, intellectual disability, short stature, and delayed sexual development)
- [Deafness-dystonia-optic neuropathy syndrome](#)
- Late-onset [hexosaminidase A deficiency](#) (ataxia, upper and lower motor neuron disorders, dementia, and psychotic episodes) [Perlman 2002]
- Two autosomal dominant ataxias with sensory neuropathy – spinocerebellar ataxia type 4 (SCA4) [Flanigan et al 1996] and SCA25 [Stevanin et al 2004] – may present with FRDA-like phenotypes (see [Ataxia Overview](#)).

Spasticity. Friedreich ataxia (FRDA) is rare among individuals with uncomplicated (isolated) autosomal recessive spastic paraparesis [Wilkinson et al 2001, Badhwar et al 2004] (see also [Hereditary Spastic Paraplegia Overview](#)). However, autosomal recessive spastic ataxia of Charlevoix-Saguenay ([ARSACS](#)) may present with early-onset ataxia and areflexia, Babinski sign, loss of vibratory sensation, and pes cavus without spasticity [Shimazaki et al 2005].

Multisystem atrophy. VLOFA caused by a shorter GAA expansion allele may mimic multiple-system atrophy of the cerebellar type [Berciano et al 2005].

Huntington disease. Rarely, FRDA can present as a phenocopy of Huntington disease [Wild et al 2008].

Management

Guidelines have been published to assist with management of FRDA [Corben et al 2014] (www.curefa.org).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Friedreich ataxia (FRDA), the following evaluations are recommended, if not performed as part of the evaluation that led to diagnosis:

- Neurologic assessment
- Physical therapy and occupational therapy assessment of strength and balance, need for adaptive aids, and the home and work environment
- Speech and swallowing assessment
- Assessment for significant scoliosis; assessment by an orthopedic surgeon, as needed
- EKG and echocardiogram for evidence of cardiomyopathy; assessment by a cardiologist if abnormal
- Bladder function with referral to a urologist if severe symptoms are present
- Assessment for obstructive sleep apnea and referral for formal assessment and management if present
- Random blood glucose concentration for evidence of diabetes mellitus
- Ophthalmologic assessment if ophthalmologic symptoms are present
- Hearing assessment and referral for amplification apparatus if required
- Psychological assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

There is little objective evidence regarding management of FRDA. A multidisciplinary approach is essential for maximal benefit because FRDA affects multiple organ systems:

- Prostheses, walking aids, wheelchairs, and physical therapy as prescribed by a physiatrist (rehabilitation medicine specialist) to maintain an active lifestyle
- In-patient rehabilitation, which has been shown to improve physical function as measured by the Functional Independence Measure [Milne et al 2012]
- Occupational therapy assessment to ensure a safe home and work environment
- To manage spasticity: physical therapy including stretching programs, standing frame and splints, pharmacologic agents such as baclofen and botulinum toxin. Intrathecal baclofen can be beneficial where oral administration is unsuccessful or side effects are excessive [Berntsson et al 2013]. Orthopedic interventions, both operative and non-operative, for scoliosis [Milbrandt et al 2008] and foot deformities [Delatycki et al 2005] may be necessary.
- Speech therapy to maximize communication skills
- Management of dysphagia that may include dietary modification and, in the late stages of disease, use of nasogastric or gastrostomy feeding
- Treatment of cardiac disease to reduce morbidity and mortality, including antiarrhythmic agents, anticardiac failure medication, anticoagulants, and pacemaker / implantable cardioverter defibrillator insertion [Lynch et al 2012a]. Cardiac transplantation is more controversial but has been used particularly when there is severe cardiac disease in the setting of mild neurologic symptoms [Sedlak et al 2004, Yoon et al 2012, McCormick et al 2017].
- Antispasmodic agents for bladder dysfunction, with some individuals requiring botulinum toxin for the bladder and some requiring intermittent or permanent catheterization
- Treatment of sleep apnea by continuous positive airway pressure
- Treatment of diabetes mellitus with diet and, if necessary, oral hypoglycemic agents or insulin
- Hearing aids, microphone, and receiver as needed [Rance et al 2010] (See also [Hereditary Hearing Loss and Deafness Overview](#).)
- Psychological (counseling and/or pharmacologic) support for affected individuals and family

Prevention of Secondary Manifestations

Measures include the following:

- Active management of spasticity with physiotherapy and botulinum toxin to prevent permanent contracture and the need for surgery
- Treatment of scoliosis with physiotherapy, botulinum toxin, and surgery to prevent cardiopulmonary complications that can result from severe scoliosis
- Treatment of diabetes mellitus to prevent complications that can arise from untreated / inadequately treated diabetes
- Treatment of cardiac complications of FRDA to prevent arrhythmias that can result in mortality
- Treatment of sleep apnea to prevent neurologic and cardiopulmonary complications that can result from untreated sleep apnea

Surveillance

Published clinical management guidelines provide detailed discussion of recommended surveillance [Corben et al 2014, www.curefa.org].

The following are appropriate.

- If EKG and echocardiogram performed at the time of initial diagnosis are normal, annual repeat testing
- Annual fasting blood sugar to monitor for diabetes mellitus
- Hearing assessment every two to three years or more often if symptoms are present. This should include testing of hearing in background noise, as it is more often abnormal than the common audiogram assessed in a quiet environment [Rance et al 2008].
- Sleep study to investigate for obstructive sleep apnea if concerns are raised by clinical history or a screening test such as the Epworth Sleepiness Scale

Agents/Circumstances to Avoid

Alcohol can exacerbate ataxia and should be consumed in moderation. Illicit drugs may well affect neuronal well-being and may exacerbate FRDA and thus should be avoided. Environments that place an ambulant individual at risk for falls (e.g., rough surfaces) should be avoided.

Medications that are toxic or potentially toxic to persons with FRDA comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association [website](#) (pdf) for an up-to-date list of medications that are potentially toxic to persons with CMT or a related neuropathy.

Evaluation of Relatives at Risk

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

Pregnancy Management

Close cardiac monitoring is recommended in any woman with FRDA during pregnancy.

Therapies Under Investigation

A summary of therapies under investigation can be found [online](#).

Deficiency of frataxin results in abnormal accumulation of intramitochondrial iron, defective mitochondrial respiration, and overproduction of oxygen free radicals with evidence of oxidant-induced intracellular damage (see Molecular Genetics).

Antioxidant therapy by free radical scavengers (coenzyme Q₁₀, vitamin E, and idebenone, a short-chain analog of coenzyme Q₁₀) and chelation therapy have been considered potential treatments for slowing the progression of FRDA.

Antioxidant Therapy

Coenzyme Q₁₀ and vitamin E

- Following three to six months' antioxidant treatment with coenzyme Q₁₀ and vitamin E, Lodi et al [2001] showed improved ATP production in the heart and skeletal muscle of individuals with FRDA. An open-label trial of these agents in ten individuals for 47 months resulted in sustained improvement in bioenergetics and improved cardiac function, as assessed by increased fractional shortening [Hart et al 2005].
- A study that compared low-dose coenzyme Q₁₀ (30 mg/day) to high-dose coenzyme Q₁₀ (600 mg/day) and vitamin E (2,100 IU/day) over two years found no difference in the change in International Cooperative Ataxia Rating Scale (ICARS) score between the two groups [Cooper et al 2008]. A significant proportion of individuals with FRDA had low serum coenzyme Q₁₀ levels.

Idebenone has shown promise as a treatment for FRDA:

- A reduction in left ventricular hypertrophy has been found in some studies [Hausse et al 2002, Buyse et al 2003, Mariotti et al 2003] but not in others [Lagedrost et al 2011].
- A Phase II clinical trial of three doses of idebenone (5, 15, and 45 mg/kg) compared to placebo suggested a dose-related neurologic benefit as measured by the ICARS [Di Prospero et al 2007]. However, no significant neurologic benefit was shown in a Phase III study of idebenone conducted on 70 individuals with FRDA age eight to 18 years [Lynch et al 2010].
- The results of another Phase III study from Europe are expected to be published shortly.

A0001 (α -tocopheryl quinone) is an antioxidant with superior bioavailability to idebenone. It showed promise in a small one-month placebo-controlled study [Lynch et al 2012b].

EPI-743. A0001 is no longer being developed but a related compound, EPI-743, is being evaluated in placebo-controlled studies in adults and children with FRDA. Results from this study have not yet been published.

Chelation Therapy

Iron chelators have been proposed as a possible therapy for lowering the intramitochondrial iron overload. Nonspecific iron chelators (e.g., desferrioxamine) for the specific reduction of mitochondrial iron overload may not be effective; a clinical trial was terminated for lack of efficacy.

The oral iron chelator deferiprone showed promise as a treatment for FRDA in an open-label study [Boddaert et al 2007]. Iron in the cerebellar dentate nucleus was reduced as measured by MRI; neurologic benefit was suggested. However, a Phase II placebo-controlled study of deferiprone demonstrated worsening of ataxia in those treated with 40 mg/kg/day with reduced left ventricular mass index in those on 20 and 40 mg/kg/day [Pandolfo et al 2014].

An 11-month open-labeled study of combined low-dose deferiprone and low-dose idebenone (both given at 20 mg/kg/day) found a significant reduction in intraventricular septum thickness and left ventricular mass index over the course of the study [Velasco-Sánchez et al 2011]. Although there was no significant change in the International Cooperative Ataxia Rating Scale score, some subscale scores showed significant increases and others showed significant decreases over the course of the study.

Desferrioxamine along with pyridoxal isonicotinoyl hydrazone, a mitochondrial permeable ligand, limited cardiac hypertrophy in a conditional *Fxn* knockout mouse model [Whitnall et al 2008].

Increasing Frataxin Levels

Because the abnormal GAA repeat expansion results in reduced quantities of normal *FXN* transcript and frataxin protein, a number of studies have been conducted to identify compounds that increase their levels. This is achieved mainly by increasing *FXN* expression and stabilizing the *FXN* transcript and frataxin protein. In some cases the exact mechanism underlying the increase in frataxin levels is not yet understood. Agents that have been found to increase frataxin levels in cellular models include hemin, butyric acid [Sarsero et al 2003], and erythropoietin [Sturm et al 2005].

- An open-label study of erythropoietin resulted in increased frataxin levels and significant decrease in the levels of urinary 8-hydroxydeoxyguanosine and serum peroxides, which are markers of oxidative stress [Boesch et al 2007].
- An in vitro study showed that carbamylated erythropoietin, which does not bind to the erythropoietin receptor and therefore is non-erythropoietic, increased frataxin to levels similar to native erythropoietin [Sturm et al 2010]. A Phase II study of carbamylated erythropoietin did not identify any clinical benefit nor evidence of increase in frataxin levels after 43 days' treatment [Boesch et al 2014].
- A small six-month placebo-controlled study of erythropoietin did not identify any biochemical or clinical benefit of treatment [Mariotti et al 2012].

- A placebo-controlled study of epoetin alfa did not identify benefit for peak oxygen uptake in an exercise test, frataxin levels nor neurologic outcomes [Saccà et al 2016].

Specific histone deacetylase (HDAC) inhibitors show much promise as treatments for FRDA through upregulation of *FXN* expression [Herman et al 2006, Libri et al 2014, Soragni et al 2014]. A Phase I human trial of RG2833, a class I HDAC inhibitor molecule that is known to reverse the epigenetic silencing in FRDA [Soragni et al 2014, Chutake et al 2016], was shown to be well tolerated and resulted in increased production of *FXN* transcript in vivo [Soragni et al 2014]. Nicotinamide (vitamin B₃), a class III HDAC inhibitor, was shown to increase frataxin expression in FRDA cell and mouse models [Chan et al 2013]. An open-label dose escalation study of nicotinimide in FRDA showed a dose-dependent increase in *FXN* transcript and protein, achieving levels seen in asymptomatic carriers [Libri et al 2014]. However, no changes were observed in clinical measures in this short eight-week trial.

Interferon gamma was found to upregulate frataxin in cell and mouse models of FRDA [Tomassini et al 2012]. It also prevents pathologic changes in dorsal root ganglia and improves motor performance in a FRDA mouse model. An open-label study of interferon gamma showed evidence of neurologic improvement as assessed by FARS score, without any increase in frataxin levels [Seyer et al 2015]. A placebo-controlled study was subsequently performed and failed to meet its primary end point [Author, personal communication].

Resveratrol has also been shown to upregulate frataxin expression in vitro and in vivo [Li et al 2013]. An open-label study of 1 g/day and 5 g/day of resveratrol for three months did not result in increased lymphocyte frataxin levels [Yiu et al 2015]. Those on 5 g/day had significant improvement in a number of neurologic tests and in the oxidative stress marker F2-isoprostanes. A placebo-controlled study is to commence shortly.

Other Therapies

Varenicline, an agent used to assist with smoking cessation, was identified as a possible therapy for ataxia [Zesiewicz et al 2009]; however, a Phase II study was prematurely terminated because of concerns about safety and tolerability of the drug.

PPAR gamma agonists have been suggested as therapies for FRDA because they increase frataxin levels in vitro [Marmolino et al 2009] and improve antioxidant responses [Marmolino et al 2010]. A Phase II study of one PPAR gamma agonist, pioglitazone, is under way.

An open-label study of thiamine (vitamin B₁) in 34 individuals with FRDA (100 mg intramuscular 2x/week for between 80 and 930 days) revealed improvement of neurologic symptoms as measured by SARA, reappearance of deep tendon reflexes in 57%, and reduction in intraventricular septal thickness [Costantini et al 2016].

Gene therapy to supplement the loss of function of frataxin is also under consideration. The cardiomyopathy of a conditional cardiac *FXN* deletion mouse model was both prevented and reversed by intravenous *FXN* delivered by an adeno-associated virus vector [Perdomini et al 2014].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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 obligate heterozygotes (i.e., carriers of an *FXN* pathogenic variant).
- Depending on the pathogenic variants present in the proband, each parent may have one of the following:
 - A pathogenic expanded allele (i.e., a GAA trinucleotide repeat allele that is in the disease-causing range)
 - Another deleterious *FXN* pathogenic variant
 - A premutation allele (i.e., a GAA trinucleotide repeat allele that is predisposed to expand into the abnormal range)
- Carriers (heterozygotes) of one *FXN* pathogenic variant are asymptomatic.
- Note: Carriers of premutation alleles are rare and, although their exact prevalence is unknown, they are far less common than carriers of pathogenic expanded alleles. Consequently, expansion of premutation alleles as a means of transmitting FRDA is very unusual.

Sibs of a proband

- If both parents carry a full-penetrance allele, or one parent carries a full-penetrance allele and the other parent carries another pathogenic *FXN* variant,
 - At conception, each sib has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
 - If an adult at-risk sib is unaffected, the statistical risk of the sib being a carrier is 2/3. However, the wide range in age of onset and variable intergenerational instability of the GAA expansion dictate the use of caution in diagnosing an at-risk sib as unaffected based on clinical findings alone (i.e., without using molecular genetic testing).
- When one parent carries a full-penetrance allele or another pathogenic *FXN* variant and the other parent carries a premutation allele, sibs have a less-than-25% chance of being affected.

Offspring of a proband

- All offspring inherit one pathogenic *FXN* allele from the affected parent.
- Offspring have a 50% chance of being affected only if the reproductive partner of the proband is a carrier of a full-penetrance allele or another pathogenic *FXN* variant.
- If the reproductive partner of the proband carries a premutation allele, the risk to each offspring of developing FRDA is less than 50%.
- If the reproductive partner of the proband does not carry an expanded *FXN* allele, the risk to each offspring of developing FRDA is very low but not zero because of the possibility of the presence of another *FXN* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *FXN* pathogenic variants in the family.

Carrier testing is possible for individuals whose reproductive partner is a known carrier of a *FXN* pathogenic variant.

Note: Carriers of one FRDA-causing variant of *FXN* are not at risk of developing this autosomal recessive disorder.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *FXN* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for FRDA and preimplantation genetic testing are possible.

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](#).

- **Friedreich Ataxia Research Association (Australasia)**
179 Queen Street
Level 6
Melbourne Victoria 3000
Australia
Phone: 03 9867 1910
Email: varlli@fara.org.au
www.fara.org.au
- **Friedreich's Ataxia Research Alliance (FARA)**
Phone: 484-879-6160
Fax: 484-872-1402
Email: info@CureFA.org
CureFA.org
- **MedlinePlus**
[Friedreich's Ataxia](#)
- **National Library of Medicine Genetics Home Reference**
[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

www.ataxia.org.uk

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**

United Kingdom

Email: lporter@ataxia.org.uk

www.euroataxia.org

- **Muscular Dystrophy Association (MDA) - USA**

Phone: 833-275-6321

www.mda.org

- **National Ataxia Foundation**

Phone: 763-553-0020

Fax: 763-553-0167

Email: naf@ataxia.org

www.ataxia.org

- **Spanish Ataxia Federation (FEDAES)**

Spain

Phone: 34 983 278 029; 34 985 097 152; 34 634 597 503

Email: sede.valladolid@fedaes.org; sede.gijon@fedaes.org; sede.bilbao@fedaes.org

fedaes.org

- **CoRDS Registry**

Sanford Research

Phone: 605-312-6300

CoRDS Registry

- **European Friedreich's Ataxia Consortium for Translation Studies (EFACTS) Patient Registry**

Germany

EFACTS Patient Registry

- **Friedreich's Ataxia Research Alliance Patient Registry**

Friedreich's Ataxia Research Alliance

533 West Uwchlan Avenue

Downingtown PA 19335

Phone: 484-879-6160

Fax: 484-872-1402

Email: info@CureFA.org

Friedreich's Ataxia Research Alliance 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
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Table A. continued from previous page.

FXN	9q21.11	Frataxin, mitochondrial	FXN database	FXN	FXN
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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

Gene structure. *FXN* encodes frataxin via a major transcript ([NM_000144.4](#)) composed of five coding exons (1-5a) [Campuzano et al 1996]. Minor transcripts, produced via alternate splicing with two other exons (5b and 6), have been detected, but their role(s) remain unknown. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. The most relevant variability in normal *FXN* alleles is the length of the GAA repeat sequence in intron 1 (see Establishing the Diagnosis, **Allele sizes**).

Pathogenic variants. Inactivating pathogenic variants in *FXN* are essentially of three types: the GAA repeat expansion, nonsense or frameshift variants resulting in aberrant or premature termination of translation, and loss-of-function missense and splicing variants. Rare affected individuals have been identified with one allele having either a large intragenic deletion or whole-gene deletion of *FXN* and the second allele with a full-penetrance expanded GAA repeat [Zühlke et al 2004, Anheim et al 2012, Hoffman-Zacharska et al 2016]. See Establishing the Diagnosis for explanation of the four classes of GAA repeats.

Note that interpretation of the pathogenicity of expanded alleles may be complicated by the possibility that the size of the expanded GAA trinucleotide repeat in leukocytes may not necessarily be the same as that in pathologically relevant tissues such as the dorsal root ganglia and heart. Some differences in allele lengths were noted between different tissues in a study involving six autopsies; however, larger studies will be needed to uncover any consistent correlation between GAA repeat sizes in blood versus pathologically affected tissues [De Biase et al 2007].

Normal gene product. *FXN* encodes frataxin, a 210-amino acid protein ([NP_000135.2](#)) that is predominantly located in the mitochondria. The carboxy-terminal region of frataxin is highly conserved in evolution and is a target for pathogenic missense variants. The tissues primarily affected in FRDA are known to express high levels of frataxin. Frataxin binds iron and is required for the synthesis of iron-sulfur clusters and, thereby, for the synthesis of enzymes in the respiratory chain complexes I–III and aconitase.

Abnormal gene product. All pathogenic variants (i.e., GAA repeat expansion, nonsense or frameshift variants resulting in aberrant or premature termination of translation, and loss-of-function missense variants) result in loss of frataxin function. The latter two classes of pathogenic variant result either in deficiency of frataxin levels or in functional deficiency of frataxin despite normal levels. The expanded GAA repeat results in transcriptional silencing of *FXN* via at least two mechanisms:

- Epigenetic silencing via repressive chromatin formation in the sequence flanking the expanded GAA repeat and near the *FXN* promoter and transcription start site, which interfere 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 structures, which interferes with transcriptional elongation [Bidichandani et al 1998, Ohshima et al 1998, Grabczyk & Usdin 2000, Sakamoto et al 2001]

These pathogenic mechanisms result in deficiency of *FXN* transcript levels and ultimately in deficiency of frataxin protein. Frataxin deficiency results in secondary deficiency of iron-sulfur cluster-containing enzymes,

mislocalization of cellular iron, and increased sensitivity to oxidative stress. Together these result in impaired mitochondrial respiratory function and increased oxidative stress. Indeed, the deficiency of frataxin is directly proportional to the length of the expanded GAA repeat [Pianese et al 2004; Chutake et al 2014b], which is the molecular basis for the correlation of repeat length with disease severity and rate of progression.

Chapter Notes

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