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Patients featured are paid spokespersons for Biogen.

A resource for exploring the pathology, clinical manifestations, and diagnostic considerations for Friedreich ataxia (FA)

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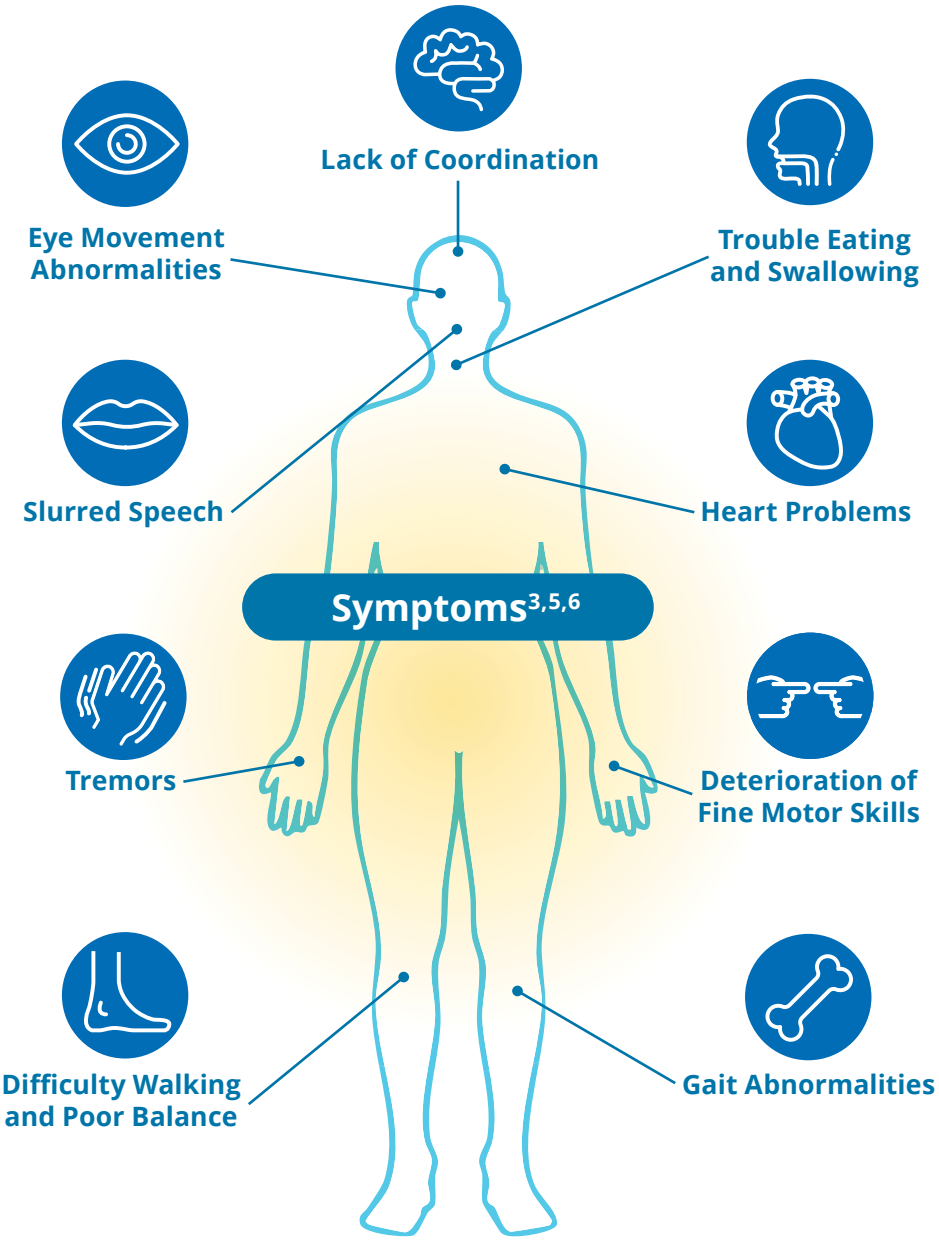
Common presenting characteristics of ataxia are issues with muscle control, coordination, and gait[1,2]

Ataxia symptoms are caused by cerebellar, vestibular, or proprioceptive sensory dysfunction[3,4]

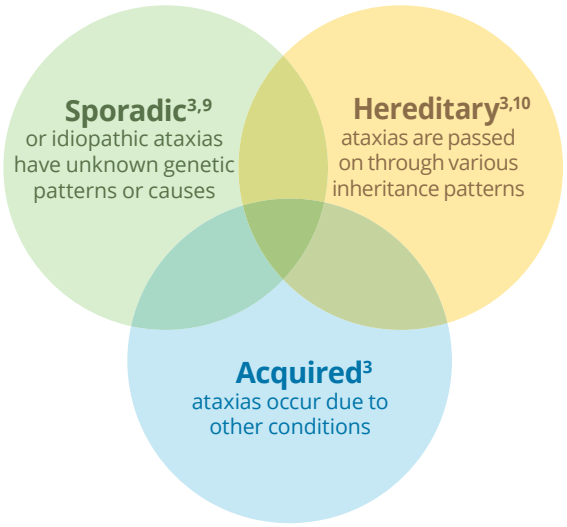
Dysfunction in the nervous system may affect muscle control in the arms and legs, leading to balance and coordination issues.[3,4]

Depending on the type of ataxia, patients may experience a wide range of symptoms or a single stand-alone symptom.[3] Symptoms that may be present in patients with ataxia include:



Ataxias may be acquired, but etiology is commonly genetic[7,8]

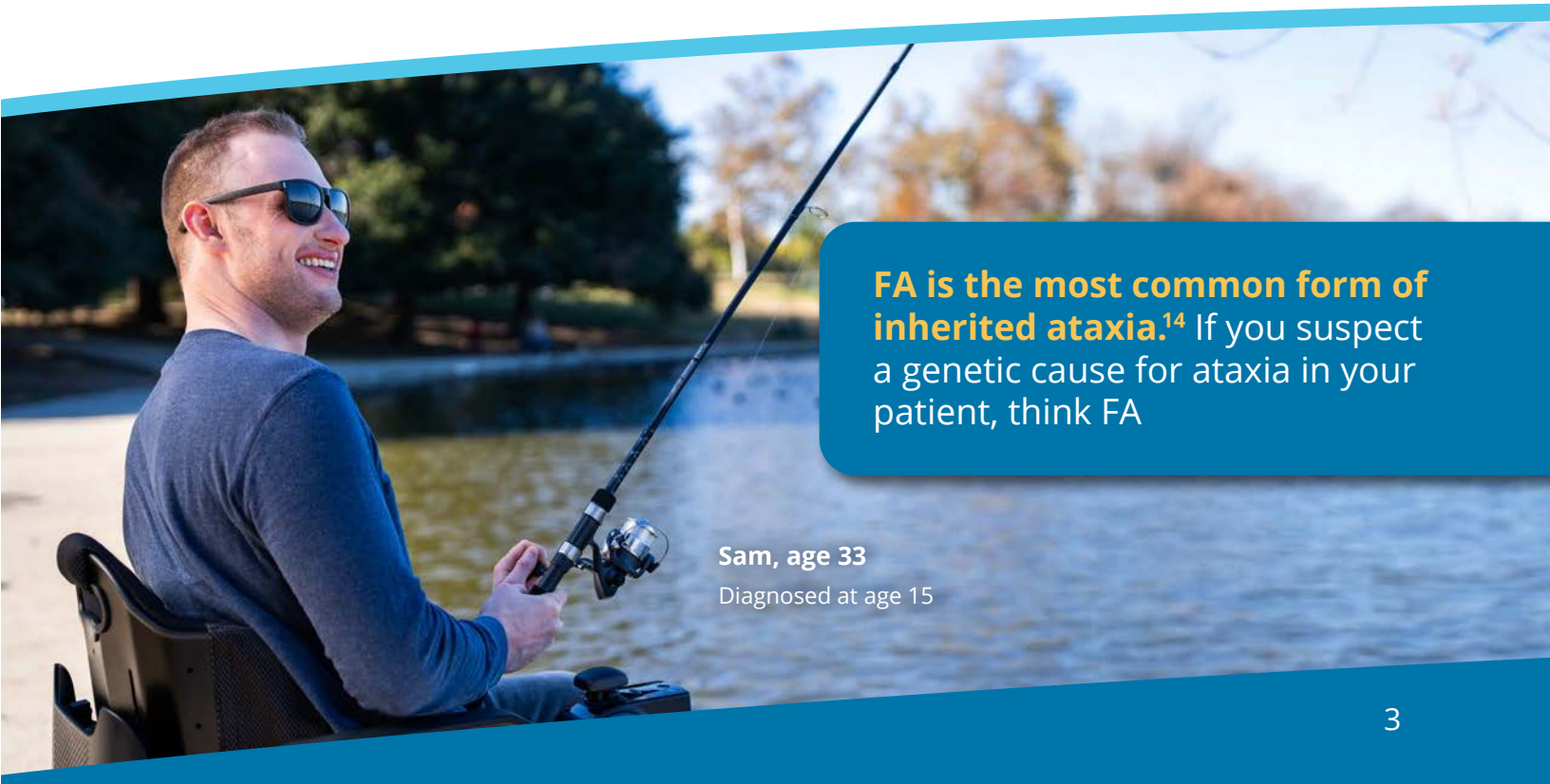
Ataxias can be broadly categorized as acquired, genetic, or sporadic[3]



Among hereditary ataxias, there are 4 primary modes of inheritance[11]:

- Autosomal dominant
- Autosomal recessive
- X-linked
- Maternal mitochondrial inheritance

- Acquired ataxias may be caused by physical changes in the brain due to complications from a tumor or stroke. They could also be the result of prolonged exposure to environmental toxins[9]
  - Diagnostic testing or blood and urine testing may help rule out possible acquired ataxia[9,12]
- Sporadic or idiopathic ataxias have unknown genetic patterns or causes[3,9]
- Hereditary ataxias, like FA, are inherited from the patient's parents. There are several potential inheritance patterns, characteristic of specific genetic ataxias, that may help narrow down the cause of the ataxia[13]



FA is the most common form of inherited ataxia.[14] If you suspect a genetic cause for ataxia in your patient, think FA

Sam, age 33
Diagnosed at age 15

Friedreich ataxia (FA) is a progressive, incapacitating neurodegenerative disease[15]

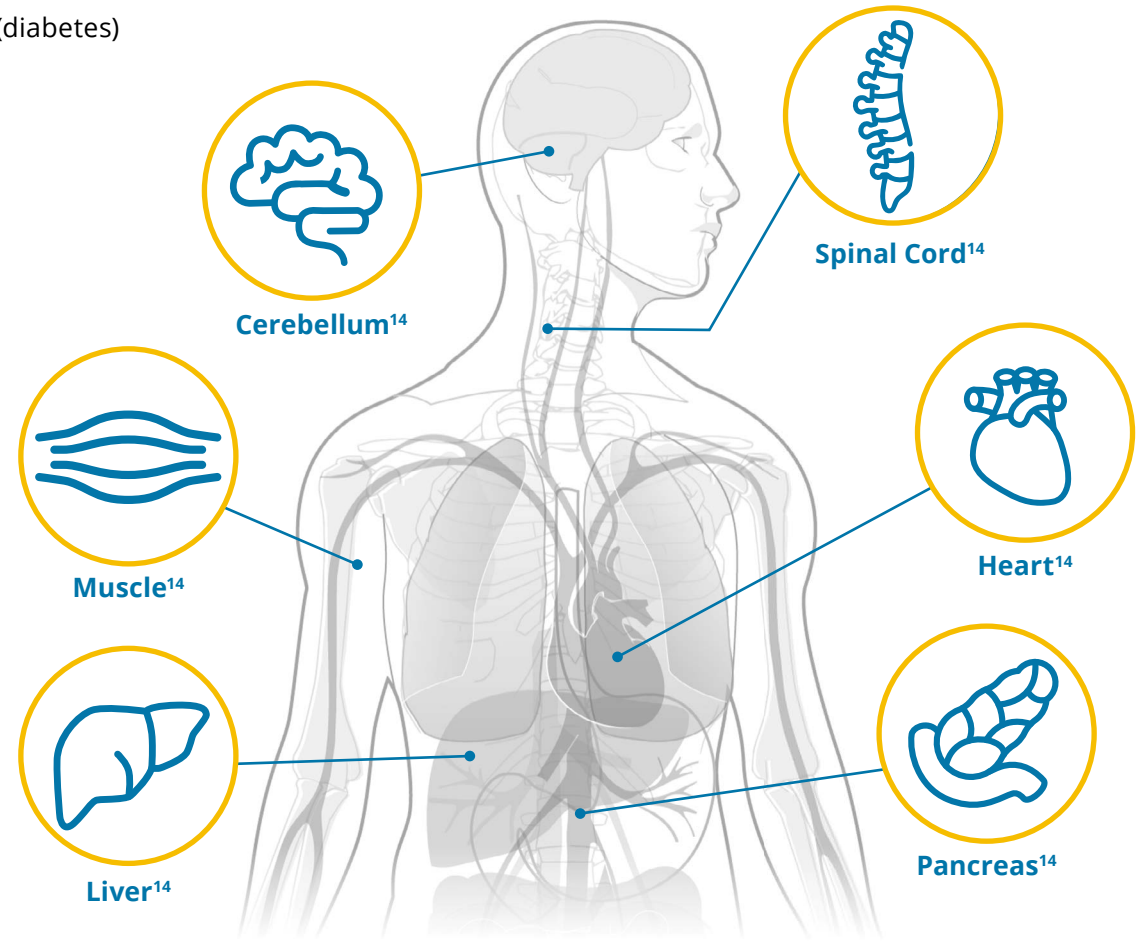
As the most common form of inherited ataxia, FA affects approximately 5000 or more people in the United States.[14,16]

FA is caused by a mutation in the frataxin (*FXN*) gene, which results in impaired mitochondrial function and subsequent neurodegeneration[14]

Frataxin protein is found throughout the body but is highly expressed in many critical organs.[17]

Symptoms of FA occur in **organs with high frataxin expression**, such as the[14,18]:

- Nervous system (ataxia, dysarthria)
- Heart (cardiomyopathy)
- Pancreas (diabetes)



Visit ThinkFA.com for an in-depth video on the mechanism of disease for FA

FA is a multisystem disorder that presents with a wide range of symptoms[2]

The initial symptoms of FA may vary for each patient.[2]

When you see any single symptom or a combination of these symptoms, think FA FIRST[2,15,19,20]:

Falls (gait ataxia)

- Clumsiness, dizziness, or trouble playing sports
- Ataxia can also result in difficulty with handwriting, getting dressed, or carrying items

Imbalance (poor proprioception)

- Inability to walk steadily
- Dependence on walking aids (furniture, walls, people, crutches, canes, walkers)

Reflex loss (areflexia)

- Absence of deep tendon response
- Loss of reflexes in the lower limbs is present in almost all patients

Sensation loss (neuropathy)

- Inability to sense vibration and joint position
- Estimates of vibrational sensation loss vary from 73% to 88%

Tiredness (fatigue)

- Exhaustion with regular or extended physical activity
- Weakness becomes more severe in the later stages of FA

Additional signs that may be present throughout the course of disease:

Cardiomyopathy may be present in younger patients with more severe FA[2]

Loss of bulbar function may result in slurred speech and increased difficulty swallowing[2,21]

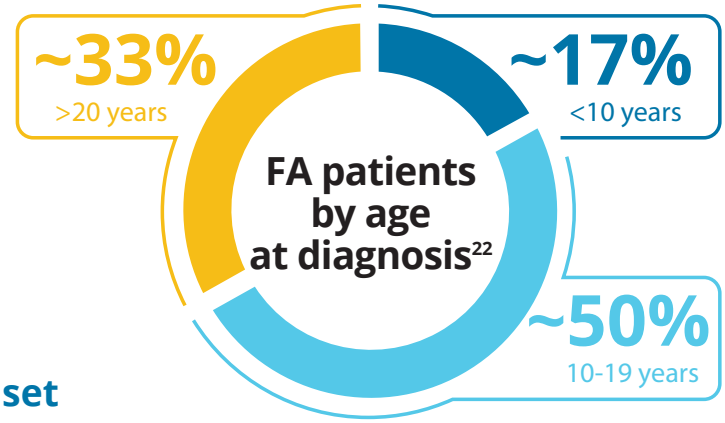
Scoliosis may be an initial indicator of FA when accompanied by imbalance or other neurological signs[2]

Symptom onset for Friedreich ataxia (FA) can occur at nearly any age[2]

Signs of FA typically appear between the ages of 10 and 15 years, but about one-third of patients with FA are diagnosed in adulthood[2,22]

Patient age at symptom onset strongly correlates with FA severity[23]:

- Patients who experience symptom onset at a younger age generally have more rapid disease progression, often resulting in loss of ambulation[23]
- Later-onset FA patients often have similar symptoms, but severity may vary, including retaining ambulation abilities[24]



Patients who experience symptom onset later in life may present with atypical symptoms

Patients who experience an onset of symptoms after age 25 may have symptoms outside the traditional profile of FA.[25] Atypical symptoms may include spasticity, retained reflexes, chorea, and/or severe optic atrophy.[26,27]

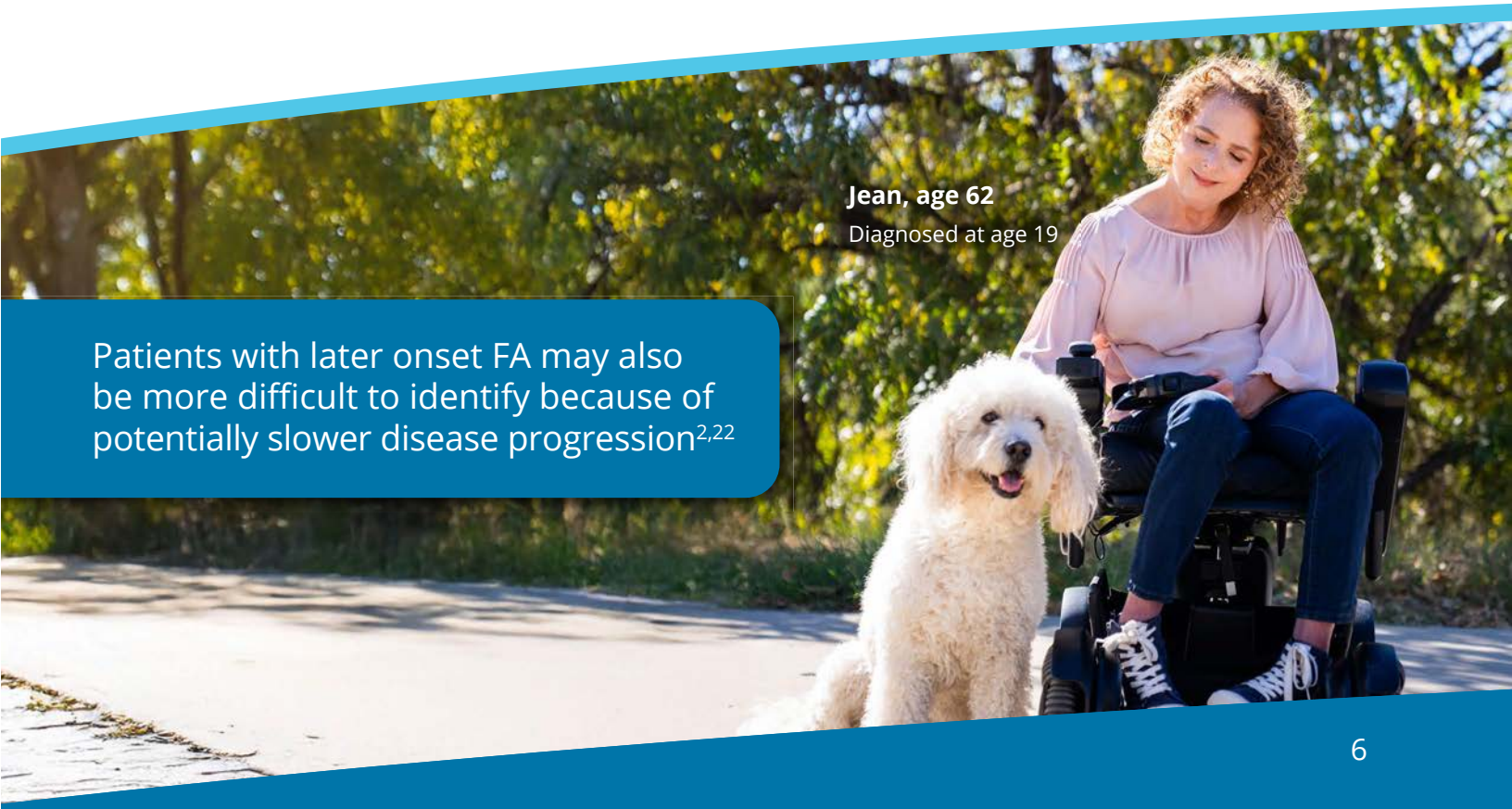

Later onset (>20 years)


Spasticity


Retained reflexes


Chorea

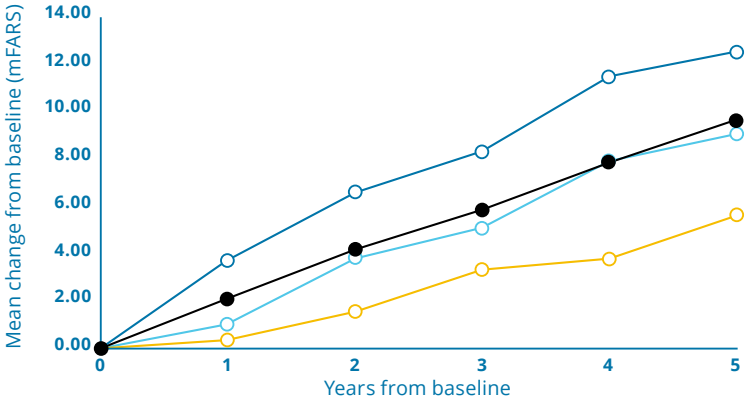

Severe optic atrophy



Patients with later onset FA may also be more difficult to identify because of potentially slower disease progression[2,22]

Symptoms of FA are progressive and irreversible, regardless of age of onset[15,28]

Typical disease progression by age group[28]



○ Subjects <16 years old* ○ Subjects 16-40 years old*

○ Subjects >40 years old* ● Overall cohort (n=812)*

*Noted ages or sample size are at baseline.

The Friedreich Ataxia Clinical Outcome Measures Study (FA-COMS), a natural history study following patients with FA longitudinally, found that patients across every age group progress over time.[28]

Worsening of disease progression over time may reflect loss of function that could affect everyday tasks such as[28]:

- Walking
- Brushing teeth
- Getting dressed
- Eating
- Putting on socks/shoes
- Turning a doorknob
- Taking a shower
- Communicating clearly

The longer it takes to diagnose FA, the more the disease is likely to have progressed[28]

Time is function for patients with FA

While each person's experience is unique, every patient with FA progresses down a neurodegenerative path toward loss of ambulation.[29]

FA symptoms become apparent
Falls, clumsiness, feeling unbalanced, loss of sensation, fatigue[2,19,20]

Lower limb coordination
declines and mobility aids such as canes or walkers may be useful[2]

Speech starts to sound slurred
as bulbar function becomes more affected[2]

Hands and arms
become less coordinated[2]

Many patients require the use of a wheelchair
10 to 15 years after onset of symptoms[2]

Diabetes and/or cardiomyopathy
may develop or worsen over time[2,15]

Shortened life expectancy
to 37.5 years on average, although later-onset patients may live longer[2]

As many as 1 in 4 patients with Friedreich ataxia (FA) have been misdiagnosed[22]

Early symptoms of FA often overlap with other similar ataxias and neurological disorders

Because FA typically presents with nonspecific symptoms such as balance and coordination disturbances, diagnostic delay or misdiagnosis may occur.[22,26]

Inherited ataxias that may have symptoms that overlap with symptoms of FA include[2,30]:

- Spinocerebellar ataxia (SCA), ICD-10 codes G11.2 and G11.8
- Ataxia-telangiectasia, ICD-10 code G11.3
- Unspecified ataxia, ICD-10 codes G11.9 and G11.10

Any patient with a G11 diagnostic code can be considered for genetic testing to identify FA

FA may also overlap with other neurological conditions and neuropathies

Feature	Friedreich ataxia[14,15,30] (ICD-10 G11.11)	Multiple sclerosis[30-34] (ICD-10 G35)	Charcot-Marie-Tooth disease[30,35-37] (ICD-10 G60)	Cerebral palsy[30,38-43] (ICD-10 G80)
Age of onset	**~10 to 15 years (range: ~2 to >50 years)**	20 to 40 years	~5 to 25 years	<1 year
Brain atrophy	**Cerebellar**	Frequent	Rare or absent	Atypical (<10% cerebellar)
Pyramidal signs	**Frequent**	Present	Present	Frequent
Peripheral neuropathy	**Present (sensory axonal)**	May be present	Frequent	Atypical
Cardiomyopathy	**Present**	Not present	Absent	Absent
Associated gene(s)	**Frataxin (*FXN*)**	Unconfirmed	Polygenic	Polygenic (14% of cases)

Genetic testing is the only way to confirm an FA diagnosis[44]

When diagnosing patients who present with symptoms of ataxia or re-engaging patients who may have been misdiagnosed, ordering a genetic test should be considered once acquired ataxia has been ruled out.[9]

Determine the cause of ataxia: acquired, genetic, or sporadic[10]

- Common ataxia symptoms
- **FIRST** symptoms for FA

Age of onset (young, old)[1,9]
Rate of progression (fast, slow)[9,12]
Family history[2]

- Younger age of onset is likely to have classic FA symptoms[2]
- Atypical symptoms in older age of onset[2]

Blood tests[9,12]
Urine studies[9,12]
Diagnostic imaging[9,12]

- MRI reveals cervical spinal cord atrophy[15]
- Electrophysiological tests appear abnormal[15]
- Nerve conduction studies indicate sensory loss[15]

Multi- or single-gene testing[44,45]

- Test must include a GAA triplet-repeat expansion analysis to detect FA

Ordering the right genetic test is key to clarifying clinical and diagnostic evaluations[44]

Genetic testing should be considered for any patient suspected of having FA[5]

FA is caused by a variant within the *FXN* gene called a GAA triplet-repeat expansion.[46] Nearly all cases (96%) are caused by this variant in both alleles, while about 4% are attributable to a second *FXN* mutation.[46] A genetic test that includes a GAA triplet-repeat expansion analysis is the only way to confirm an FA diagnosis.[44]

Two primary genetic testing approaches for FA include[45]:

Multigene panel—these tests search for multiple genes simultaneously. These are commonly used when patients have various symptoms that could result from different genetic conditions.[45]

A broad-panel genetic test that uses whole-exome or next-generation sequencing may not detect GAA triplet-repeat expansions.[47]

Single-gene test—these tests look for gene changes in a specific gene and are most often used when a specific gene is the known cause of a disorder.[45] Family members of a patient are likely to use this test.

! Double-check your test

Whether you use a multi- or single-gene test, confirm that the test includes a GAA repeat-expansion analysis, which may be denoted by the CPT code 81284.[44,48]

Additional testing may be needed when only one allele is expanded

In rare cases (~4%), your patient may only have one expanded allele, sometimes denoted in reports as "inconclusive" status. An additional sequencing test is recommended to determine if this patient has a second *FXN* mutation in the other allele (CPT code 81286).[45,48]

This additional step of sequencing the *FXN* gene can often be missed when diagnosing patients with FA. **If your patient is symptomatic but GAA triplet-repeat expansion testing only shows one expansion, consider ordering an *FXN* sequencing test to definitively rule out or confirm FA.**[45]

Christian, age 26
Diagnosed at age 9

No-cost genetic testing may be available for your patients

Eligible patients who are suspected of having FA may qualify for **no-cost genetic testing** through FA Identified, a program sponsored by Biogen and offered through PreventionGenetics. Your patients may be eligible if they meet the following criteria:

- Suspected of having or have a clinical diagnosis of FA
- Aged 16 years old or older
- Reside in the United States or Puerto Rico

The FA Identified program includes:

- Multiple testing and screening options
- Easy ordering of kits and DNA collection methods
- Results within ~3 weeks of testing, with expedited testing available

Specimen collection kits are provided along with a test requisition form. Simply complete the form and send it along with the collected specimen to PreventionGenetics for testing.

While Biogen provides financial support for these programs, at no time does Biogen receive identifiable patient information.

Learn more about the FA Identified genetic testing program at **FAidentified.com**.

Tricia, age 44
Diagnosed at age 29

When ataxia symptoms are present, think FA, the most common form of inherited ataxia[2]

1. Friedreich ataxia (FA) is a **progressive neurodegenerative** form of ataxia. Disease progression is **irreversible**, making it crucial to identify and address symptoms early.[15]

2. FA is a multisystem disease and **clinical manifestations** can **vary widely**.[2,19,20] FA most frequently presents in late childhood, but symptoms can emerge in adulthood for **late-onset patients**.[2]

3. **One in 4** patients with FA are **misdiagnosed**, often with other hereditary ataxias, but also with conditions like multiple sclerosis or Charcot-Marie-Tooth disease.[22,49]

4. **Genetic testing** should be considered for anyone suspected of having FA.[5] It's important to select a test containing a **GAA triplet-repeat expansion analysis**.[44]

Learn more about identifying and diagnosing patients with FA at ThinkFA.com

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