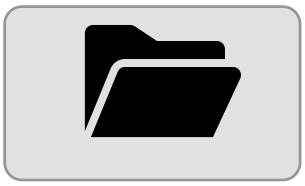
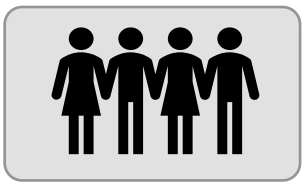
New Patient Process



Read the New Patient Packet information

- Contact FARA with any questions at info@curefa.org

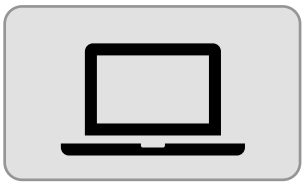


Join the FA Patient Registry

- It is the central database for being contacted about research studies and clinical trials.
- More information is available at curefa.org/patient-registry

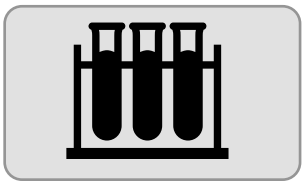
Find a Collaborative Clinical Research Network (CCRN) Site

- Clinicians who specialize in FA and participate in research.
- A detailed list is available at curefa.org/care
- Review the clinical care guidelines for FA with your physician.



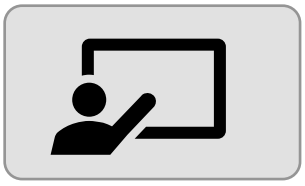
Engage with the FA Support Community!

- Join an online community; multiple are available for families, friends, and patients living with FA.
- curefa.org/support



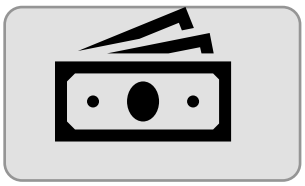
Learn about current research and clinical trials for FA

- Visit curefa.org/trial for information on active studies.
- Visit curefa.org/pipeline to view the current treatment pipelines.



Attend a Patient Symposium

- Learn about the most recent advancements in FA and meet other members of the FA community.
- Visit curefa.org/events



Get involved in FARA's fundraising efforts

- FARA-organized events, like rideATAXIA and Energy Ball, raise money to advance research for FA.
- Visit curefa.org/grassroots for resources to organize a local event.

FARA Friedreich's Ataxia Research Alliance

Friedreich's Ataxia Fact Sheet

What is FA?

Friedreich's ataxia (FA/FRDA) is a genetic, neurological disorder characterized by

- progressive gait and balance instability
- impaired coordination affecting all muscles
- dysarthria (difficulty with speech)
- scoliosis (curvature of the spine)
- loss of sensation in the arms and legs
- cardiomyopathy and arrhythmia (heart conditions)
- diabetes
- hearing and vision loss

FA affects ~1 in 50,000 people with an estimated U.S. prevalence of 4,000 patients and a global prevalence of 15,000 patients. FA predominantly affects people of Caucasian European descent. Most people with FA are diagnosed between ages 5-15, though 15% of people are diagnosed after the age of 25.

What Causes the Symptoms of FA?

The protein associated with FA, called frataxin, is made by the FXN gene and is required for proper functioning of the energy producing units of cells called mitochondria. When frataxin is deficient in mitochondria, tissues that depend on high energy (ATP) production, such as the nervous and cardiac systems, degenerate over time. Although FA is a systemic disease, brain development and cognitive functioning are preserved.

Treatments for FA

Currently, treatment for FA focuses on symptom management by a multidisciplinary team. Guidelines have been published at curefa.org/clinical-care-guidelines, though every individual is different and may have specific needs. All FA patients need a dedicated team to ensure a tailored approach to their individual needs. The Collaborative Clinical Research Network (CCRN) for FA can help coordinate a patient's care. Treatments for FA aim to prolong independence and maintain quality of life for patients.

Clinical Trials for FA

While no treatment is currently approved to halt the progression of disease, there are more than a dozen therapies and drugs currently being studied to treat FA. These clinical trials require many steps to ensure the efficacy and safety of the medication before it can be approved for widespread use. Some are still in early investigative phases, while others have advanced to phase III. For more information on current studies and to learn if a patient is eligible for one of the many ongoing trials, please visit curefa.org/network, and talk to your doctors about trials they may be aware of.

Who is FARA?

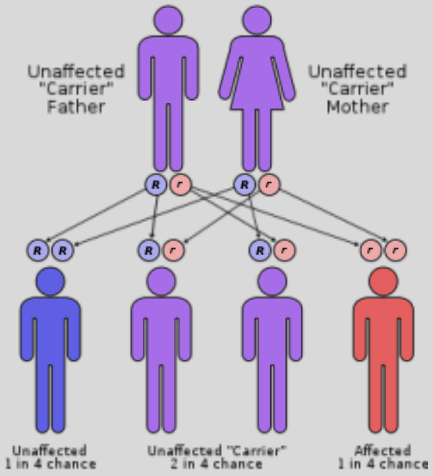
The Friedreich's Ataxia Research Alliance (FARA) is a national, public, 501(c)(3), non-profit, tax-exempt organization dedicated to the pursuit of scientific research leading to treatments and a cure for Friedreich's ataxia. The mission is to marshal and focus the resources and relationships needed to cure FA by raising funds for research, promoting public awareness, and aligning scientists, patients, clinicians, government agencies, pharmaceutical companies and other organizations dedicated to curing FA and related diseases.

For more information, visit curefa.org or contact the FARA office at (484) 879-6160 or email questions to info@curefa.org.

FARA Friedreich's Ataxia Research Alliance

Genetics of Friedreich's Ataxia

Friedreich's Ataxia (FA)



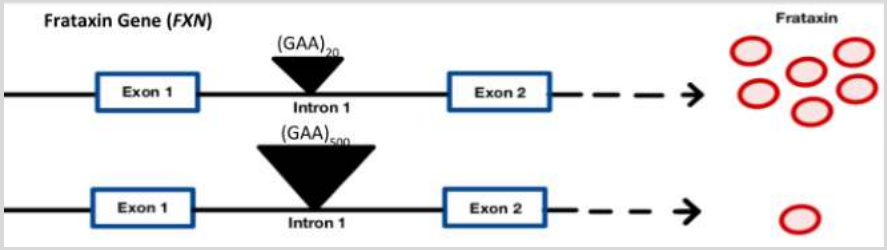
Friedreich's Ataxia (FA) is a genetic, neurological disorder caused by mutations in the FXN gene on chromosome 9. It is inherited in an autosomal recessive pattern. Parents (carriers) are asymptomatic and may not know they are carriers until they have a child with FA. The FXN gene may be non-functional due to a point mutation or an expanded trinucleotide GAA repeat.

Autosomal recessive conditions are inherited when non-functioning copies of a gene are passed down from both parents (see diagram at left). Therefore, with two carrier parents, each pregnancy has a ¼ chance of resulting in an affected child. In FA, the child inherits two non-functioning copies of FXN.

Triple Repeat Disorder

FA is known as a *triplet repeat disorder* since it is caused by an expanded trinucleotide repeat. In those affected with FA, there are significantly more GAA repeats in the first intron of the FXN gene (see below). If repeat number exceeds 100, protein output is affected with an insufficient amount of the frataxin protein made. Low frataxin protein levels lead to dysfunction in mitochondria and the symptoms associated with FA. Often, more severe symptoms and earlier age of onset are seen as the number of repeats increases. Alternatively, a point mutation in the FXN gene can also reduce the amount of frataxin that is produced.

Frataxin Gene



Frataxin, the protein produced by the FXN gene, works in mitochondria to help to create energy. Normally, frataxin works to regulate iron and sulfur molecules in the mitochondria while also working as an antioxidant to reduce oxidative stress. Both of these processes allow the mitochondria to efficiently produce ATP, the source of cellular energy. The nervous and cardiac systems require high levels of ATP, and these two systems are predominantly affected in symptoms of FA.

In people with two fully functioning FXN genes, frataxin is made at maximum levels. In those with only one functioning gene (carriers), only 50% of the normal amount of frataxin is made, but they remain asymptomatic. However, in those with two affected FXN genes, very minimal amounts of frataxin protein is made.

With limited frataxin, iron-sulfur clusters in mitochondrial proteins cannot form properly, causing a reduction in energy production. Additionally, insufficient frataxin makes mitochondria especially sensitive to free radicals, causing increased damage and destruction of cells. Cells in the brain, spinal cord and muscles that are damaged or have low energy supplies degenerate over time, causing the signs and symptoms associated with FA.

FARA

Clinical Trials & FDA Regulatory Process

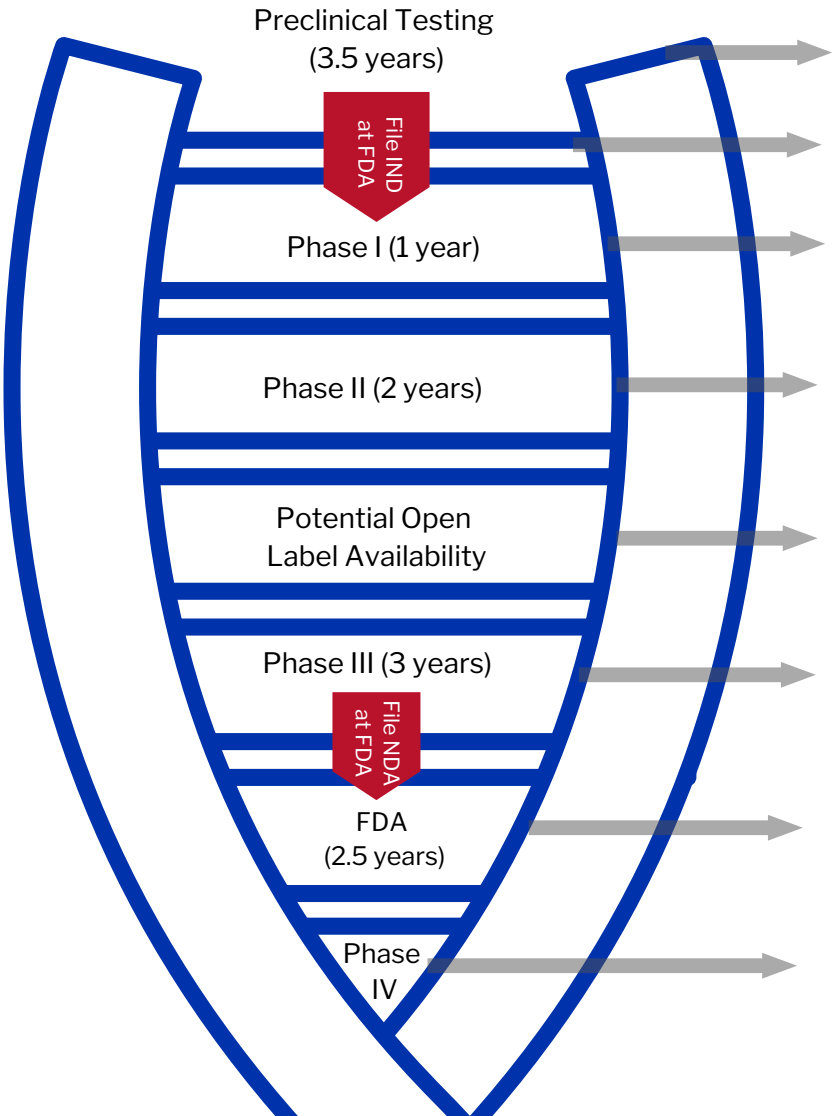
Clinical Trial

A *clinical trial* evaluates a specific intervention according to a research protocol created by investigators. These interventions may be products such as drugs or devices, procedures, or changes to participants' behavior (for example, diet). Clinical trials compare a new medical approach to a standard approach that is already available or to a placebo. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or have no different effect than available alternatives. The investigators determine the safety and efficacy of the intervention by measuring certain outcomes in the participants.

At FARA, we work to maintain a collaborative approach with physicians, pharmaceutical companies, and others to provide the resources needed to further research processes. With this collaborative approach, we hope to expedite the regulatory process detailed below to arrive at treatments and cures for FA as soon as possible.

For more information about available clinical trials for Friedreich's ataxia, please visit curefa.org/trial or search for Friedreich's ataxia at clinicaltrials.gov.

NOTE: This diagram represents the typical regulatory process. For rare diseases, the number is smaller for enrolled trial participants, and sometimes phases can be combined to test safety and efficacy.



- Laboratory & animal studies to assess safety and biological activity.
- Approx. 5,000 compounds evaluated.
- Approx. 5 compounds might enter Phase I clinical trials.
- 20-80 healthy people/patients enrolled to determine safety and appropriate dosage for the medication.
- 100-300 patient volunteers enrolled to evaluate for effectiveness and side effects.
- Medication available to eligible patients at discretion of pharmaceutical company.
- Concurrent with phase III preparation.
- 1,000-3,000 patient volunteers enrolled to verify effectiveness and monitor adverse effects from long term use.
- FDA reviews data from Phases I-III
- Approx. a total 12-year process from preclinical to filing an NDA.
- Medication becomes available by prescription.
- Post marketing testing data collected and reviewed by FDA for continued safety and efficacy.

IND: Investigational New Drug
NDA: New Drug Application

Friedreich's Ataxia Global Patient Registry

Friedreich's Ataxia Global Patient Registry

Patients can accelerate the drug development and treatment process by registering for the *Friedreich's Ataxia Global Patient Registry*. Being part of the registry is a great opportunity to keep updated on what is happening and to possibly participate in clinical trials. It is very important that all FA patients are represented in the patient registry.

Why is a Patient Registry Vital to Advancing Knowledge about FA?

When pharmaceutical companies begin the journey of developing a drug for FA, one of the first questions asked is "Where are FA patients located around the world?" The answer to this question is important because:

- Pharmaceutical companies want to know where patients are located when they plan for clinical trials. They also need this information for eventual drug distribution, so they are aware of the regulatory processes in each country where patients are treated.
- Pharmaceutical companies will need to plan for physician education about drug availability in any country where FA patients are being diagnosed and treated.

There are an estimated 15,000 individuals affected with FA worldwide. Currently, the registry includes only 1/3 of all FA patients globally. The registry provides a way to notify FA patients about upcoming clinical studies and trials and avoids delays in the drug development process.

What the Patient Registry *Doesn't* Do?

- Patient registry information is never used for fundraising.
- Patient registry information is not shared with researchers and pharmaceutical companies without appropriate protocol review. Data shared with researchers is anonymized.

Please Join the FA Global Registry

We need YOU to help advance research to treatments and a cure!

Please, join the FA Global Registry: curefa.org/registry
{If you have already joined the registry, please keep your contact and clinical information up-to-date.}

Please contact FARA_Patient_Registry@curefa.org for access issues and questions.

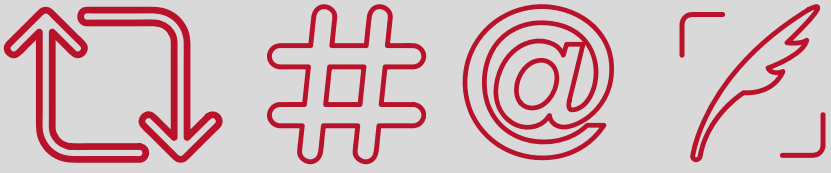
Sign up for our email list at curefa.org/contact

CONNECT WITH US!

Website: curefa.org
Email: info@curefa.org
Office Phone: (484) 879-6160

Patient Registry: curefa.org/registry

Facebook: facebook.com/curefa
Twitter: @curefa.org
Instagram: @curefa_org
Youtube:
youtube.com/user/FARA1998



Glossary of Terminology and Abbreviations

Medical

Term	Definition
ADLs	Activities of daily living
Ambulatory	Able to walk
Arrhythmia	A condition where the heart beats in an irregular or abnormal rhythm
Ataxia	Loss of coordination
Cardiomyopathy	Condition of the heart muscle where tissue is thickened between the ventricles; weakens heart function over time
Dysarthria	Difficulty of speech; slow, slurred speech
Dysphagia	Difficulty swallowing
HbA1c	Measurement in diabetes of glycated hemoglobin over a 3-month time period; normal = <5.6%
Natural History	Description of the progression of disease over time
Scoliosis	Abnormal curvature of the spine
Clinical diagnosis	Diagnosis made on the basis of medical signs and patient-reported symptoms
Genetic confirmation	Laboratory analysis of DNA to aid in the diagnosis of disease; can confirm a diagnosis or help predict likelihood of symptoms before they appear

Genetics

Term	Definition
Allele	Different forms of the same gene
DNA	Deoxyribonucleic acid; double-helix (double-stranded) molecules that contain genetic instructions; transcribed to RNA
Exon	The region within a gene that directly codes for a protein
Gene	Region of DNA that is a molecular unit of hereditary; gene for FA is frataxin (*FXN*)
Genotype	Genetic makeup of an individual organism
Heterozygous	Having two different alleles of a gene
Homozygous	Having two of the same alleles for a gene
Intron	The region within a gene that does not directly code for a protein but may have regulatory functions
Loss of function mutation	A mutation in a gene that causes the gene to not work as well as normal or produce less protein than it should
Phenotype	The physical manifestation of our genes; symptoms of a condition
Point mutation	A change in a single letter of DNA which may/may not affect protein structure
RNA	Ribonucleic acid; single-stranded molecules that contain genetic code and control gene expression; translated to proteins
Triplet Repeat Expansion	Increase in the number of three nucleotide units within a gene beyond the normal number; GAA expansion in FA causes the dysfunction in the *FXN* gene and low levels of frataxin protein to be made in the mitochondria

Friedreich's Ataxia

Term	Definition
FA/FRDA	Friedreich's Ataxia
FXN	Frataxin gene
frataxin	Protein produced by *FXN* gene
mitochondria	Energy producing units within cells; produce ATP for cellular function

Research and Clinical Trials

Term	Definition
Biomarker	A biological measure or molecule that can be found in blood, other body fluids, or tissues as a sign of a normal or abnormal process or an indicator of disease; may be measured to see how the body responds to a treatment for a disease
CBER	Center for Biologics Evaluation and Research; part of FDA
CCRN	Collaborative Clinical Research Network; FA specialty clinics
Clinical Study	Allows investigators to research humans affected by a disease to provide further medical knowledge of the condition
Clinical Trial	An investigation to explore if a medical strategy, treatment, or device is safe and effective for humans
COA	Clinical outcome assessment; measures how a patient feels or functions and is used to determine whether a treatment has demonstrated a benefit
CRU	Clinical research unit
Ex vivo	Procedure where organ, tissue, or cells are taken from a living organism, treated, and then returned to the living body; this term describes procedure for gene therapy
FARS/mFARS	(m=Modified) Friedreich's Ataxia Rating Scale - measures upper and lower limb coordination, upright stability, bulbar function, and peripheral nervous system function
FDA	Food and Drug Administration; regulates the drug development process
Gene editing	Methodology to directly change the sequence of DNA within a gene to correct genetic disorders
Gene therapy	The transfer of a normal gene into cells in replace missing or defective genes to correct genetic disorders
Half-life	The time required for a drug concentration to reach half its original value in the body
IND	Investigational new drug
In vitro	Studies performed on biological material (cells, tissues) outside their normal biological environment; opposite of in vivo; allows for control over what is introduced during the study to assess the outcome; this term describes type of studies performed during pre-clinical research
In vivo	Studies performed within a living organism (animals, humans); opposite of in vitro; this term describes type of studies performed in drug clinical trials
NCATS	National Center for Advancing Translational Sciences; part of NIH
NDA	New drug application

NIH	National Institutes of Health
Oligonucleotide	Short DNA or RNA molecules, called oligomers, that have a wide range of applications in genetic testing and research
Outcome measures	An assessment of physical performance used in clinical trials; examples include the timed 25-foot walk and the 9-hole pegboard test
Oxidative stress	Imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants. A free radical is an oxygen containing molecule that has one or more unpaired electrons, making it highly reactive with other molecules
p-value	Probability value; defines statistical significance; the lower the p-value (usually <0.05), the greater the likelihood the result/outcome did not happen by random chance
Peak-value	The time during which a drug has its maximum biological effect
Pharmacodynamics	Biochemical and physiological effects; relationship of drug concentration and biological effect
Pharmacokinetics	Measurements of how a drug is taken up and distributed throughout the body; sometimes described as “half-life” of clearance of drug from body
Placebo	A substance that has no therapeutic effect; used as a control within clinical research for comparison to what is being evaluated in the study
PROs	Patient reported outcomes; description directly from a patient about his/her own health status, and, ideally, implicates the symptoms that are most meaningful for targets of drug development
Prospective study	the researchers want to determine an outcome by following groups of people over time after a drug is administered or by recording medical and/or lifestyle changes
Randomized controlled study	Clinical study that randomly (by chance) assigns participants to two or more groups of observation or treatment; **double-blind randomized controlled study is** a study where neither the participants nor the investigators know who is getting the drug and who is getting the placebo to avoid bias in interpreting observations and measurements
Retrospective study	researchers already know the outcome and are searching for the correlation, influencing factors, or cause
SAE	Serious adverse event; can occur during evaluation of a potential treatment – drug or medical device – and must be reported to FDA
Statistical significance	defines numerical data where it is very unlikely that the result (outcome) occurred by random chance
Vector	Biological vehicle used to deliver gene therapy to cells (ex. viruses)