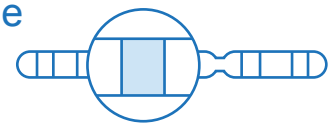
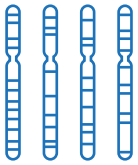
Friedreich ataxia (FA) is a progressive neurodegenerative disease resulting from frataxin deficiency with clinical manifestations in multiple organs[1,2]

FA is the **most common recessively inherited ataxia**.[2] Around 5,000 people in the US have FA.[1]

5,000

FA is caused by a **mutation in the *FXN* gene**, which encodes the protein **frataxin**.[3,4] **Genetic testing** to identify GAA trinucleotide repeat expansion in *FXN* can **confirm a diagnosis** of FA.[5]



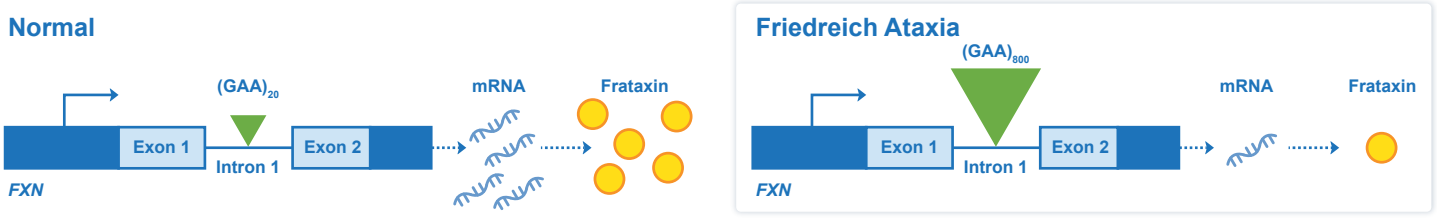


FA is caused by an **expansion of GAA repeats** in the first intron of *FXN* on chromosome 9.[6]

FA is an **autosomal recessive** disease—it requires mutations in both copies of *FXN* for onset.[6]

GAA repeat expansion results in **reduced *FXN* mRNA** and, subsequently, **reduced frataxin protein.**[3]

Molecular Basis of FA[7]



FA is a neurological disorder with multisystem manifestations. It is characterized by **slowly progressive ataxia** and **onset before age 25**.[8,9]

ONSET BEFORE AGE 25

Most frequent **neurological signs**[2]:

- Ataxia/gait abnormality
- Dysmetria of arms and legs
- Dysarthria
- Atrophy and weakness of distal extremities
- Absence of muscle stretch reflexes

Other signs **(comorbidities)** that accompany ataxia[2]:

- Scoliosis and foot deformity (pes cavus)
- Cardiomyopathy
- Diabetes mellitus (delayed in the course of the illness)

Progression is variable and life shortening

- Mean (SD) age of onset is 15.5 ± 8 years[8]
- 11-15 years from symptom onset to wheelchair dependence[8]
- Progression is more rapid with younger onset[8]
- Average life expectancy: 40–50 years[10]

Most **common causes** of death[8]:

- Cardiac complications (~60% of deaths)
- Pneumonia
- Aspiration
- Diabetic coma
- Stroke
- Trauma sequelae

Frataxin is required for the **mitochondrial synthesis** of iron-sulfur clusters (ISCs), which are critical to the functions of various proteins.[4,11]

Frataxin deficiency

↓

Dysfunction of ISC-containing proteins

Dysfunction of **electron transport** chain proteins[11,12] + **Iron overload** in mitochondria[11,13]

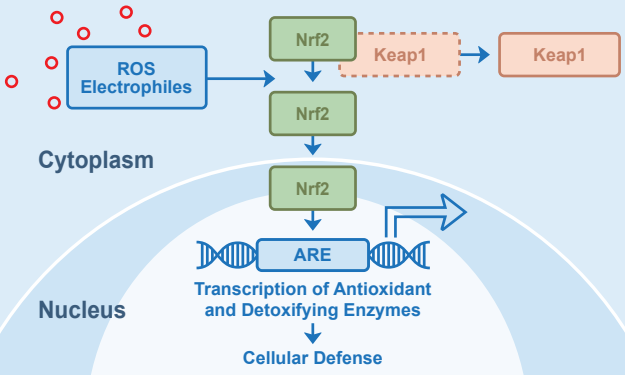
↓

Mitochondrial dysfunction[11,12] | Reduced ATP production[11,12] | **Increased ROS production** → **Oxidative Stress**[11,13]

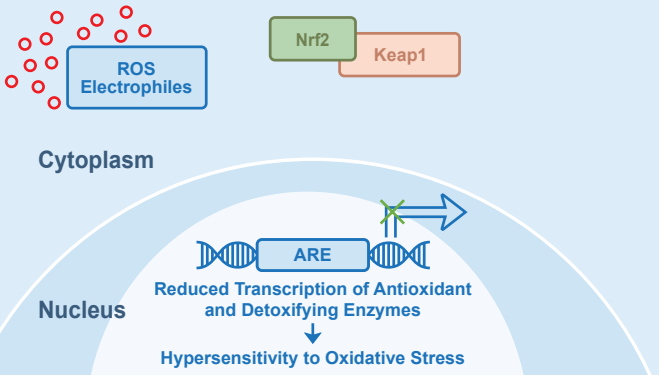
+

The **Nrf2 Antioxidant Pathway**, which ordinarily regulates the expression of genes involved in cellular antioxidant response, **is impaired in FA**[11,13-15]

Basal Conditions[14,15]



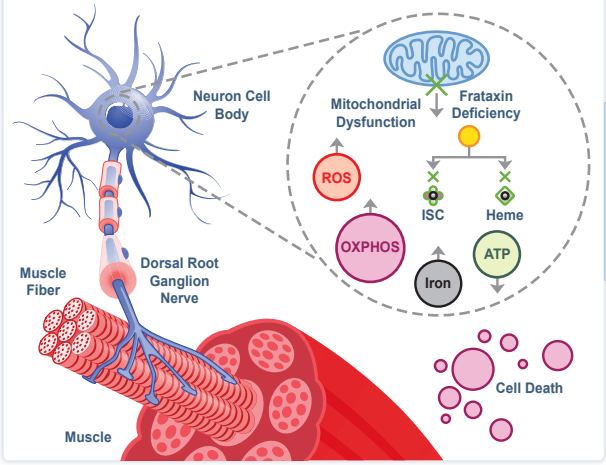
FA[14,15]



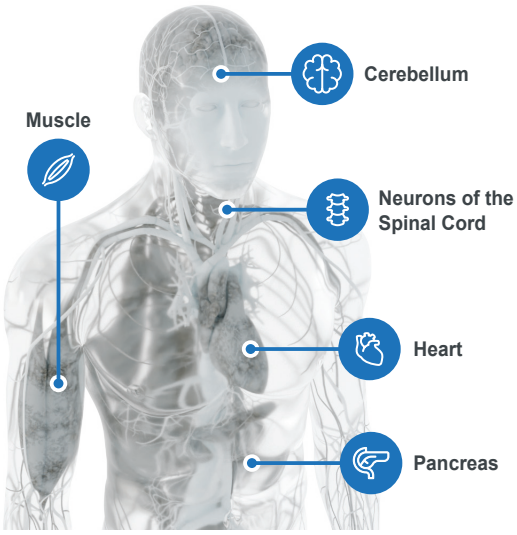
Disregulation in antioxidant defenses + frataxin deficiency → oxidative stress and FA pathology[11–13]

Increased ROS → severe oxidative stress → damage to proteins, DNA, and lipid membranes[4]

These effects ultimately lead to cellular degeneration and cell death[4,12,13]



Culminating in injury to tissues, especially those with a high metabolic rate[17]



ARE, antioxidant response element; ATP, adenosine triphosphate; DNA, deoxyribose nucleic acid; FA, Friedreich Ataxia; GAA, guanine adenine adenine; ISC, iron-sulfur cluster; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; SD, standard deviation.

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