

The Nature of Friedreich's Ataxia

Kelly Drake

Human Anatomy & Physiology

Radford University

November 2007

History of Disorder and Origin of Eponym

Friedreich's ataxia is a neurodegenerative disorder with an autosomal recessive origin that affects voluntary movement control and causes muscle weakness. Friedreich's ataxia, also known as FRDA or FA, is the most common early-onset hereditary ataxia, accounting for nearly half of all the inherited spinocerebellar ataxias (Pandolfo, 2002). The key clinical features of FA include gait ataxia or loss of muscular control, dysarthria or slurred speech, drastic decrease or absence of reflexes in lower extremities, and progressive muscle degeneration. Loss of leg muscle mass, heart disease, increased occurrence of diabetes mellitus, nystagmus or involuntary eye movement, hypoacusia or partial hearing loss, scoliosis, and foot deformities such as pes cavus are often observed in FA patients (Koenig and Durr, 2000).

Friedreich's ataxia was first discovered and named by Nicholas Friedreich in 1863. Friedreich, appointed Chief Professor of Medicine in Heidelberg in 1858, first began studying ataxia in the 1850s and soon recognized a distinction in symptoms from the common locomotor ataxia that served as the diagnosis for many of the patients he studied. Friedreich's growing curiosity led him to discover the involvement of the lower portion of the spinal cord in the initial stages of the disorder. Further investigation led him to ascertain that the disease eventually spreads to the medulla oblongata upon progression. Microscopic analysis helped Friedreich to incorporate the involvement of the lateral columns within the thoracic region of the spinal cord. Degeneration of the cells found within Clarke's column of the posterior thoracic nucleus and the hypoglossal nuclei in the cranial nerve nucleus also characterize the disorder. Another distinguishing factor from other spinocerebellar ataxias is the presence of significant fatty degeneration of cardiac muscle (Chakravarty, 2003).

Friedreich's discovery was initially ill-received in the medical world, with most physicians and researchers believing the disorder to be a variant of tabes dorsalis, which is slow degeneration of nerve cells and fibers. Friedreich's newfound disorder was temporarily left claiming little distinction from the syndrome of locomotor ataxia. FA had previously been lumped together with similar diagnoses and considered a variation of other diseases, such as the syndrome of locomotor ataxia, tabes dorsalis, and multiple sclerosis. None of these disorders identically incorporated the problems within the dorsal columns of the spinal cord that set FA apart. Friedreich argued that nerve atrophy and deterioration, demyelination of axons, and replacement by fine fibrillary tissue seen in the proposed FA patients was not observed during microscopic assessment of locomotor ataxic patients. He also pointed out the absence of some visual and sensory ailments that characterize the general locomotor ataxia that served to differentiate the newly discovered form of ataxia. Once the relevance was established and acceptance of the new disorder became widespread, physicians began to diagnose patients of cerebellar ataxia with FA, even though the form was oftentimes autosomal dominant in origin. Misdiagnosis continued until Anita Harding established the autosomal recessive transmission of FA. Harding also identified several additional, more specialized symptoms of the disorder that extend beyond the criterion set forth by Friedreich and are used in the diagnosis process today (Chakravarty, 2003).

Embryology/Developmental Aspects

Ataxia is uncoordinated movements and clumsiness unrelated to muscular weakness or decreased muscle tone that causes difficulties associated with the rate, abundance, breadth, and force of muscular movements (Periman, 2006). FA is exemplified by autosomal recessive inheritance associated with chromosome 9, and its onset usually ranges from early childhood to

adolescence. There are several different forms of FA, which include the most common form as well as atypical forms. The most common form, affecting approximately 75% of FA patients, is known as 'classic' or 'typical' FA. The less common forms that have the FA phenotype but lack certain diagnostic criterion typical of FA include: late onset Friedreich's ataxia (LOFA) that occurs after age twenty-five, very late onset Friedreich's ataxia (VLOFA), Friedreich's ataxia with retained reflexes (FARR), Acadian type or Louisiana form, and spastic paraparesis without ataxia. Molecular differentiation that causes these distinctions remains ambiguous (Cardeiro, 2007; Pandolfo, 2002).

FA is characterized by sixty-six or more repeats of GAA that serves as the primary cause of the disease. The involvement of the GAA expansion is proven by the substantial inverse correlation between the size of the different expansions and the age of symptomatic FA onset, along with the intensity of symptoms (Koenig and Durr, 2000). Genetic testing is encouraged for all prospective Friedreich's ataxia sufferers, as well as for determining the presence of defected genes that occur in the carrier state. A potential carrier would possess a normal copy and a defective copy of the frataxin gene. Amniocentesis or chorionic villus sampling can be used during pregnancy to determine if the fetus will develop FA. Those who wish to know their chances of producing affected children, such as adult siblings, are among the most common recipients of DNA testing for non-carriers of the Friedreich's ataxia gene (Cardeiro, 2007).

The average age of onset is 7.5 to 23.5, but the range extends from 2 to 51 years (Koenig and Durr, 2000). Diagnosis of FA is based on the results of several clinical tests of mobility and physical functioning levels, and is solidified by genetic testing. Physical exams and reviews of medical history account for the clinical portion of diagnoses, and genetic testing determines the expansion of GAA repeats that causes the dysfunction of frataxin. The initial sign of the

disorder is usually difficulty walking or gait ataxia, and there are many tests to measure one's level of physical functioning that aid in diagnosing the disorder. Loss of vibration or position sense and tendon reflexes in childhood or adolescent ages are also key factors that aid physicians in determining FA diagnosis (Cardeiro, 2007).

Some of the tests used to establish diagnosis are genetic testing, electromyography, conduction nerve study, computed tomography or CT scan, cerebral and cervical magnetic resonance imaging or MRI, spinal tap, echocardiogram, electrocardiogram, and blood and urine analysis of glucose levels (Cardeiro, 2007). Cerebral MRI is used to determine cerebellar abnormality or atrophy, while cervical MRI can confirm thinning of the cervical spinal cord. Echocardiograms are performed regularly to identify any irregular cardiac arrhythmias in patients. Blood glucose analysis tests for glucose tolerance, and are a standard portion of follow-up procedures due to the widespread occurrence of diabetes mellitus and diminished glucose tolerance in patients (Koenig and Durr, 2000). Performance measures are very helpful in determining the extent of neurological damage and genetic abnormalities. The performance measures most widely used to assess ataxia disorders are the timed 25-foot walk, or T25FW, the 9-hole peg test, or 9HPT, and various tests for cognitive functioning. The T25FW helps in the assessment of walking and mobility abilities and the 9HPT aids in determining level of arm strength and performance (Lynch, *et al.*, 2006).

Although gait ataxia is most often the initial symptom of FA, scoliosis and cardiomyopathy have also been documented in rare cases as having occurred before the gait ataxia. Cardiomyopathy is disease of the heart muscle that causes inflammation and limits ample functioning. Most patients experience some degree of reflex decrease in upper and lower extremities, as well as progressive weakness in the lower limbs. 70% of FA patients suffer from

other symptoms, such as decreased extensor plantar reaction, lowered vibration sense in ankles, and cardiomyopathy. Less than half FA patients encounter sensory problems such as hypoacusia and visual acuity decrease, which are observed in the later stages of the disorder if present. Nystagmus, or involuntary eye movement, is also seen in many people with FA and acts as a potential cause of vision impairment that is seen in numerous patients. Optic atrophy, however, is rare but has been documented in several cases of FA. Pes cavus, a deformity characterized by a high-arching foot and inward-facing heel, is present in over half FA patients. Scoliosis, an unnatural curvature of the spine, is present in 60% of cases. Upper extremity coordination and ability, as well as normal speech capability, can remain within the first five years beyond diagnosis or presentation of initial symptoms (Koenig and Durr, 2000).

Although the speed of progression in FA patients widely varies, the majority of those who suffer from FA lose the ability to walk within fifteen years of initial symptom onset. By the age of forty-five, 95% of patients require the use of a wheelchair to maintain mobility (Cardeiro, 2000; Chakravarty, 2003). The average age in which patients are confined to a wheelchair is twenty-five, although necessity for a mobility aid may be much later, depending strongly on age of disease onset. A relatively strong correlation has been established between the occurrence and degree of cardiomyopathy in the patient and wheelchair use (Koenig and Durr, 2000).

Histology

The FDRA or FRDA1 gene located on chromosome 9 is at least partially responsible for the development and progression of Friedreich's ataxia, although the full etiology is not yet clear. The disease is due to a triple repeat, or trinucleotide, expansion of the DNA base sequence known as GAA (guanine-adenine-adenine). A person with FA must obtain one mutated or inactivated FDRA gene from each parent that ultimately accounts for the number of repeats of

GAA. The normal distribution of this base sequence on chromosome 9 ranges from five to thirty-five times in people that do not suffer from FA or other autosomal recessive disorders. The abnormality seen in FA patients is most apparent through the excessive repeats of GAA, which can range in repeat abundance from sixty-six to seventeen hundred. This particular pattern of gene mutation is found within about 95% of FA patients, whereas approximately 4% have the specific GAA gene sequence alteration in only one of the FDRA genes adopted from the parents, and the remaining FDRA gene fosters a point mutation that differs from the other gene. Since the discovery of the GAA mutation, there have been rare cases involving FA patients that did not suffer from the alterations associated with chromosome 9, thus proving that FA has another potential etiology (Cardeiro, 2007).

The variation in clinical symptoms found in FA has struck up intense curiosity among researchers due to the fact that such variability is not typically found in autosomal recessive disorders. Some of the factors in focus include the differences in severity of symptoms, age of initial onset, and the speed of progression. Because of such variation in the same categorical disorder, several divisions have been generated so all patients may be categorized and placed into relevant grouping. The subdivisions devised include late onset FA, very late onset FA, spastic paresis without ataxia, FA with retained reflexes, and Acadian or Louisiana form FA. Matching patients' specific symptoms helps not only in the diagnosis portion of the clinical aspect, but also in the physical and psychological treatment methods that are more personal and unique to each patient's case. The presence of other clinical disorders such as diabetes mellitus and cardiomyopathy that are only seen in some FA patients also leaves room for speculation of potential molecular differences within the same classified disease (Pandolfo, 2002).

The process of pinpointing the specific gene location associated with the onset of FA has been a long process. Numerous studies have been initiated since the detection of the FRDA gene that have attempted to identify any secondary factor contributing to the disease. A mitochondrial protein named frataxin has been found to have an impact on the level of severity within FA patients. Although frataxin has many functions within the human body, the direct effects of frataxin remain unclear. The focus of many studies within the last decade has been on the ambiguous nature of frataxin that attempt to isolate its role in FA (Babady, *et al.*, 2007).

Frataxin, made up of approximately 210 amino acids, is the encoded mRNA protein that is compatible with the first five exons of chromosome 9 (Pandolfo, 2002). Frataxin plays a key role in iron distribution and homeostasis. Deficiency of the gene causes excessive iron deposits within the mitochondria that result in amplified oxidative stress vulnerability. With increased oxidative stress within cells, immensely reactive free radicals soon develop and stimulate dysfunction and eventual demise of cells (Klein, 2007). Frataxin also has a significant effect on iron storage and delivery within cellular mitochondria and is now recognized as an iron-assisting gene that plays a role in heme synthesis (Babady, *et al.*, 2007).

The abnormal abundance of genetic repeats present in FA patients is shown to interrupt and disturb the coding sequence of the frataxin gene. The number of repeats of GAA directly affects the display and severity of symptoms in patients, with the most repeats being present in the most severe cases. The most common hyperexpansion of the repeat ranges from 600 to 900, but repetitions can reach beyond 1,000 (Pandolfo, 2002). The number of repeats directly depends on level of function carried out by frataxin, in which the most frataxin-deficient cells show the greatest amount of GAA expansion (Koenig and Durr, 2000). FA is the only disease discovered to date that is unquestionably associated with a GAA trinucleotide repeat. There is

no documentation of point mutations being present on both copies of the frataxin gene on chromosome 9 in any FA patients (Pandolfo, 2002).

Frataxin mRNA is expressed in all cell types in the human body. The frataxin gene is most copious within the spinal cord and cardiac muscle, partially explaining the atrophy and degeneration of dorsal root ganglia and heart disease seen in many FA patients. Cells rich in mitochondria have a higher concentration of frataxin, making the effects of frataxin deficiency especially visible in the nervous system. The thoracolumbar segment of the spinal cord is the main focus of the disease due to the symptoms of frataxin deficiency that have the potentially debilitating effects that characterize FA. Although the cardiac muscle and neurons of the spinal cord are the most abundant, the liver, pancreas, skeletal muscle, and cerebral cortex of the brain also have relatively high amounts of the frataxin gene. Different degrees of GAA expansions in the same patient have been examined within the various cell types, which leads researchers to believe there is a large measure of volatility during cellular mitosis in FA patients (Pandolfo, 2002).

Physiology and Pathophysiology

The complete pathophysiology of Friedreich's ataxia is yet to be thoroughly deciphered. Many leaps have been made in finding answers, especially within the last decade. Researchers have become increasingly intrigued by the ambiguous nature of the disorder that seems to carry a secondary etiology. Since the discovery of frataxin and its possible role in the quantity of expansions of GAA, many studies have been conducted that have focused on pinpointing and possibly halting the repeats on the effected chromosome 9. Progression in the pathophysiology promises to lead to new treatment options and preventative measures to fight the ongoing battle with the relentless disease (Babady, *et al.*, 2007).

Acting as a 'sidekick' to iron, frataxin cooperates with the mitochondrial scaffold protein known as IscU2 and its yeast homologue called Isulp. Alongside IscU2 and Isulp, frataxin initiates the first steps in [2Fe-2S] synthesis. Another major function of the gene involves the union with ferrochelatase. Ferrochelatase is the enzyme that catalyzes porphyrin metabolism and the final step in heme production. These reactions due to the binding of frataxin to IscU2 and ferrochelatase could only be detected in the company of iron molecules, therefore leading to the conclusion that frataxin has a vital part in the delivery of iron. The frataxin gene has been proven to break down and disperse excess iron that can form harmful deposits in skeletal and cardiac muscles. Frataxin's multi-functional quality makes obvious the potential problems that may arise as a result of cellular deficiency (Babady, *et al.*, 2007).

Many malfunctions that epitomize FA are now proven to occur as a result of frataxin deficiency or inadequacy within the cells of the human body. Since frataxin is most abundant in cardiac muscle and the thoracolumbar section of the spinal cord, deficiency will unquestionably call for major functional problems within the cells of these regions. FA is distinguished by the mutilation and ruin of neurons within the spinal ganglia. Deterioration of the posterior column of the spinal cord is the direct cause of the gait ataxia that symptomatically initiates the progression of the disease in the majority of patients (Pandolfo, 2002). The most distinct motion irregularities can be amply observed during the commencement and conclusion of a complete movement. Decreased control and maintenance of posture is apparent as the disease progresses caused by the combination of involuntary muscular contraction and atypical vertebrae position. Ataxic symptoms worsen with aging and the progression of the disorder, and eventually debilitate the patient to a level of physical dependency that is usually fulfilled by wheelchair use (Periman, 2006).

Although deterioration of the spinal column is present in all FA patients, the expression is significantly lower than that of the posterior column of the sensory pathway. Frataxin loss can be directly linked to the Clarke columns and the spinocerebellar tracts of the posterior column, but the degeneration seen in the dorsal root ganglia within the vertebral column may be inferior to the frataxin gene malfunction. The cells of the granular layer of the cerebellum also have normally high levels of frataxin, but expression of the frataxin gene in FA patients is severely decreased. The identification of the explicit locations that carry abnormal amounts of frataxin played a substantial role in deciphering the pathology of the disorder. The strong relationship between the amount of the gene in various sites and the expression of the gene has aided in pinpointing which parts of the body are most affected by the disease (Koenig and Durr, 2000).

Neurons and cardiocytes are especially sensitive to deficiency of the frataxin gene because these mitochondria-rich structures operate solely on aerobic metabolism. Defects within the cellular mitochondria caused by decreased frataxin concentration results in the malfunctions typically seen in FA patients. The presence of cardiomyopathy and diabetes mellitus is not essential for a patient to be diagnosed with FA, but there is an occurrence of heart disease in approximately 70% of patients and diabetes or impaired glucose tolerance in around 35% of individuals suffering from FA (National Organization for Rare Disorders, 1995; Koenig and Durr, 2000). The incidence of diabetes mellitus and hypertrophic cardiomyopathy in many FA patients has now been partially credited to the low concentration of frataxin in the organs that are normally abundant. The increase of diabetes mellitus is due to the oxidative malfunctions within the β cells of the pancreas caused by a decreased level of the frataxin gene within the structure (Koenig and Durr, 2000). Inappropriate insulin secretion has also been found in some FA patients, likely caused by the damage to the β cells of the pancreas induced by the lack of

adequate frataxin supply (Chakravarty, 2003). A deficiency of frataxin is also believed to be the cause of the prominent occurrence of cardiac malfunctions in FA patients due to the highly sensitive nature of the cardiac myocytes that engage exclusively in aerobic metabolism (Koenig and Durr, 2000).

There are numerous clinical symptoms that are characteristic of FA but of which diagnosis is not dependent. The neurological damage caused by FA results in dysarthria in many cases. Dysarthria is a disorder that involves many facets of speech, causing irregular breath control, difficulty producing ordinary audible sounds, frequent choking, and trouble swallowing. Since FA is primarily characterized as a movement disorder, many aspects of physical capability are taken into account during diagnosis and treatment of the disease. Dyssynergia, or jerky motions in the course of complete movements, is seen in most FA sufferers and is often the initial symptom after onset. Dymetria is difficulty in carrying out movements accurately and usually develops as the disease progresses. Decrease in muscle tone is apparent and results in unsteady posture. The feet are usually set farther apart than normal to help the patient maintain balance and aid in walking. The abilities to walk in a straight line and balance on one foot are lost following the onset of truncal movement symptoms. Joint sensation is also greatly decreased, causing excessive difficulty during walking and other physical motions (Periman, 2006).

Epidemiology

Being the most widespread inherited neurodegenerative ataxia, FA makes up for about half of the various hereditary forms of ataxias. FA accounts for about 75% of all early-onset ataxia cases that involve initiation of clinical symptoms before the age of twenty-five. There are clearly identifiable cultural differences in the frequency of the disorder, making a universal prevalence

estimate unlikely to calculate (Koenig and Durr, 2000). The variability within the disease initially leads some physicians in the wrong direction when attempting to diagnose and treat FA patients. The abundance of misdiagnosis also makes an accurate estimate of FA prevalence very improbable to conclude (National Organization for Rare Disorders, 1995).

Overall prevalence is estimated to be between 1 in every 50,000 to 1 or 2 in every 100,000 people (Koenig and Durr, 2000; Chakravarty, 2003). Estimates for the occurrence of FA in the United States vary from 2,000 to 20,000 cases (National Organization for Rare Disorders, 1995). The most accepted estimate for the United States, however, is between 3,000 to 5,000 people who suffer from FA. More accurate estimates are sure to ensue following the recent determination of the role of the frataxin gene in the number of GAA repeats in sufferers. Recent discoveries should drastically lower the incidence of misdiagnosis by encouraging genetic testing to verify FA as the correct disorder (Cardeiro, 2007).

There is a clear distinction in prevalence of FA between cultures and ethnicities. Like the variations of clinical symptoms within the disorder, the reasoning for these differences has not yet been determined. Chief prevalence is seen within particular populations of southern Italy and Cyprus inhabitants. Elevated occurrence is also observed in the French-Canadian populations that originated in the province of Quebec. Another group that has a striking rate of FA is the Acadians from Louisiana, which accounts for the Acadian type or Louisiana form of FA. The rate of occurrence in Caucasians is estimated to range from 1 in 25,000 to 1 in 50,000. Caucasians have the highest carrier frequency, with the prevalence of carrying a defective copy of the frataxin or FRDA1 gene being approximately 1% (Cardeiro, 2007).

Hyperexpansion of GAA is highest in French and German populations, with the frequency being approximately 1 in 85. This finding suggests that the overall estimated prevalence may be

an understatement with such a high occurrence in some groups (Cardeiro, 2007). Diagnosis of FA is especially scarce in Japanese and African populations, but the cause for this deficit is uncertain (Koenig and Durr, 2000). FA is also very rare in descendants of Asian and African cultures (Cardeiro, 2007). The precise rate of FA in India has not yet been determined. The occurrence of FA is common to exist in siblings due to the solely genetic factors that contribute to its onset (Chakravarty, 2003).

Current Research

Since no curative treatment is yet available for FA patients, many research projects have focused on treatment and cures for FA and its comorbid ailments. Since the discovery of the gene at fault in the battle against FA, research that targets chromosome 9 specifically has become more common. Many symptomatic treatment methods have been adapted as a result of intense study of positive effects in actual FA patients. The most promising studies to date involve the administration of the idebenone drug (Cardeiro, 2007).

Idebenone is a short-chain counterpart of the coenzyme Q10, and has been the focus of many studies dealing with cardiac disease. Cardiomyopathy has been drastically decreased in patients who received necessarily high doses of idebenone according to numerous clinical projects. Regular prescription of idebenone to cardiomyopathic patients has not been approved yet, but science is creeping closer to the possibility. A safety profile for the drug and clarification of many questions about the effects and methods of treatment need to be answered before the drug will be in the reach of the FA population (Chakravarty, 2003).

Clinical trials have been conducted under the leadership of the National Institute of Neurological Disorders and Stroke in the United States that have made great leaps to find a cure for FA. Idebenone is a synthetic form of an antioxidant that has been proposed by researchers in

the United States and Britain to help ease symptoms seen in cardiomyopathic patients. This drug has been the focus of many clinical trials and has shown a decrease in left ventricle hypertrophy for many FA patients (Cardeiro, 2007). Idebenone was administered to 38 patients in a 5 to 10 mg/kg/day dosage in a trial performed in Britain. There were no serious side effects associated with the drug, making it a possibility for very promising treatment for cardiac hypertrophy in FA patients (Hausse, *et al.*, 2002). Idebenone was dispensed in high dosages based on body weight to some FA patients in a randomized and placebo-controlled study conducted by Rustin and his colleagues. Researchers from this study concluded that the idebenone treatment was well tolerated among participants, and resulted in unquestionable progress in the neurological functioning of the individual (Di Prospero, *et al.*, 2007).

Works Cited

- Babady, Ngolela E., Carelle N, Wells RD, Rouault TA, Hirano M, Lynch DR, Delatycki MB, Wilson RB, Isaya G, and Puccio H. Advancements in the pathophysiology of Friedreich's Ataxia and new prospects for treatments. *Molecular Genetics and Metabolism*. 2007.
- Cardeiro, Dawn. MS, CGC. Friedreich Ataxia. *Gale Encyclopedia of Neurological Disorders*, Eds. Stacey Chamberlin and Brigham Narins. Vol. 1. Detroit: Gale, 2005. p. 374-377.
- Chakravarty, A. Friedreich's ataxia – yesterday, today and tomorrow. *Neurology India*. 51.2. 2003.
- Di Di Prospero NA, Baker A, Jeffries N, and Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomized, placebo-controlled trial. *The Lancet Neurology*. Vol. 6, Issue 10. 2007.
- Durr, Alexandra and Michel Koenig. *Friedreich's Ataxia*. New York: Marcel Dekker, Inc., 2000, p. 151-158
- Hause AO, Aggoun Y, Bonnet D, Sidi D, Munnich A, Rotig A, and Rustin P. Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *British Medical Association*. 2002.
- Klein, Christopher J. The Inherited Neuropathies. *Neurologic Clinics*. Vol. 25, Issue 1. 2007.
- Lynch DR, Farmer JM, Tsou AY, Periman S, Subramony SH, Gomez CM, Ashizawa T, Wilmot GR, Wilson RB, and Balcer LJ. Measuring Friedreich ataxia: Complementary features of examination and performance measures. *American Academy of Neurology*. Vol. 66, Issue 11. 2006.
- National Organization for Rare Disorders. Ataxia, Friedreich. *Physicians' Guide to Rare Diseases*. Dowden Publishing Co. Montvale, New Jersey, 1995, p. 272-273.
- Pandolfo, Massimo. The Molecular Basis of Friedreich Ataxia. *Triple Repeat Disorders of the Nervous System*. New York: Kluwer Academic / Plenum Publishers, 2002, p. 99-114.
- Periman, Susan L. Ataxias. *Clinics in Geriatric Medicine*. Vol. 22, Issue 4. W.B. Saunders Co. 2006.