

# THE WAITING ROOM

THIS WAY IN

## Friedreich's Ataxia

**T**here is promising news on the horizon for people with Friedreich's ataxia, a neurological disease that causes progressive muscle weakness, difficulty walking, slurred speech, and heart problems. The discovery of the mechanism for a potential drug treatment was reported in the September 25, 2009 issue of the medical journal *Chemistry & Biology*.

A team of researchers led by Joel Gottesfeld, Ph.D., professor of molecular biology at the Scripps Research Institute in LaJolla, CA, discovered the specific enzyme target of a compound called 4b that stops the progression of the disease in mice. Dr. Gottesfeld's team discovered the compound three years ago but didn't know how it worked. Now, having identified the particular enzyme that 4b blocks, they are developing targets for treatment.

The term "ataxia" can refer to problems with movement and coordination that occur with several different neurological conditions. The term also indicates a group of degenerative and progressive diseases of the nervous system that occur sporadically or—as in the case of Friedreich's ataxia—through genetics.

Friedreich's ataxia affects 1 in every 20,000 to 50,000 people in the United States. Men and women are equally affected. The cause of Friedreich's ataxia is a defect in a gene, located on chromosome 9, that reduces the amount of a protein called frataxin in patients. Frataxin is found in the energy-producing parts of the cell. Without a normal level of frataxin, certain cells in the body cannot effectively produce energy or rid themselves of toxins, resulting in degeneration. For example, the spinal cord becomes thinner, and nerve cells that control limb movement lose some of their myelin sheath (the covering on all nerve cells that helps conduct nerve impulses).

Researchers believe the genetic defect attracts a group of enzymes known as histone deacetylases, which inactivate expression of the frataxin gene. In 2006, Dr. Gottesfeld's team reported that 4b blocked activity of these enzymes, jumpstarting frataxin production in white blood cells taken from Friedreich's patients. Later work showed that a close derivative of 4b increased frataxin production in a mouse model for Friedreich's ataxia. The most recent work has identified the specific histone deacetylase enzyme that is blocked by 4b.

The degeneration of nerve tissue in Friedreich's ataxia leads

CONTINUED ON P. 13



Kyle Bryant is founder of FARA's Ride Ataxia cycling Fundraiser. For more information about FARA and Ride Ataxia, go to: [CureFA.org](http://CureFA.org).

Research is ramping up in this disease, with many potential treatments, such as idebenone and histone deacetylase inhibitors.

### Ataxia Resources

- ▶ Friedreich's Ataxia Research Alliance (FARA)  
703-426-1576, [CureFA.org](http://CureFA.org)
- ▶ Genetic Alliance  
202-966-5557 or 800-336-GENE (4363)  
[geneticalliance.org](http://geneticalliance.org)
- ▶ Muscular Dystrophy Association  
520-529-2000 or 800-344-4863, [mda.org](http://mda.org)
- ▶ National Ataxia Foundation  
763-553-0020, [ataxia.org](http://ataxia.org)
- ▶ National Organization for Rare Disorders (NORD)  
203-744-0100 or 800-999-NORD (6673), [rarediseases.org](http://rarediseases.org)
- ▶ National Society of Genetic Counselors  
312-321-6834, [nsgc.org](http://nsgc.org)

SLOGOGRAPHY

CONTINUED FROM P. 12

to muscle weakness and wasting in the hands, feet, and lower legs, which is why patients are often confined to a wheelchair within 10 to 20 years of the appearance of symptoms. Typically, symptoms begin in patients ages 5 to 15. Difficulty with walking is usually the first symptom to appear. As the disease progresses, patients may experience a gradual loss of sensation in the extremities; rapid, involuntary eye movements; slow, slurred speech; spinal curvature (scoliosis); and heart disease and heart failure.

The rate of progression and the life expectancy varies from person to person. Most people with Friedreich's ataxia die in early adulthood if they have significant heart disease (the most common cause of death in these patients). Some people with less severe symptoms of Friedreich's ataxia live into their sixties or seventies.

In order to diagnose Friedreich's ataxia, neurologists perform a careful clinical examination. They may also perform tests such as an electromyogram (EMG), which measures the electrical activity of muscle cells; electrocardiogram (EKG), which shows the beat pattern of the heart; magnetic resonance imaging (MRI) or computed tomography (CT) scan, which show a picture of the brain and spinal cord; a spinal tap to examine the cerebrospinal fluid; nerve conduction studies, which measure the speed with which nerves transmit impulses; blood and urine tests to look for high glucose levels; and genetic testing to identify the affected gene.

Adaptive devices (such as canes or walkers), therapies (such as speech therapy to improve speech and aid swallowing), and medications for accompanying complications (like heart problems) can assist patients.

Although there is no effective treatment or cure for Friedreich's ataxia, researchers are hard at work.

"Idebenone has shown some efficacy in preventing or reversing the associated heart disease, but even idebenone has failed to reverse or slow progression of the neurological symptoms," Dr. Gottesfeld says. "Our compounds—called histone deacetylase inhibitors—target the loss of frataxin protein, which is the cause of the disease. They do this by reactivating the gene that is silenced in Friedreich's ataxia."

Dr. Gottesfeld will continue to study how the enzyme blocked by 4b controls frataxin production and its relationship to inactivating the frataxin gene. Repligen Corporation, which was involved in Dr. Gottesfeld's study, is doing all of the pre-clinical testing necessary to initiate a human safety trial.

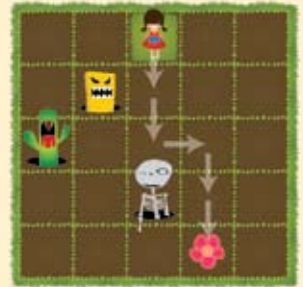
"Erythropoetin has also been found to increase the levels of frataxin protein, and this drug is in clinical trials," Dr. Gottesfeld adds.

Genetic testing assists with prenatal diagnosis, clinical diagnosis, and carrier status determination. Psychological counseling and support groups may also help patients and their families cope. —Elizabeth Stump

## NEUROBICS

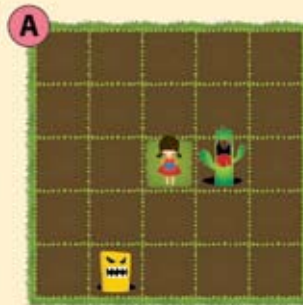
### Monster Garden

The garden at right is divided into squares. The gardener in the green square wants to find the shortest path to the flower that avoids all the monsters. In this case she can get there in just five steps by following the arrows.

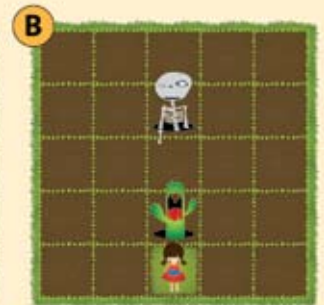


Now it's your turn. Your job is to find the shortest path from the gardener to the flower. But this time you'll have to use your memory. Look at garden A below. Memorize the positions of the gardener and the two monsters. Got it? Once you have the positions memorized, turn the page and continue reading.

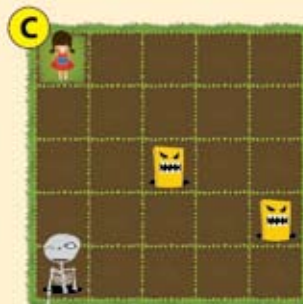
GO TO P. 15



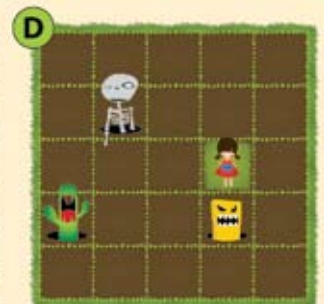
Remember these positions



Remember these positions



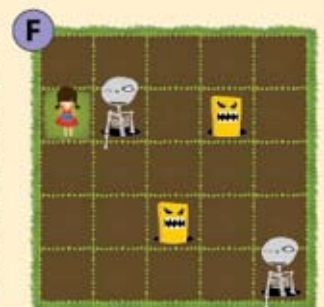
Remember these positions



Remember these positions



Remember these positions



Remember these positions