FAST FACTS About FA

This special report, written in December 2010, outlines the latest findings in Friedreich's ataxia (FA), an inherited neurodegenerative disease affecting approximately one in every 50,000 people in the United States.

First described by German physician Nikolaus Friedreich in 1863, FA mainly affects the heart and nerve cells of the brain and spinal cord, as well as the peripheral nerves.

FA affects males and females equally. It typically manifests in the early teens but has been diagnosed in some as young as 2 years old and in others as old as 50.

Symptoms vary in onset and speed of progression, but typically include loss of balance and coordination (ataxia), and muscle weakness that begins in the legs and torso and spreads to the arms and hands. Some experience difficulty with speech and swallowing, muscle tightness (spasticity), loss of sensation and skeletal abnormalities. FA's effects on the heart range from mild to life-threatening.

FA has a recessive inheritance pattern, requiring two gene flaws (one on each chromosome, each from one parent). An individual who has only one abnormal copy of the gene is a healthy asymptomatic carrier and can, in turn, pass on the affected gene to offspring.

Since 1975, MDA has invested more than $12,056,711 in FA research. The Association's current commitment through 2013 includes 10 grants totaling $2,030,758.

In Focus: Friedreich's Ataxia

Table of Contents

©2010 MDA

FA: A Case of Impaired Ironworks

From childhood science classes, you may remember the periodic table listing all the known chemical elements. You might also recall, in approximately the center of the table, the symbol "Fe" signifying the metal iron.

Produced inside large stars in distant space, iron is the most common element on Earth. From earliest times, humans have used it in everything from paint pigments, cookware and tools to buildings, bridges and cars.

Longer still, humans have relied on iron as a biological workhorse, necessary for survival.

Iron-containing proteins are involved in a vast array of vitally important functions in the body including:

- formation of red blood cells;
- oxygen transport via blood and oxygen storage in muscle; and
- cellular energy production.

Distribution and storage of iron is carefully balanced and regulated by cells.

Too little can result in iron deficiency anemia, characterized by weakness and fatigue, and impairment to the immune system.

Too much iron, or iron overload, is toxic, with a broad range of effects that may include cell damage, organ damage (such as in the pancreas, heart and brain), metabolism problems and neurodegenerative disease.

The inability to properly manage iron lies at the heart of the neurodegenerative disease Friedreich's ataxia (FA).

Finding the FA gene

In 1996, two teams of scientists — one led by then-MDA-grantee Massimo Pandolfo at Baylor College of Medicine in Houston, and the other by Michel Koenig in France — published their discovery of the underlying molecular cause of FA: an expanded sequence of extra DNA in a gene on chromosome 9. The gene carries instructions for production of the *frataxin* protein.

It wasn't an easy find, but it was the crucial first step in providing researchers with targets at which to aim therapies for the disease.

"Finding the gene — it was a big, exciting time," recalls Sanjay Bidichandani, MDA vice president for research, who was part of Pandolfo's team on the gene identification project, with MDA support.

Bidichandani, also a former member of MDA's Medical Advisory Committee (MAC), noted that pinpointing the gene was particularly difficult. While a majority of genetic diseases are caused by mutations in the "coding" regions, or *exons*, of genes (that is, the parts of the gene that carry instructions for protein synthesis), the defect responsible for FA turned out to reside in a "noncoding" region of the gene, or *intron*.

Genetic mutations in FA

Although two types of FA-causing mutations exist, by far the most common is a GAA *trinucleotide repeat expansion* — a region of DNA containing greater-than-normal numbers of the chemical phrase "GAA."

Five to 30 GAA repeats are within normal range, but in people with FA the repeats number in the hundreds to thousands, with the larger repeat expansions generally correlating with earlier onset and greater disease severity.

Approximately 96 percent of people with FA have two GAA repeat expansions, one on each chromosome. The other roughly 4 percent possess two different mutations: an

©2010 MDA

expansion on one chromosome, and a conventional gene mutation (most of which are truncations, or deletions) on the other.

Importantly, every individual with FA has at least one GAA expansion mutation, which has important implications for therapy development.

"There has never been a single Friedreich's ataxia patient reported to date who has conventional, or point mutations on both chromosomes," Bidichandani says. "That's important when it comes to developing therapeutic strategies, because it implies that treatments targeted to the repeat or its consequences should apply to every patient that exists."

The location of the GAA expansion in an intron holds additional positive implications for treatment because the exons and the protein-making instructions they contain are left unaffected. The introns are removed, or "spliced out," in the RNA stage (the intermediary step between DNA and protein synthesis in cells).

The implications of this particular sort of defect are "enormous," says Pandolfo. People with FA "have the disease because they make too little of a protein, frataxin, but the protein they make is normal.

"So, if one can boost its synthesis, the basic defect in the disease may be corrected."

In other words, "if we can bypass the problems caused by the repeat expansion," Bidichandani explains, "the genetic instructions will allow production of a perfectly normal frataxin protein."

Frataxin's function

The frataxin protein does its work in mitochondria, the energy-producing "powerhouses" in cells.

Although the protein is present in all tissues of the body, "only certain cells are exquisitely sensitive to frataxin depletion," says Grazia Isaya, professor of biochemistry and molecular biology and pediatrics at the Mayo Clinic College of Medicine in Rochester, Minn., and a member since 1998 of MDA's Medical Advisory Committee. These include cells in the heart and pancreas, and large sensory neurons (nerve cells) associated with the spinal cord.

"In fact, even in the central and peripheral nervous system, there are only certain neuronal cells that are particularly susceptible to frataxin deficiency," Isaya explains. "Maybe other tissues are sensitive as well, but not to the extent that it becomes clinically obvious — and we do not yet understand why this is the case."

Isaya cautions that the basic function of the frataxin protein is a polarizing topic among researchers in the field, with some maintaining that frataxin's function is not yet known.

"My view is the opposite. I think we understand the basic function of the protein, which is to bind iron and make it available to other mitochondrial proteins," Isaya says. "We certainly don't understand the details of how it's accomplished at the molecular and atomic levels, but I think the main function of the protein is well-known."

What *is* agreed upon — at least by most — is that in FA, the physical increase in the amount of DNA in the gene for frataxin directly or indirectly results in a decrease in transcription of instructions into RNA and, by extension, decreased levels of frataxin.

Why isn't there enough frataxin?

The first mechanism posited to explain the decrease in frataxin transcription was proposed by Massimo Pandolfo and colleagues when they initially identified the GAA expansion.

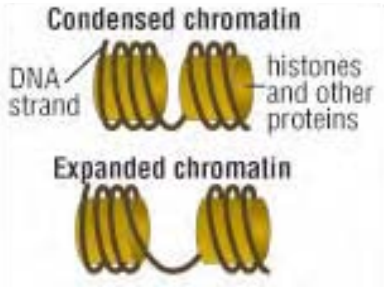
The group theorized that the repeats would form an abnormal "triplex" DNA structure, one variant of which was dubbed "sticky DNA."

Such abnormal structures have been shown in bacterial and various mammalian cell culture models to reduce transcription.

"So these early data showed that the expanded GAA repeat was capable of reducing frataxin RNA production," Bidichandani says. "In other words, no other factors, such as epigenetic modification [a sort of biochemical gene regulation mechanism], are necessary."

More recent work indicates that the GAA expansion also regulates activity of the frataxin gene through epigenetic controls that cause *gene silencing*.

©2010 MDA



Chromatin structure affects gene activation. Closed, or condensed, chromatin restricts access to the gene, while open, or relaxed, chromatin allows the cell's machinery to access the genes and make proteins.

In the case of FA, this involves compacting *chromatin*, the structure formed by DNA and the proteins that DNA is wrapped around, called *histones*.

With such "condensed" chromatin, DNA is closed, preventing the cell's protein-building machinery to access the genetic instructions. (See the January 2010 Quest magazine article Epigenetics: Above and Beyond Genes.)

"With the epigenetic story, you get a closed chromatin formation near the expanded repeat sequence," Bidichandani explains. "We also have new evidence that this might be occurring near the area of the gene where transcription starts as well."

The two mechanisms — abnormal DNA structure and epigenetic gene silencing — aren't mutually exclusive and may in fact overlap.

In any case, decrease of frataxin RNA leads to decrease in frataxin protein production, which in turn leads to abnormal iron overload and metabolism in the mitochondria.

Iron overload

Over the last several years, MDA grantee Des Richardson and colleagues at the University of Sydney, Australia, have focused on pinpointing the pathways that lead to iron accumulation.

In 2008, the group published study results describing the downregulation of three iron-trafficking pathways caused by decreased frataxin production: *mitochondrial iron storage*, *iron-sulfur cluster* (ISC) *synthesis* and *heme synthesis*.

ISCs and heme are important molecules that drive a number of vital cellular processes affecting every compartment and a number of different pathways in the cell.

"Normally, iron comes into the mitochondria, and it's utilized very efficiently for the synthesis of iron-sulfur clusters and heme," Richardson explains. "It comes in, it incorporates into the ISCs, incorporates into the heme, and then very quickly these complexes are shuttled out, back into the cell."

Without frataxin to handle iron safely and efficiently, mitochondria are no longer able to generate the ISCs and heme. When the cell detects the problem, it senses it as a situation of iron insufficiency and works to fix it by bringing more iron into the cell.

On its surface, the cell increases the levels of a molecule called the *transferrin receptor*, which brings in more iron from a protein in the blood called *transferrin*.

The iron is targeted to the mitochondria, but when it gets there it's unable to be used. It accumulates and the mitochondria become iron-loaded at the same time other areas of the cell exhibit iron deficiency.

"It's a paradoxical situation," Isaya says. "The cells feel that they are depleted of iron, when in fact they're accumulating it in the mitochondria."

Oxidative stress

In addition to the disruption of ISC and heme generation, and inappropriate iron levels, the problem of iron overloading in the mitochondria can lead to extensive cellular damage via oxidative stress.

Because the mitochondria are unable to direct the binding of iron with proteins to make the complexes necessary for ISC or heme synthesis, iron is left "free," able to induce the conversion of energy-production byproducts into toxic chemicals called *free radicals*.

When produced in excess, or when cells become unable to detoxify them, free radicals become dangerous, causing extensive damage to cellular structures, including DNA, and eventually killing the cell.

Among the variety of outcomes associated with iron-triggered free radical activity are heart disease and neurological problems.

An understanding of free radical damage led to some of the first treatment strategies for FA.

FA treatment strategy: Antioxidants

Antioxidants are drugs designed to offer some protection against free radical damage in cells and to enhance mitochondrial energy pro-

©2010 MDA

duction by rendering free radicals harmless.

Coenzyme Q10, *vitamin E* and *idebenone* were among the first antioxidant compounds to be tested in FA after the frataxin gene discovery. These studies, particularly of idebenone, continue today. A long history of clinical trials of the drug has produced some intriguing results. (See Idebenone on Trial, page 9.)

Idebenone (under the brand name Catena) is not approved for use in the United States. It did receive conditional market approval for FA treatment in Canada in July 2008. Around that same time, however, it failed to obtain marketing approval in Europe, where its trade name is Sovrima.

Although antioxidants alone can't cure FA, this class of drug may provide some benefit, alone or in combination, with other therapies.

FA treatment strategy: Iron chelation

Des Richardson and colleagues have done extensive work on *iron chelation*, a therapeutic strategy that aims to target toxic mitochondrial iron and remove it via compounds called *iron chelators*.

In July 2008, Richardson's team published study results showing that treatment with iron chelation significantly decreased iron levels in the heart, and limited the harmful increase in the size of the cardiac muscle (a condition called *myocardial hypertrophy*) in mice that don't express frataxin in the heart. (For more about this study, see Research Updates in the December 2008 Quest.)

Precision in iron chelation therapy is crucial.

"You have to be very careful — you're on the knife's edge," Richardson explains. "You have to give an appropriate dose that potentially will remove the iron from the mitochondria without causing whole-body iron depletion."

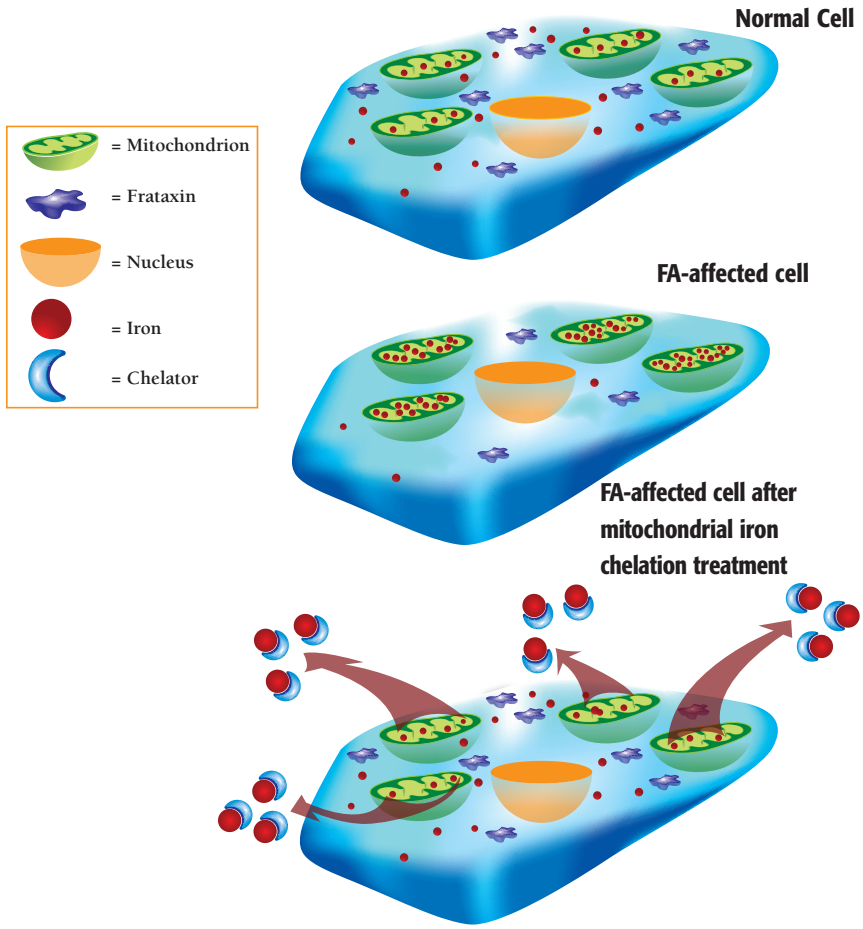
Although Richardson's team has demonstrated that iron chelation can improve symptoms in a mouse with an FA-like disease, in the end the animal still gets ill and suffers from heart problems.

"This is because — despite removing the toxic iron — we couldn't replace the function of the frataxin, which is essential for the synthesis of iron-sulfur clusters and heme," Richardson says.

The role for iron chelation as a treatment for FA is thus limited.

Results from an ongoing clinical trial with study sites in Belgium, France, Italy and Spain may increase understanding of how iron chelation may (or may not) fit into an FA therapy regimen.

The study aims to assess the tolerability and safety of the iron chelation drug *deferiprone* in people with FA. In development by the pharmaceutical company ApoPharma, headquartered in Canada, the drug has been licensed for treatment in Europe and



In FA, a deficiency of the frataxin protein changes the way the body regulates iron levels, leading to toxic levels of iron in the cellular "energy factors" called mitochondria. Chelators designed to penetrate the mitochondria target the iron accumulation and remove it.

©2010 MDA

Asia of the iron-loading disorder *thalassemia*.

"I'm cautious but hopeful that iron chelators might be used to reduce the amount of toxic mitochondrial iron, but again it will not fix the problem — that is the lack of frataxin," Richardson says.

"Eventually we have to generate a technology that will restore or replace frataxin function, and that's really the 'Holy Grail.'"

FA treatment strategy: Erythropoietin

Erythropoietin, or *EPO*, is a sugar-coated protein, or *glycoprotein*, secreted by the kidneys.

In addition to its neuro- and cardio-protective properties, EPO:

- stimulates production of red blood cells;
- works as a powerful growth factor that can increase cell size and numbers of mitochondria; and
- increases frataxin protein production through an as-yet-undetermined mechanism.

Limitations to prolonged EPO treatment include harmful side effects such as increased blood-cell production and the risk of tumor growth.

In 2005, a group of Austrian investigators targeted human erythropoietin to cultured lymphocytes (a type of white blood cell) taken from people with FA, and found the cells significantly increased production of frataxin protein.

The researchers also studied people with end-stage kidney disease who were being treated with EPO, and found a significant increase in frataxin production in those patients within 48 hours of treatment.

In 2010, another Austrian research team (including some of the same researchers from the 2005 study) reported results of a small "proof-of-concept" trial in which 12 people with FA received EPO injections three times a week for eight weeks.

Eight of the 10 trial participants exhibited a stable increase of frataxin levels over the study period, with individual increases ranging from 15 to 63 percent.

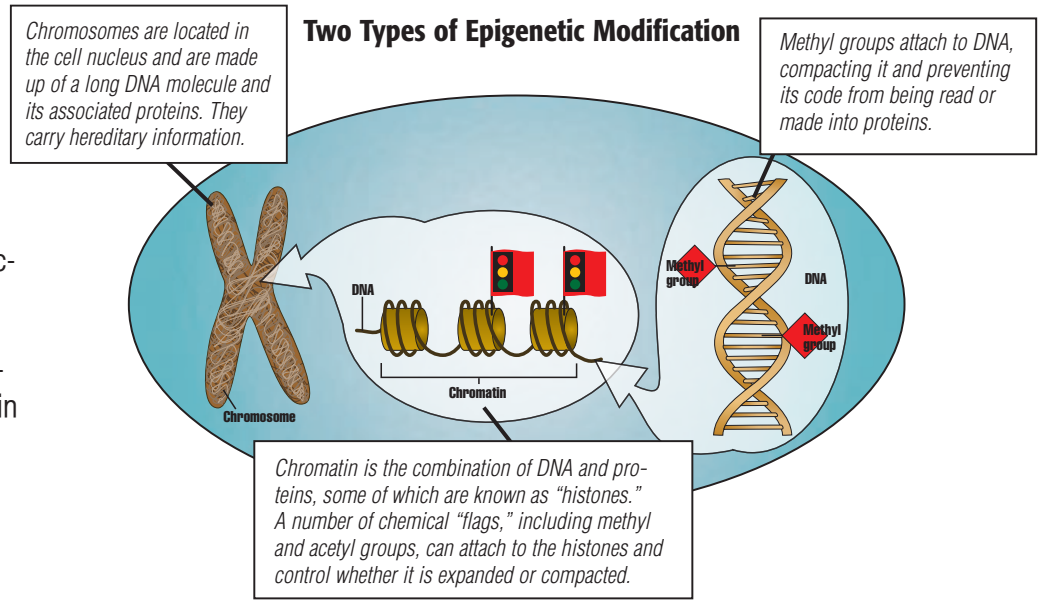
Ataxia severity, as measured by the assessment and rating of ataxia (SARA) scale, showed a 6 percent improvement in study participants, and measures of oxidative stress were significantly reduced.

In an open-label follow-up study, eight of the 10 participants from the first trial underwent a six-month extended treatment phase. Results included significant clinical improvement based on measurements from two different ataxia rating scales, with changes in locomotion and speech contributing the most to overall score improvement. Parameters indicative of oxidative stress also were markedly reduced after treatment.

Finally, building on their earlier studies, several members of the Austrian group, with colleagues, showed that a derivative of EPO called *carbamylated erythropoietin (CEPO)* increases frataxin levels in FA-affected cells, but does not, as EPO does, stimulate increased blood-cell production. This makes it a potential alternative for treatment of FA.

FA treatment strategy: HDAC inhibitors

Using a class of drugs called *histone deacetylase (HDAC) inhibitors*, scientists hope to "turn back on" the frataxin gene, allowing cellular machinery to read its genetic instructions and produce the frataxin protein.



Gene silencing can be the result of "epigenetic" control. In the case of FA, chemical flags called acetyl groups, which signal to the cell that the gene is open and ready for its protein-making instructions to be read, are lost. HDACs prevent the loss of these flags, essentially maintaining the gene's "active" status.

©2010 MDA

produce the frataxin protein.
Early attempts with a synthetic small molecule reversed the deleterious effects of the GAA repeat expansion and turned the frataxin gene back on to a small extent in cell culture studies. In further testing, however, in Massimo Pandolfo's mouse model for FA, it was found that the molecule didn't get into the brain.

"That got me thinking that the mechanism of gene silencing may have something to do with chromatin and epigenetics," says Joel Gottesfeld, professor in the department of molecular biology at Scripps Research Institute in La Jolla, Calif.

"And that led me to propose that molecules that could revert inactive chromatin to active chromatin might be of benefit."

Gottesfeld's lab began a search for HDAC inhibitors that could turn the frataxin gene back on, and found one, a molecule called BML210. A chemist in the lab synthesized a collection of derivatives of the compound, eventually leading up to a molecule called 106.

The 106 molecule was passed on to Pandolfo's lab, where it was shown that it does activate the frataxin gene in both the brain and heart of their FA mouse model, and subsequently leads to increased protein levels.

After a number of preliminary experiments to show the molecule wasn't toxic even in prolonged treatment situations, Gottesfeld and Scripps filed a provisional patent application and began looking for a commercial partner to help move the drug forward.

A number of companies expressed interest, Gottesfeld says, and in April 2007, Repligen Corp. of Waltham, Mass., entered into a commercial license with Scripps for exclusive rights to further develop the compound.

"Repligen made Scripps the best offer — not just financially, but in terms of our confidence in them sincerely wanting to take this forward," Gottesfeld says.

"That's even more important than the dollars that the company may pay to Scripps for the rights, because it's of no use unless the company really is dedicated to do the work."

James Rusche, Repligen senior vice president of research and development, says, "We are really excited about this approach. It's not treating a symptom — it actually treats the fundamental basis of the disease."

Repligen has since synthesized hundreds of derivatives of 106, one of which, RG2833, has been designated for clinical development.

Studies have confirmed that RG2833 is most potent against HDAC3, an enzyme that, when blocked, increases frataxin production.

"We think this is a sound and exciting opportunity to develop a treatment for FA," Rusche says. "Small molecule drug development for a neurodegenerative disease is difficult, but with support from academic and patient advocacy groups we feel Friedreich's ataxia is the right place to try."

MDA provided Repligen with two grants to fund the early stages of the RG2833 program. The first, awarded in late 2007, totaled nearly $1 million. In December 2009, MDA awarded a new grant to the company totaling $731,534, to support the ongoing development of RG2833, including completion of the preclinical testing required to move the experimental drug toward human clinical trials.

Repligen has filed an Investigational New Drug application with the U.S. Food and Drug Administration (FDA) for a phase 1 study of RG2833. Pending approval by the FDA, the study, which will enroll up to 40 healthy volunteers without FA, will evaluate the safety and pharmacokinetic profile (the way the drug behaves in the body) of the compound.

Researchers also will evaluate biochemical indicators called *biomarkers* in the participants' blood as a means of measuring RG2833's activity.

This study will be the first step in the clinical development of RG2833 as a potential treatment for FA.

The FDA has granted RG2833 *orphan drug designation*, which may qualify Repligen to receive seven years of market exclusivity in the United States, provided that it is the first company to receive approval for RG2833 for FA.

Combining the use of different treatment strategies is likely, says Gottesfeld.

"A treatment for Friedreich's ataxia may turn out to be a combination of treating symptoms with either an iron chelator and/or an antioxidant, plus boosting levels of frataxin protein — either by protein replacement or by our means, turning the gene back on."

©2010 MDA

FA treatment strategy: Gene therapy

Various gene therapy-based strategies also hold the potential to benefit individuals with FA. Although it's relatively early in the game, a limited number of studies in mice and human cells have yielded some encouraging results.

In a 2005 study, researchers used *lentiviral* or *adeno-associated viral (AAV)* vectors to carry the human frataxin gene into *fibroblasts* (cells that mature into a variety of connective tissue types) from FA patients. (A *vector* is a delivery vehicle for therapeutic genes.)

Results included increased frataxin protein levels and a reduction in the treated cells' sensitivity to oxidative stress.

A 2007 study analyzed the feasibility of gene insertion via the emptied-out shell of the *herpes simplex virus type 1 (HSV-1)*, partnered with a stretch of DNA called an *amplicon* that helps the vector target a specific cell type.

Results in FA-affected mice and human cells showed highly efficient DNA transfer and increased levels of frataxin production.

Similar positive results in 2007 came from a Spanish study in which mice were engineered so that researchers could eliminate, or "knock out," frataxin activity specifically in motor neurons.

The mice developed neurological symptoms after four weeks, but achieved full recovery in as few as four weeks after receiving injections of HSV-1 amplicon vectors carrying DNA that codes for human frataxin.

A Spanish study published in 2010 describes the successful use of artificial chromosomes and similar constructs called *episomes* to act as vectors for transporting genes to their targets.

R. Mark Payne, a professor of pediatrics and a pediatric cardiologist at the Indiana University School of Medicine in Indianapolis, is working on gene replacement therapy for FA.

His strategy involves using a construct called *TAT-frataxin fusion proteins* as a mechanism for replacing the missing FA gene product.

(For an interview with R. Mark Payne about heart problems in FA, see Treating the FA-Affected Heart, page 18.)

Where are we now?

The FA disease process is extremely complex. Scientists still are refining their knowledge of its causes and effects, but a great deal of progress has been made. Still, more needs to be done.

It's becoming clear that in addition to mitochondrial consequences, there are other far-ranging cellular consequences. A number of pathways that are normally active in cells are lost in the absence of frataxin and their loss then contributes to the progression of FA symptoms, Grazia Isaya notes.

"This may explain why single drugs like antioxidants or iron chelators alone cannot be entirely successful in terms of improving the disease in patients.

"Perhaps only by increasing the levels of frataxin can one ultimately treat the disease."

To see a listing of current and completed clinical trials in FA, go to www.clinicaltrials.gov and enter "Friedreich's ataxia" in the search box.

©2010 MDA

Idebenone clinical trials

Overall, idebenone has been shown to be safe and well-tolerated in a number of phase 1, 2 and 3 human clinical trials dating back to 1999. The most common side effects are mild to moderate gastrointestinal issues such as diarrhea, nausea and indigestion. Early trials at low doses first demonstrated the potential for idebenone to reduce FA-associated *cardiomyopathy* (heart muscle abnormality). Over the past decade, the drug has consistently demonstrated in a number of trials its ability to improve heart structure by reducing FA-related abnormal thickening (*cardiac hypertrophy*) of tissues in particular areas of the heart. Specific measurements used to determine such improvement include interventricular septal wall thickness (SWT), left ventricular posterior wall thickness (PWT) and left ventricular mass index (LVMI). In addition, results from some trials have suggested a reduction in cardiac strain, as indicated by a measurement called *shortening fraction*, which measures performance of the heart by assessing the change in diameter of the left ventricle between the contracted and relaxed states. The decrease in cardiac strain was associated with improved heart function.
A number of studies found that cardiac benefits varied significantly among individuals. Most indications in earlier trials of idebenone's potential to improve or stabilize neurological dysfunction found no benefit. More recent trials, however, particularly those in which higher doses of the drug have been tested, have demonstrated improved neurological function.

- **ADL**: Activities of Daily Living. This ratings system assesses the ability of an individual to perform day-to-day activities such as dressing, eating, moving, toileting, taking medication, using a telephone or other technology, and others.
- **CAGRS**: Cooperative Ataxia Group Rating Scale. This scale measures neurological function/dysfunction.
- **FARS**: Friedreich's Ataxia Rating Scale. Another measurement of neurological function/dysfunction.
- **ICARS**: International Cooperative Ataxia Rating Scale. This measurement of neurological function/dysfunction currently is the preferred scale.
- **Catena/Sovrima**: Catena is the brand name for idebenone in Canada and the United States. Sovrima is the brand name for the drug in Europe.

Date, Location, Trial	Trial Objective & Description	Trial Results
2010 Spain *Combined Therapy with Idebenone and Deferiprone in Patients with Friedreich's Ataxia*	Aims of this study included evaluation of the effects of combined idebenone-deferiprone therapy on neurological signs and heart function. Twenty individuals with FA were treated with idebenone (20 mg/kg/day) and the iron chelator deferiprone (20 mg/kg/day) for 11 months.	No significant differences were observed in total ICARS scores when comparing status at the beginning of the study (baseline) and the end of the study in the whole group of patients. However, differences were noted in specific ICARS categories. Namely, posture and gait scores worsened, while fine-motor function improved significantly. Heart-imaging (echocardiography) data showed a significant reduction in abnormal thickness of a part of the heart called the septum. MRI testing showed statistically significant reduction, between baseline and after 11 months of therapy, of iron deposits in a part of the brain called the dentate nucleus. Results suggest combined idebenone-deferiprone therapy in people with FA confers an overall stabilizing effect in neurological dysfunction, and significant improvement in heart hypertrophy (abnormal enlargement) and iron levels in the brain. The therapy was well-tolerated with mild side effects. Noted risks include neutropenia (an abnormal decrease in levels of a particular type of white blood cell) and reduction of blood iron levels.

©2010 MDA

Date, Location, Trial	Trial Objective & Description	Trial Results
2010 Europe *Mitochondrial Protection with Idebenone in Cardiac or Neurological Outcome Study (MICONOS)*	This study was designed to evaluate the safety and efficacy of three different doses of Catena/Sovrima versus that of placebo. A total of 232 individuals (primarily adults) with FA received the low (180/360, depending on body weight, mg/day), medium (450/900 mg/day) or high dose (1,350/2,250 mg/day), or placebo, every day for 12 months.	The MICONOS trial missed its primary endpoint, which was mean change in ICARS score as measured at the beginning, and again at the end, of the study. No significant difference was noted between those receiving idebenone and those receiving placebo. In addition, no difference was noted between the active and placebo groups in measurements of key anatomical and functional cardiac parameters. Data still is being culled from long-term extension studies following this trial. The MICONOS extension was listed as "ongoing, but not recruiting patients" as of Aug. 20, 2010 on Clinicaltrials.gov.
2010 Canada *Intermediate-Dose Idebenone and Quality of Life in Friedreich's Ataxia*	This phase 3 observational study examined the effect of intermediate-dose idebenone (20 mg/kg/day) on quality of life and neurologic function measures. Seven patients with FA, ages 13 years to 18 years (four male and three female) were administered treatment for a period of one year.	Patients were assessed using the Pediatric Quality of Life Inventory, the ICARS, and an Activities of Daily Living Scale, both before starting idebenone and after one year of therapy. Physical scores on the Pediatric Quality of Life Inventory were universally worse after one year, and correlated with decreased activities of daily living scores. Despite worsening physical scores, there was a trend toward improved total, emotional, social and school components of quality of life scores. There was no statistically significant change in Pediatric Quality of Life Inventory scores from the beginning to the end of the study. Functional ability, as measured by activities of daily living scores, appeared to have the most influence on the perception of physical quality of life.
2009 United States *Idebenone Effects on Neurological ICARS Assessments study (IONIA)*	This phase 3 study compared the safety, tolerability and efficacy, of two different doses of Catena versus placebo. The low dose was 450 or 900 mg/day, depending on body weight. The high dose was 1,350/2,250 mg/day. Seventy individuals with FA, ages 8 years through 18 years, who still were ambulatory, were assigned to one of three treatment groups: low-dose idebenone, high-dose idebenone or placebo. Doses were administered daily over a period of six months.	The IONIA study missed its primary outcome measure, which was the mean change in ICARS scores taken at baseline and again after 24 weeks. Patients who received idebenone improved by 2.5 points on mean ICARS score compared with baseline, while patients in the placebo group improved by 1.3 points. Patients who took idebenone also improved by 1.6 points on the FARS, while patients taking placebo declined by 0.6 points. For both end points, the difference between the idebenone and placebo groups was not statistically significant. (It should be noted that the IONIA study was designed using parameters from the prior U.S. phase 2 NICOSIA study. Compared to the placebo group, improvement in both IONIA groups taking Catena measured only about half as much as had those in the prior U.S. Phase 2 NICOSIA study. It was observed that those in the IONIA placebo group did not deteriorate to the extent expected from the NICOSIA study or as described in literature, possibly skewing the results.)

©2010 MDA

Date, Location, Trial	Trial Objective & Description	Trial Results
2009 Italy *Low-Dose Idebenone Treatment in Friedreich's Ataxia with and without Cardiac Hypertrophy*	This study was a retrospective analysis of 35 individuals with FA (20 with cardiac hypertrophy, 15 without), who were treated with idebenone 5 mg/kg/day for up to 60 months.	The heart's responsiveness to treatment with idebenone varied greatly among trial participants. The researchers observed no correlation with sex, age, size of GAA repeat expansion, or severity of cardiomyopathy prior to the study. In those who had cardiac hypertrophy at the beginning of the study, no changes in heart tissue thickness measurements were noted. In those who began the study without cardiac hypertrophy, measurements showed the thickening of particular areas of heart tissue consistent with cardiac hypertrophy. No neurological benefits were noted. There was significant progression of neurological dysfunction over the time period studied.
2008 Switzerland United States *NIH Collaboration with Santhera in Ataxia (NICOSIA) trial*	This phase 2 study aimed to establish safety data and effect on neurological symptoms of high-dose idebenone in young individuals with FA. The trial enrolled 48 people with FA, with 12 in each of three dose groups, and 12 in a placebo group.	Results showed that idebenone was safe and well-tolerated, and that it produced a positive effect as measured by ICARS as well as with activities of daily living scales. Analysis revealed that those treated with the drug showed a trend toward dose-proportional improvement in neurological function, as measured by ICARS, after a six-month course of treatment.
2008 Spain *Idebenone Treatment in Pediatric and Adult Patients with Friedreich's Ataxia: Long-Term Follow-Up*	The aim of this study was to assess the effectiveness of long-term treatment with idebenone in people with FA. Ten children with FA (ages 8 years to 18 years) and 14 adults (ages 18 years to 46 years) with genetic diagnosis of FA were treated with idebenone (5-20 mg/kg/day) for a period of three years to five years.	Neurological status was evaluated using ICARS, and heart health was tested using a type of heart-imaging test called an echocardiogram. ICARS scores showed initial improvement in children, with stabilization over the long term. In adults, scores showed significant worsening of neurological function. Analysis also showed the treatment prevented progression of cardiomyopathy in both children and adult patients. The authors suggested that, based on these results, effectiveness of idebenone therapy may depend on the age at which it's initiated.
2007 United States *Neurological Effects of High-Dose Idebenone in Patients with Friedreich's Ataxia: A Randomized, Placebo-Controlled Trial*	This trial enrolled 48 people with FA between the ages of 9 years and 17 years. Each was randomly placed into a placebo or one of three idebenone treatment groups. Those in the treatment groups received fixed daily doses of idebenone, (180/360 mg/day, 450/900 mg/day or 1,350/2,250 mg/day, depending on body weight) over a period of six months.	Treatment with doses of idebenone was generally well tolerated at all doses up to 2,250 mg/day. At higher doses the treatment was associated with a trend toward improvement (but not a significant difference) in neurological function and activities of daily living in patients with FA. The degree of improvement correlated with the dose of idebenone, suggesting that higher doses may be necessary to have a beneficial effect on neurological function. Overall, analysis showed no significant difference in FARS, ICARS or ADL scores. In one experiment, however, in which patients who required wheelchair assistance were excluded, a significant improvement in ICARS scores and apparent dose-related response in ICARS, FARS and ADL scores was observed.

©2010 MDA

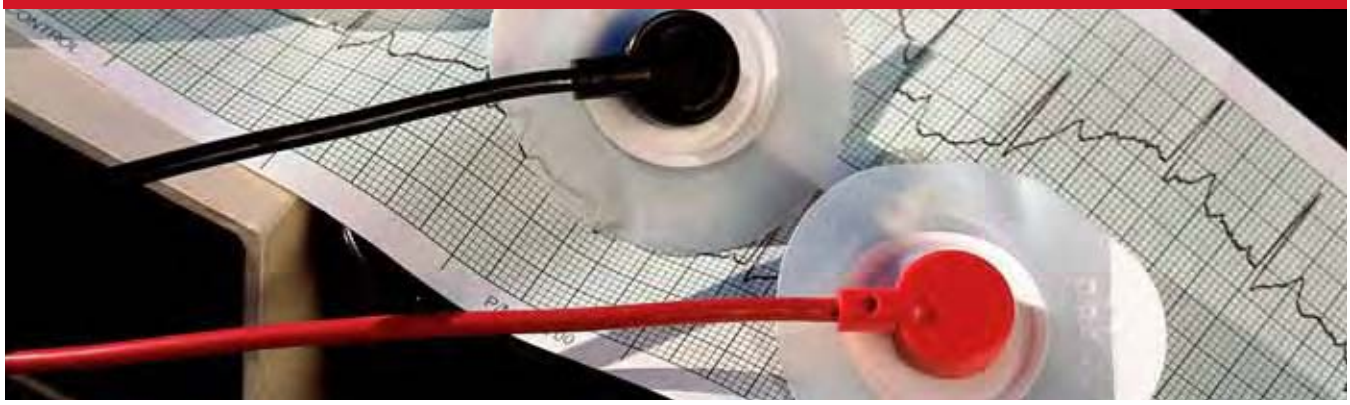
Date, Location, Trial	Trial Objective & Description	Trial Results
2007 France *Neurological, Cardiological and Oculomotor Progression in 104 Patients with Friedreich's Ataxia During Long-Term Follow-Up*	Researchers followed 104 people with FA every six months over a period averaging five years, using a standardized measurement protocol. No trial participants were receiving antioxidant therapy prior to the beginning of the study. Eighty-eight were treated with idebenone at 5 mg/kg per day; 16 declined the treatment.	The neurological condition of FA patients deteriorated slowly over time, even with idebenone treatment. It was suggested that overall progression may have been underestimated ICARS scores, which plateaued in those patients with long disease courses. Although cardiac hypertrophy decreased under treatment, cardiac function did not improve. Specifically, ICARS scores worsened during follow-up, regardless of whether the patients received idebenone. Worsening of the ICARS scores increased faster in patients with onset before age 15 years compared with the others. Oculomotor (eye movement) function deteriorated slightly.
2006 France *Expanding View of Phenotype and Oxidative Stress in Friedreich's Ataxia Patients with and without Idebenone*	The goal of this study was to examine neurological effects of idebenone. Investigators also looked at the drug's effect on blood levels of malondiadehyde (MDA), an organic compound known to indicate oxidative stress. Twenty adults with FA were treated with 5 mg/kg/day to 10 mg/kg/day idebenone over periods varying from several months up to three and a half years.	Overall ICARS scores did not improve, but improvements in neurological function were seen in speech, increased hand dexterity and decreased fatigue. Treatment with idebenone was positively correlated with an increase in blood levels of MDA.
2003 Belgium *Idebenone Treatment in Friedreich's Ataxia: Neurological, Cardiac and Biochemical Monitoring*	Researchers studied eight people with FA, between the ages of 9 years and 27 years, with cardiomyopathy. All trial participants received 5 mg/kg/day in three doses (maximum 300 mg/day) for one year.	Evaluations of ataxia, cardiac structure and function, biochemical markers and adverse effects were conducted at the beginning of the study and after four, eight and 12 months of treatment. As indicated by CAGRS scores, idebenone did not halt the progression of ataxia. At the end of therapy, cardiac ultrasound demonstrated significant reduction of cardiac hypertrophy in six of eight patients. Analysis showed this reduction of hypertrophy was preceded by an early and linear improvement in cardiac function.
2003 Italy *Idebenone Treatment in Friedreich Patients: One-Year-Long Randomized Placebo-Controlled Trial*	The goal of this trial was to determine cardiac and neurological effects of idebenone in people with FA. Twenty-nine study participants with FA, ages 21 years to 32 years, were placed into idebenone and placebo groups (14 and 15, respectively. Each received either idebenone (5 mg/kg/day) or placebo three times daily.	No serious side effects were associated with idebenone treatment. Effects of idebenone on the heart varied greatly among the trial participants. Analysis revealed significant reductions in measurements indicative of cardiac hypertrophy in the treatment group; these results were not observed in the placebo group. No improvement was noted in various other heart ultrasound measures or in neurologic condition. Although the overall cardiac changes were moderate, the findings suggested idebenone may reduce cardiac hypertrophy in people with FA.

©2010 MDA

Date, Location, Trial	Trial Objective & Description	Trial Results
2002 France *Idebenone and Reduced Cardiac Hypertrophy in Friedreich's Ataxia*	The aim of this trial was to assess the efficiency of idebenone on cardiac hypertrophy in FA. Idebenone was given orally (5 mg/kg/day) to 38 trial participants with FA, ages 4 years to 22 years (20 males, 18 females).	After six months of treatment, cardiac ultrasound indicated a reduction in parameters indicative of cardiac hypertrophy in approximately half of the trial participants. Cardiac hypertrophy was largely stabilized in the other half and in none of them did the hypertrophy significantly increase over the six-month trial period. No correlation was found between responsiveness to idebenone and age, sex, initial ultrasound indices, or the number of GAA repeats in the frataxin gene.
2002 Spain *Friedreich's Ataxia: Idebenone Treatment in Early-Stage Patients*	The aim of this study was to assess the effects of idebenone treatment in cardiac health and neurological function in people with FA. Nine trial participants with FA, ages 11 years to 19 years, were treated with idebenone (5 mg/kg/day) for one year.	No changes were noted in cardiac measurements taken prior to and after the study. Concentrations of idebenone in trial participants' blood showed significant positive correlation with ICARS scores before and 12 months after the start of the study. Significant improvement was observed in ICARS scores measured three months after start of treatment. Notable improvement in part of the brain called the cerebellum (responsible for motor function and balance) was observed in patients with mild cases of the disease after three months of therapy. Treatment at early stages appeared to reduce cerebellar degeneration.
2001 Germany *Idebenone in Patients with Friedreich's Ataxia*	In this study, researchers examined effects of idebenone on cardiac function. Nine FA patients, ages 9 years to 54 years, received either 360 mg/kg/day of idebenone or placebo for a period of one and a half months.	MRI results showed impairment in skeletal muscle of all FA patients, which idebenone did not help. No positive benefits were noted, and heart imaging tests (echocardiograms) failed to confirm results from a preliminary study suggesting improvement of FA-associated cardiomyopathy with idebenone. The study authors noted that the duration of treatment probably was too short to make a valid conclusion.
2000 Germany United States *Oxidative Stress in Patients with Friedreich's Ataxia*	The aim of this study was to determine the effects of idebenone on a particular biochemical indicator "biomarker" for oxidative stress. Eight people with FA were treated with idebenone (5 mg/kg/day) for a period of two months.	The small molecule biomarker, 80H2'dG 8-hydroxy-2' –deoxyguanosine, measured in urine output, decreased by 20 percent with idebenone treatment — a possible indicator of reduced oxidative stress.
1999 France *Effect of Idebenone on Cardiomyopathy in Friedreich's Ataxia: A Preliminary Study*	Three individuals, ages 11 years, 19 years and 21 years, received 5 mg/kg/day of idebenone for a period of four to nine months.	Results showed a reduction of abnormal thickening in measurements of three areas of the heart. Note: One individual who continued the treatment for five years exhibited decreased cardiac hypertrophy.

©2010 MDA

Everything is treatable, even if not yet curable



Susan Perlman, M.D., director of the Ataxia Clinic, Department of Neurology, University of California-Los Angeles, is a neurologist who's been doing research in, and taking care of individuals with, Friedreich's ataxia (FA) for some 30 years. In November 2010, she sat down to talk with Margaret Wahl, MDA's medical and science editor.

Q: What are some of the treatable aspects of Friedreich's ataxia?

A: First of all, everything is treatable. Any symptom somebody has, there is something that is available right now that can be used to make things milder and improve functional ability and quality of life.

Q: What about the cardiac problems in FA?

A: There are probably symptoms of cardiomyopathy [heart muscle abnormality] in more than half the people with Friedreich's. In some of them, the symptoms are relatively mild. They may notice palpitations, they may feel a little short of breath when they're exercising, and ultimately the workup will show, Yes, you have cardiomyopathy, and it's related to your Friedreich's.

There is often thickening of the heart muscle, called "hypertrophic" cardiomyopathy, especially on the left side of the heart. Sometimes it can get to the point where the muscle is so thick that blood has trouble flowing out of the heart. That's known as "outflow obstruction." More often, the heart muscle just gets thick, which makes it hard for it to pump blood efficiently.

In some cases, the heart muscle is so damaged by the frataxin protein deficiency caused by Friedreich's ataxia that it can actually thin out and stretch like a flabby rubber band. That also makes it harder for the heart to pump the blood out.

Another thing that we've noticed, besides a heart muscle that gets too thick or too thin, is a heart muscle that becomes stiff. It's not all stretched out and flabby, and it's not particularly thick. It just becomes stiff. There's probably scar tissue or fibrous tissue building up between the heart muscle fibers. On an echocardiogram, the heart size may look relatively normal, but it can't function well because it's stiff.

Normal cardiac function can usually be maintained into a patient's 20s, requiring no medication. Some people will require medication earlier.

Small studies suggest that an abnormality in heart thickness is the first thing that's picked up in youngsters and that it may or may not cause symptoms; but that as they get older, they may develop palpitations, fatigue and shortness of breath. In their 20s, some Friedreich's patients may begin to lose heart function, so that, instead of the heart pumping the normal 60 percent or so of the blood out

©2010 MDA

60 percent or so of the blood out with each contraction, it's pumping maybe 30 percent.

The kinds of medications that are used that can help preserve heart function are called beta blockers [examples are propranolol and metoprolol] and ACE inhibitors [examples are captopril and enalopril].

These drugs take some of the load off the heart muscle so that it's not working as hard. They're becoming standard care among many cardiologists who see people with Friedreich's ataxia.

We've seen individuals with Friedreich's and measurable thickening of the heart who have started the antioxidant idebenone, and a year later, their heart is back to normal. These are just single patient observations, but both idebenone and the related supplement coenzyme Q10 seem to reverse some of the thickening of the heart. We don't have all the data yet. But I recommend starting either coenzyme Q10 or idebenone, the earlier the better, while research continues.

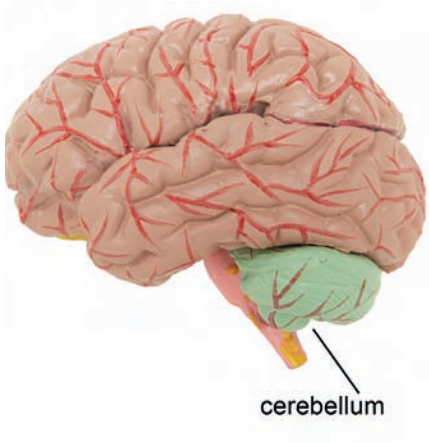
Some individuals with more advanced heart problems may require pacemakers or implanted defibrillators to reduce the risk of the heart going into a severe rhythm problem that could cause the heart to stop.

Q: Are the pathways related to both sensation and movement — the sensory and motor pathways — involved in FA?

A: Yes. There are two aspects here, the sensory pathways and the motor pathways.

In the central nervous system [the brain and spinal cord], it's the long nerve tracts that are the most affected. These normally convey information through the spinal cord to the brain, particularly the cerebellum, the movement coordination center; and from the brain down the spinal cord to the peripheral nerves and muscles.

Also involved is the peripheral nervous system, the nerve fibers outside the spinal cord that send signals to the muscles and relay information from the periphery of the body back to the spinal cord and brain.



The longer the nerve fiber, the more energy it needs to transport substances. So it's the spinal long tracts and the long peripheral nerve fibers that are targeted primarily in Friedreich's. Symptoms come up initially in the legs and then, after a few years, will be noticed in the arms. The pathways are a little shorter going to the arms and can resist the stress of deficient frataxin and low energy production a little longer. Ultimately, there will be changes in speech and possibly swallowing, vision or hearing.

Some parts of the nervous system, such as the thinking and emotion-experiencing parts of the brain, appear to have more energy reserves and to tolerate energy deficiency better than the motor and sensory fibers.

The cerebellum, where movements are coordinated, has a very low safety factor. It doesn't store a lot of energy, so if energy production goes down, areas within the cerebellum itself will ultimately show some stress and atrophy [shrinkage].

The weakness that patients with Friedreich's ataxia experience is not because the muscle is being directly damaged, with the exception of the heart muscle. Skeletal muscle is an innocent bystander that experiences the consequences of its peripheral nerve connections weakening. [When signals from motor nerves fail to reach muscle, the muscle can't contract.]

The sensory loss and loss of coordination are often more of a problem than the weakness. The very first symptoms in the average person with Friedreich's are problems with balance, clumsiness, and trouble running without tripping, rather than overt weakness.

The nerve fibers that bring signals from the joints about the position of the limbs are also undergoing damage. If you lose the sense of where your foot is, where your leg is, because you don't have joint position sense, it will be extremely difficult to control signals that you're sending to move the leg. When we see a teenager with Friedreich's who all of a sudden is having a lot more difficulty with

©2010 MDA

is having a lot more difficulty with walking and balance, it's usually not because of weakness. It's usually because of the progression of the sensory changes to the cerebellum and the flawed output from the cerebellum, which are causing balance difficulties.

Q: *Is physical therapy helpful in FA?*

A: Exercise, whether it's for muscle conditioning, strengthening or stretching, or whether it's coordination-based exercise, is extremely important.

If patients with ataxia engage in a regular program that includes coordination and balance exercise, they seem to be able to turn the clock back on their symptoms. The disease will continue to progress, but at least you can bring people up a notch or two and then level them out for a period of time. We've seen this over and over again.

So we encourage all of our ataxia patients, especially Friedreich's ataxia patients, to get involved with regular daily exercise, which includes appropriate balance and coordination training and core exercise. Depending on what their limitations are, they also can do some muscle conditioning, strengthening and stretching. We recommend that a patient work with a physical therapist and do a home exercise program.

Q: *Among the most troubling symptoms in FA is the difficulty with speech, because it can make other people think the person with FA isn't intelligent. Can you comment on that?*

A: Exactly. That, and the fact that they're sitting in a wheelchair and are below eye level. These are terrible assumptions and behaviors in society that we have to change.

Q: *Does speech therapy help?*

A: Speech therapy helps, and we usually recommend it. Usually, the younger patients, if they speak slowly, can develop reasonable breath control and make their speech intelligible. Some older patients may decide to use speech-generating devices.

Q: *What about hearing and vision in FA?*

A: In young people with Friedreich's, before the age of 25, it's unusual to see noticeable vision or hearing problems. If we did very sensitive hearing or vision testing, called evoked potential testing, we would probably see very mild changes. It wouldn't affect their ability to read or see, and it wouldn't affect their ability to hear.

But as the disease slowly progresses, many people with Friedreich's will develop high-frequency hearing loss, meaning there is hearing loss at the higher pitches, such as the speech pitches. They have trouble picking out a conversation in a noisy room. It can often be compensated for with the same measures you would use for anybody with hearing loss, such as hearing aids.

Vision loss is more subtle and generally not as disabling, at least early on, as the hearing changes. For the most part, we recommend that people do all the things that people do who are visually impaired for other reasons, such as using large-print materials, magnifying devices and so forth. We encourage patients who are having functional problems with vision to work with the Braille Institute. (The Braille Institute at www.brailleinstitute.org and (800) 272-4553 offers many resources for people with poor vision.)

Q: *A relatively rare problem in FA is diabetes. It's connection to FA seems somewhat mysterious. Can you help us understand it?*

A: It is mysterious. People with Friedreich's ataxia can develop dysfunction of the beta cells in the pancreas that normally produce insulin. Why the pancreas? We don't know, but there's something about this pathway that is affected by the Friedreich's ataxia gene mutation. Besides altered insulin production, the body's tissues may not respond as well to insulin as they normally would.

Twenty percent of people with Friedreich's ataxia have a condition called carbohydrate intolerance, which is an inability of the body to completely process carbohydrates — sugars and starches — into energy.

Ten percent of Friedreich's patients actually develop insulin-requiring diabetes.

It's not as common as some of the other features of Friedreich's ataxia, but it's something that we screen all our patients for every year until they're in their 20s. Once they hit 25, it's less likely that they'll develop diabetes related to Friedreich's, although they're not immune to it from other causes.

©2010 MDA

Q: *Do you recommend dietary restrictions?*

A: Most youngsters with Friedreich's who develop diabetes are going to require insulin. If you're an insulin-dependent diabetic, you have to know what you're taking in so you can plan your insulin regimen.

If they don't have full-blown diabetes but have carbohydrate intolerance, then I think it's important to restrict the amount of free sugar they take in. Complex carbohydrates, which are starches and fiber, are appropriate, as is a certain amount of fat and protein. So it's basically a diabetic diet. You don't have to completely eliminate carbs. Consultation with a nutritionist in planning an appropriate diet is recommended.

Q: *It's often said that Friedreich's does not cause any cognitive impairment. Has that been your observation?*

A: That has been my observation. However, I do think there is a greater risk of depression. You have to be alert and not fail to recognize depression, even if it's unrelated to Friedreich's. It's something that is treatable with medication and counseling.

Q: *Is life span affected?*

A: One thing that our patients are still telling us is that when they receive their diagnosis of Friedreich's, the doctor may tell them they can't expect to live much past the age of 30. That clearly is not the case anymore.

My impression is that the primary cause of death is the heart problem. And now that the heart problems can be managed better, I think people can expect to live a much longer life. They might be living it in a wheelchair, but from that wheelchair, they can work on a computer, speak to people, get out and so forth. I have patients with Friedreich's who are in their 50s, 60s and 70s. Many have completed college, worked in interesting fields, had families and done whatever they could to support research in Friedreich's ataxia.

©2010 MDA

TREATING THE FA-AFFECTED HEART

R. Mark Payne, M.D., professor of pediatrics at Riley Heart Research Center, Indiana University, is a pediatric cardiologist whose medical specialty is intervention in children with heart disease, and who conducts research on heart disease due to mitochondrial defects.

In Friedreich's ataxia (FA), heart problems are related to a deficiency of the *frataxin* protein, which is normally located in the mitochondria.

Q: *Are the cardiac problems in FA somewhat under-recognized?*

A: Yes. Almost all the publications on this disease are on the neurologic impact, but the heart disease is what kills people. Unfortunately, it sometimes doesn't get much attention until the patients are in severe heart failure. [Heart "failure" means the heart can't pump sufficient blood to sustain normal body functions. It doesn't mean sudden cardiac arrest.]

Typically in Friedreich's ataxia, a child who's been athletic, running and playing, begins to become more clumsy or lose his or her coordination. The parents eventually become alarmed and ultimately take the child to a neurologist, who may or may not refer them to a cardiologist, because it isn't always known that the heart is involved.

In reality, any patient who has a diagnosis of Friedreich's ataxia who hasn't seen a cardiologist needs to get to one pretty quick.

Q: *What kind of cardiomyopathy [heart muscle abnormality] do you see in FA?*

A: The cardiomyopathy in Friedreich's is typically a *hypertrophic* cardiomyopathy. That means the walls of the heart get really thick. This thickening of the heart muscle is also commonly found in mitochondrial cardiomyopathies, whether it's due to Friedreich's or not.

Patients typically get a Friedreich's ataxia diagnosis between the ages of 10 and 18. At that time, they frequently have a thick heart that functions fine. Then, over time, that thick heart begins to function worse and worse. In about 10 to 15 years, they can develop severe heart failure from this.

Q: *What are the heart symptoms that patients experience?*

A: They may have irregular heart rhythms, which they can feel as palpitations, as the heart beats faster or is irregular. It's not really painful, but it can be uncomfortable and alarming. They may have shortness of breath and difficulty breathing when lying down, so they may feel the need to be propped up when they're in bed. They may have swelling of their hands and feet, primarily their feet, as the circulation becomes sluggish.

Q: *What's going on in the FA-affected heart?*

A: A particular thing about these

©2010 MDA

hearts is that, over time, they maintain good *systolic function* [contraction of the heart muscle]. That means their ability to pump blood out seems to be OK — but because their hearts are thick, their ability to relax and accept blood to fill them is not OK.

They develop what's called *diastolic dysfunction* [the resting phase of the cardiac cycle, between contractions of the heart muscle]. As a result, they lose the ability to adapt to the demands of exercise or increased blood volume.

The FA-affected hypertrophic heart adapts to increased demands by beating faster. That's the only way it can adapt, since it can't increase its capacity to accept more blood with each cardiac cycle.

If the heart keeps having to beat faster to meet various demands, that can lead to a second problem, which is an irregular heart rhythm, or *arrhythmia*.

Q: *How are these problems treated?*

A: For mitochondrial cardiomyopathies, including Friedreich's, we may not have a cure, but we have multiple drugs that seem to help prolong life and maintain some function, when used in combination.

In general, we treat mitochondrial cardiomyopathies like Friedreich's based on analogy to other types of hypertrophic cardiomyopathies where the drugs seem to work. Unfortunately, we're not really sure yet what works in Friedreich's.

One concern I have is that many FA patients get put on *beta blockers* [drugs that decrease the force and rate of heart contractions], because that's standard therapy for hypertrophic cardiomyopathy. There are no clinical trials examining the use of beta blockers in Friedreich's ataxia.

Most patients with hypertrophic cardiomyopathy who don't have Friedreich's ataxia can still relax their hearts. They usually have good blood flow into the heart, unless their hearts are really thick. And they don't have stiff hearts with a lot of scar tissue, which may be a problem for patients with Friedreich's ataxia.

The average person with non-Friedreich's ataxia hypertrophic cardiomyopathy may have a higher-than-average heart rate, but they don't have to increase their heart rate that much.

However, if the heart has to speed up to accommodate the fact that it can't fill with blood, such as in Friedreich's ataxia, then if you slow it down with a beta blocker, the cardiac output drops and these patients will have problems. They feel bad and don't have any energy.

So, I would urge cardiologists not to reach for the beta blockers as a first-line therapy for these hearts. Instead, one of the things they may want to consider is lowering blood pressure without hurting heart performance.

That can be done with drugs called *ACE inhibitors*, like *captopril* or *enalopril*, which make the heart's work easier by dilating blood vessels and lowering the pressure against which the heart has to push to pump the blood out.

Some patients will be put on *digoxin* [a drug that increases contractile force], which may make the heart perform a little better. Digoxin also helps control arrhythmias.

Other anti-arrhythmic drugs cardiologists might use include *amiodarone* or *flecainide*. You have to treat the specific type of arrhythmia.

Q: *There's been some evidence that idebenone, an antioxidant, may help the FA-affected heart. Can you comment on that?*

A: Yes. Small studies showed that it helped thin the heart walls by a small amount, with minimal, if any, improvement in cardiac function.

That's not to say that idebenone is the wrong way to go. Idebenone for a lifetime may be very effective at maintaining heart function. We don't know until these clinical trials are conducted.

But as a cure, idebenone is not it.

Q: *What should people with FA do about their heart problems?*

A: The thing that I would ask most of all is that all patients with Friedreich's see a cardiologist and that all patients with this disease help with clinical studies in some form or fashion.

They can actually further our understanding of their disease by participating in a study. Doing so may be as simple as allowing their doctor to send their medical records to someone else to analyze.

©2010 MDA

STRATEGIES TO IMPROVE FAAFFECTED SPEECH

Anne Wallace, speech-language pathologist and clinical associate professor in the Department of Communication Sciences & Disorders, University of Iowa in Iowa City, has been at that facility for 20 years. During that time, she's had a longstanding relationship with the pediatric specialty clinics, including the MDA clinic directed by child neurologist Katherine Mathews, and has worked with many children and young adults with FA.

Q: *What are the speech-related issues in FA?*

A: The main problem is *dysarthria*, which means a motor speech disorder, not a cognitive speech disorder. Cognition is generally intact in Friedreich's ataxia.

Dysarthria is caused by things such as muscle paralysis or weakness of the muscles related to speech production or inability to coordinate these muscles. Those are the muscles of the lips, tongue and throat, and also the respiratory muscles that push air over the vocal cords. You have to have respiratory muscles working together to create air flow to make your vocal folds work.

In Friedreich's ataxia, there are breakdowns in the system of speech production. There can be varied problems that result, such as speech that is slurred or slow or problems with the pitch or loudness or rhythm of the speech.

Friedreich's ataxia speech is typically pretty slow and deliberate. The syllables are produced pretty much with equal stress on each word. For example, if I'm saying "banana peel," I'm not saying ba-na-na-peel, with the same stress on every syllable. Someone with Friedreich's might, however, do that.

There's less contrast between the stressed and unstressed syllables, so it's hard to tell, for instance, whether someone is saying "OB-ject" or "ob-JECT," which are two different things.

The underlying problem with ataxia in general has to do with *cerebellar damage*. The cerebellum is what controls coordination. The cerebellum controls a lot of the coordination aspects related to speech, as well as to other things, such as walking.

The earlier the onset of the disease, the worse the problems tend to be. For most people with Friedreich's, the speech problems occur in adulthood, and the onset is gradual. They don't happen overnight. The problems develop over time, so people have a chance to adapt to them.

Q: *Can you talk about some of the specific problems and your approaches to treating them?*

A: An average person can say so many words on a breath, and then they automatically breathe at a certain time, usually at normal phrase boundaries. They'll breathe at the end of a thought or a sentence, not in the middle.

But if all your speech is slow because of muscle coordination

©2010 MDA

problems, you still can only say so many syllables per breath. If your syllables are twice as long, you can only say half as many things. It takes the person with Friedreich's more breath and more work to say something than it does the average person. For many people, that's frustrating.

Sometimes in Friedreich's there's a voicing problem, where the person's voice is coming in and out. There can be a problem with a sudden, really loud voice in the middle of a syllable. It's related to coordination. When you make a syllable louder, you actually use more air. When you use more air, you have even less breath for finishing the rest of what you're trying to say.

They can learn to regulate these aspects of speech, which are related to control of air flow. For instance, you can work on multisyllabic words, like "computer" or "Episcopal." One strategy is called *backward building*. You take a word like "Episcopal," and you say "pull." You build it from the back all the way forward. Eventually you get the rhythm of what you need to say.

Then you play around with the stress. We work a lot on making the stresses come out on certain words, practicing phrases such as "I SEE a ball"; "I see A ball"; and "I see a BALL."

Another problem in Friedreich's is that consonant precision is not there. [Consonants are sounds that require complete or partial closure of a part of the vocal tract.] A common thing is not putting the final consonant on a word, so that "hat" becomes "ha."

I work with patients on trying to make more precise sounds, to try to make the consonants better. I work on words that have final consonants, particularly ones that have more air pressure, what we call *plosive* sounds, like t, d, k and g.

You have to show a person how they need to do that. Sometimes you can use a tactile cue, such as a hand in front of their face. If you were to do that, and say, "hat" with a lot of force, you can feel it on your hand. We also use things like mirrors, which will fog up when you say "hat" forcefully. These techniques add precision to what they say.

What you trade off in order to be able to produce those consonants and improve breath control is that it reduces the rate of speech. But it's better to slightly reduce your rate than to have all your consonants missing or have the stresses wrong.

Of course, the underlying neuromuscular system is the same, but we don't tax it as much if we reduce the speed.

Q: Do you have to adjust techniques to disease progression?

A: Yes, you do. Some people continue to be successful with minimal prompting. They learn how to adapt. But there are some people who require some augmentative systems [such as talking computers] at some point. Certainly not everybody.

I don't recommend augmentative devices lightly. You can have a high-tech system, such as a voice output device, but the more high-tech it gets, the more transporting the device becomes a problem. If you're using a wheelchair, and the device is connected to your wheelchair, then it's there for you, and it might be easily accessible. But what do you do when you're not in your chair? How do you communicate then? Do you have to always be in your chair to communicate?

Lots of times, families that have younger kids will say, "Let's get the best kind of computer." But here's the deal: You've got to haul it. The child has to haul it, and maybe they have other motor problems, making that prohibitive. Or maybe the battery won't hold a charge. There are a lot of issues.

I try to figure out what their communication demands are and match that to what their abilities are and supplement them as needed with an augmentative system or an assistive system, whether that be low-tech or high-tech. I'm not an augmentative technology expert, but I do know that it's not always an easy solution, and many times we work for years trying to find an augmentative system that works best for a person's communication needs.

The bottom line is: Can they communicate what they want with their family or in a work setting in a way so that they're not frustrated by it?

Q: Can most people achieve that?

A: I think so. At least a lot of people can. However, I do think

©2010 MDA

the communication deficit in Friedreich's does pose a lot of problems. Sometimes, people perceive Friedreich's patients as not being intelligent because of the slow, labored speech. It makes it seem like their cognitive skills are not intact. That's far from the truth, but this is a frustration.

Unfortunately, sometimes there's just less interest in interacting, because speech is a lot of work. I always hate to see that happen.

Another issue is that it's hard to listen to this speech. If you're the patient's partner or parent, there can be an urge, when you see how much work the speech is, to fill in, to jump ahead. But it can be devastating to somebody that's trying to communicate some information or a thought or an idea. It defeats somebody's purpose in trying to communicate.

We try to work with families. As long as it takes the person to say something, we tell them to try to patiently wait it out. If the person is trying, you want to support that. It doesn't help as much as you think to fill in for them. But it can be hard for families to be good listeners.

Q: Is it best for someone with FA to start a speech program as soon as they begin to develop problems, or does that matter?

A: We see patients at different points all the way along. I'm big on intervening early, though, so that people know what's available. I think what helps in the very beginning is to alert people, to tell them that these are the problems that are probably going to arise, and these are the resources that are available to you.

Then, if they see that their speech is deteriorating — for instance, if people are asking "what?" more often than not, or if they're recognizing that speech is really laborious — they know there are things they can do to address the problem.

Some early compensatory strategies could be developed that would save them effort and worry, as opposed to waiting until they're too frustrated to talk.

©2010 MDA

PHYSICAL THERAPY FOR FA: PRACTICE, PRACTICE, PRACTICE

Melinda Guttry, a physical therapist in Rehabilitation Services at the University of California-Los Angeles Health System, has worked closely with neurologist Susan Perlman (see page 14) and with FA patients since the mid-1980s.

Most of her clients with FA have been young adults, but she also has worked with people in their 40s and 50s.

Q: *What kinds of problems do you see in people with FA?*

A: It's usually movement and coordination. The nerves aren't conducting information consistently, so the muscles don't receive consistent signals about holding a position or making a limb have a smooth, coordinated movement.

A lot of the problem is in outgoing coordination signals from the nervous system. But if you have a muscle that's getting weaker because the person is not using it, then the muscle doesn't activate as readily either. There can be problems with sensing position as well.

Q: *What do you do about these problems in a rehabilitation setting?*

A: We try to have people work on exercise and work on stability, and use their muscles so that they're reminding the muscles of holding the body erect or sitting upright or making smoother movements.

If I have the person moving from a sitting to a standing position, I use the parallel bars and have them practice. I start them out by helping them set their muscles and use their muscles in a sequence. Then, as they practice, they get a better feel for the sequence. They know which muscles they're using and the feeling of the muscles as they coordinate them.

Parallel bars are heavier than they are, and they're long. The bars are solid and stable, and people get an opportunity to isolate different muscles, setting their muscles so that their trunk is more stable.

On the parallel bars, if they're trying to stand up, they might pull on the bars. I teach them to push down instead, because if they want to use a walker and they pull up on the walker, the walker won't stay on the ground.

I also work with them on *range of motion* [putting a joint through its normal movement range], to help maintain flexibility.

Q: *Can you improve function in someone who has degenerating nerve fibers?*

A: Yes, because there are many, many nerve fibers, and they all don't degenerate at one time. So it's the practice of getting all the fibers that are still functioning to do the work, to give as much information to the muscles as possible.

Q: *Have you had good results?*

A: I've seen good results. It depends on how much the person is able to practice at home.

Sometimes that's a problem. It depends on the age of the person and how motivated they are to practice versus staying in their chairs and doing something else. Sometimes that's more important to them than getting up and practicing walking.

But the more they're up and the more they practice coordinating their muscles, the more they can stay up.

©2010 MDA

SAVED BY A DOG'S LOVE

Gabrielle Ford
Age 30

(2004 photo)

As a child, Gabrielle Ford studied to be a dancer. By the time she was 12, she had put in countless hours of rehearsing ballet, jazz and tap — learning the steps, standing on tip-toes, doings dips, turns and spins — all the while dreaming of the day when she would perform professionally.

Then Ford's life took an unexpected turn. She began to lose strength and balance. Her gait grew unsteady. She was taken for a series of tests that revealed she had Friedreich's ataxia (FA). But knowing how much her daughter wanted to be a dancer, Ford's mother kept the news from her for six months.

When she learned the truth, three days after her 13th birthday, Ford didn't take it well. "I was in denial," she writes in her memoir, ***Still Dancing***. "To talk about it would make it real, and I didn't want it to be real."

All through high school, Ford kept her diagnosis a secret. Her condition worsened, yet she refused to use any adaptive equipment. As her speech slowed and she began to trip and fall, she endured cruel comments and taunts, and even physical abuse from classmates. She became increasingly isolated. She didn't want to meet other teens with FA, and she forbade her family from mentioning her condition — or even watching the MDA Telethon on TV.

At graduation, despite a twisted ankle, Ford walked across the stage to receive her diploma. But afterward, she fell into a deep depression. She became angry at the world and mean to her family.

She spent two miserable years before Izzy, a black-and-tan coonhound puppy, came into her life. That's when things began to change.

By helping her to acknowledge her FA, Izzy pulled Ford out of her shell. First, Ford had to get a wheelchair, so Izzy would grow up comfortable around wheels. (Ford, however, continued to refuse the chair until she fell and broke her arm.) Then Ford learned that Izzy had liver disease, as well as a form of muscular dystrophy that caused muscle weakness similar in some ways to FA.

Izzy's illness further forced Ford back into the world, as she had to take the dog to numerous doctors and hospitals, and to accept help, financial and otherwise, from friends and family members.

Ford and Izzy's story — the two of them helping each other with diseases that were uncannily similar — was published in local newspapers. Word spread about the unusual pair, and Ford got a call from the cable TV channel Animal Planet, which wanted to film her and Izzy's story for a segment about pets and their owners. The piece aired dozens of times, and "Gabe 'n Izzy" became famous.

The final step in Ford's redemption came when she and Izzy began visiting schools to talk to kids about the harmful effects of bullying. Ultimately, Ford was even able to speak at her old high school. She has received dozens of letters from children telling her how much her presentation meant to them, and many more inquiring about Izzy.

Even though Izzy passed away in May 2009, Ford, who lives in Fenton, Mich., continues to visit schools, speaking on stage before hundreds of kids about her experiences and encouraging them not to bully others.

She did end up performing — just not in the way she imagined.

Ford's book, as well as recent information about her anti-bullying presentations, is available on Ford's website, www.gabeandizzy.com.

©2010 MDA

FA HELPED HIM LEARN WHAT'S IMPORTANT IN LIFE

Nygel Lenz
Age 36

Growing up, Nygel Lenz was a typical active boy. He played football, soccer, basketball and baseball, and loved doing tricks like jumping ramps with his bike and skateboard. He was diagnosed with scoliosis at 11, but his life didn't really change — until he had surgery for scoliosis at age 15. His balance worsened immediately and he began seeing a neurologist, but it took almost four years to confirm that he had Friedreich's ataxia (FA).

"I experienced most of high school wondering what was wrong with my body," says Lenz, 36, of Clearwater, Fla. "My balance kept worsening. I stopped playing sports and became increasingly self-conscious, concerned that others would see me walk awkwardly and that girls would not be interested in me. I was scared, but I tried to maintain normalcy and only told my closest friends."

A good student, after high school Lenz was able to complete both college and graduate school. "I was not going to allow FA to defeat me," he reports. "However, I must admit that I did not completely accept FA or confront what the diagnosis meant. It is daunting. I used a cane for a couple of years, a walker for a couple of years, and I finally began relying upon a wheelchair after graduate school (in 2001).

"I experienced stares and questions. I still do. I experienced rejection from girls. I avoided going to events that I wanted to attend, like Gator football games when I was a student there. I had to stop driving. I could not find a job."

Lenz finally decided to learn all he could about his disease, in order to empower himself and others. He joined a support group, then began leading it in 2002 and hosted a national meeting in 2005.

"I had a lot of responsibilities in terms of leading fundraisers, seeking guest speakers, finding hotels and speaking," he says. "This is only one example of something I never would have done if I did not have FA."

His confidence boosted, Lenz was able to find a job. Since 2004, he has worked at the Pinellas County Juvenile Assessment Center, counseling troubled teenagers. Even though many of the kids he counsels are criminals and gang members, they have never given him any trouble — perhaps because they realize that Lenz knows something about struggle and hardship himself.

Like many with FA, Lenz has hypertrophic cardiomyopathy. Beginning in 1999, his heart would occasionally go out of rhythm or into atrial fibrillation, making him extremely short of breath, sweaty and exhausted. The symptoms have gotten much better since Lenz underwent two radio-frequency ablations (a procedure that uses high-frequency radio waves to treat the heart's electrical conduction system) in 2004 and 2006. He currently gets echocardiograms about once a year, and monthly EKGs and monitoring of the heart medications he takes.

Nygel Lenz and his fiancee, Carolyn Hunter at the 2010 Telethon in St. Petersburg, Fla.

Lenz participated in a study of the drug buspirone as a potential FA treatment, but it worsened his symptoms. He also tried coenzyme Q10, without benefit. He enjoys physical therapy, but his insurance does not pay for enough sessions per year to really make a difference. "I need a PT to push me and help me exercise," he says.

Lenz recently went back to school to get a second master's degree in criminology and criminal justice, so he can get the accreditation he needs to teach college. He enjoys spending time with his friends and fiancee, joking, playing games, writing and traveling.

Active in fundraising and other activities for MDA, Lenz received the MDA Robert Ross Personal Achievement Award for the state of Florida in 2009. At 36, he has lived more than half his life with Friedreich's ataxia.

"Of course I would prefer to not have had FA, but it has helped me gain some perspective and determine what is important in life — and who the important people in life are."

©2010 MDA

MULTIPLE DIAGNOSES, INCLUDING FA

Bridget Morris
Age 19

Diagnosed as bipolar and autistic while still a child, Bridget Morris grew up with a host of developmental problems. That's why, when she was tested for Friedreich's ataxia (FA) at age 10, her mother, a nurse, was "very cavalier."

Bridget had muscle tightness, weakness and scoliosis (a curved spine), her handwriting was worsening, and she had begun to fall and walk with a "wide" gait to steady herself. Nevertheless, her mother was shocked when told her daughter had FA. "When I think of that moment on the phone, hearing those impossible words, I still feel an icy chill in my bones, and the hairs on the back of my neck stand up," Alicia Morris says.

Growing up, Bridget could be engaging and witty, and was good at languages, especially Russian and French. She learned to read and write in Cyrillic and can read Chekov in Russian. Yet she also could be aggressive and combative, and needed physical, speech and occupational therapy. She had been on a multitude of prescription mental health drugs since kindergarten, which is one reason her mother initially discounted the idea that Bridget also had muscle disease.

"We used to think FA was the least of our problems," Alicia Morris says. "Not anymore."

Now 20, Bridget, of Littleton, Mass., attends a residential school for children with special needs and gets around in a manual wheelchair. Her speech has slowed a bit, but she so far has escaped heart problems, diabetes, and vision or hearing problems, which are frequent symptoms of FA.

Her mother advises other parents of children with FA to get support from an FA parent group, and to take family trips as soon as possible, because traveling can be more difficult once FA symptoms progress.

She says she has a lot of hope about the progress of research in FA, and encourages other FA families to get involved in fundraising and to participate in studies, where appropriate.

"Working hard toward a cure gives purpose and a goal to something over which we have no real control," notes Bridget's mom, Alicia.

©2010 MDA

DON'T GET MAD — EDUCATE

Pinky Patel
Age 28

Pinalben "Pinky" Patel was born in a village in Western India and moved to the United States with her family four years later. She already was starting to show symptoms of Friedreich's ataxia (FA).

"My aunt and cousin took me trick-or-treating for the first time," she says. "When we got home, my aunt complained that I kept falling down on purpose for attention. A couple years later my kindergarten teacher noticed that I wasn't placing my feet the way I should when walking."

Patel received an FA diagnosis when she was 11 years old, and began using a power wheelchair at age 13. At first, she was able to transfer in and out of the chair by herself, or with minimal assistance. Throughout high school she maintained the ability to bathe, brush her teeth and get dressed by herself.

"The beginning of my progression from just wheelchair user to 'FA-er' was in the sophomore year of high school, when I was diagnosed with insulin-dependent diabetes," reports Patel.

While Patel was in the hospital, the doctors also found a thickening of her heart walls, and she began taking medication for that, too.

Two years later, Patel fainted at school and went to the emergency room. "When I got to the hospital, the doctors found that I had bradycardia, a fancy name for slow heartbeat. They decided I needed a pacemaker implanted to regulate my heartbeat and surgery was scheduled." She now has a pacemaker, which she gets checked twice a year.

By the time Patel started college, she needed help with all her personal care. "People asked why I drove my wheelchair so drunken-like, why I didn't transfer myself to and from my wheelchair, or why I couldn't dress and bathe myself like that other wheelchair-user.

"Of course those comparing queries aggravated me, but I kept the anger in my mind. Instead of raging at the askers, I calmly educated them about FA. They are not asking to be rude; they are just ignorant. There are so many different disabilities out there, and everyone can't know about every disability."

During Patel's last year of high school, she developed a hearing problem. "My friends would tease me," she says. "They said that I only listen to what I want to hear. I remember getting annoyed at their taunting. I never liked being made fun of about anything related to my disability, but I did not know that this problem was also related to FA."

It wasn't until Patel graduated from college and began attending support groups that she learned her hearing problems were caused by FA. "It's called auditory neuropathy (AN), and it basically means I cannot hear well in crowds, on the phone, and any other situation

where there are two noises or more occurring at once."

Patel also was unaware that her weakened eyesight was the result of FA until she met others online who also were in her situation. Even after LASIK (corrective) surgery, Patel has shaky vision, poor depth perception and wears prescription glasses.

Patel received a journalism degree from Murray State University in Murray, Ky., and now works as a freelance writer in Paducah.

"I have been lucky to have friends from school (who stopped teasing me after I explained about the AN) and my support groups," Patel says. "I don't care what strangers or distant relatives think of me.

"The most important knowledge is that the people who are close to you understand your condition. Don't worry about others. It is the only way to live!"

Pinky Patel has a website at http://pinkdreams_1.tripod.com.

©2010 MDA

GET INVOLVED AND DON'T GIVE UP

Kayla Prather
Age 17

When Kayla Prather was 8 years old, she began having trouble with her balance. Her mom took her to a pediatrician, who tested her reflexes and found she didn't have any.

More tests followed, including one of Kayla's DNA, and the diagnosis of Friedreich's ataxia (FA) was confirmed.

Prather, of Hiram, Ga., says the disease didn't bother her much at first. She still could run around and play with her friends in the neighborhood. But as her symptoms worsened and her ability to get around decreased, she became less social. Now, she says, she has few friends outside of school.

"It's difficult to go to my friends' houses or spend the night because their homes are not accessible," Prather says. "Even just to go off with my friends is difficult. Usually I will meet my friends at the movies and then maybe go to dinner, but my mom has to take me and then pick me up, and take me to the dinner location because I can't ride with my friends."

At school, Prather uses a power wheelchair full time and has a "parapro," or assistant, assigned to her. "My parapro and I are very close," she says. "She goes with me to all my classes and lunch. When I am tired, she takes notes for me. I'm out of school a lot and when I am, she attends my classes, takes notes and collects my homework for me. That way I don't fall behind."

Prather visits the MDA clinic and a cardiologist for checkups every six months. She is on the drug metoprolol to treat hypertrophic cardiomyopathy, a thickening of the heart muscle that is a common problem in FA (see Treating the FA-Affected Heart on page 18). She also takes asthma medications and has been treated for scoliosis and stomach pains.

Her vision is good, but she has slight hearing loss and her speech is beginning to soften and slur. "I usually end up repeating myself a lot, and sometimes I have to try to speak louder but it tires me out when I do that."

Prather enjoys reading, surfing the Internet and going to movies. She loves the "Twilight" movies, once even attending a midnight showing. She also is active in FA support groups and awareness campaigns, and has gone door-to-door to raise money for MDA.

She encourages other young people with FA to get involved with support groups and awareness campaigns and to not give up.

"Remember, we can do most anything that others do, but we just have to learn to do it differently. Keep on persevering — don't give up!"

MDA

MDA's website is constantly updated with the latest information about the diseases in its program.

mda.org • (800) 572-1717

©2010, Muscular Dystrophy Association Inc.