

Friedreich Ataxia

Effects of Genetic Understanding on Clinical Evaluation and Therapy

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The discovery of the genetic cause of Friedreich ataxia has significantly affected our understanding of the disorder at both the clinical and basic science levels. Friedreich ataxia results from a deficiency of functional frataxin, a protein that appears to be involved in mitochondrial iron homeostasis. This leads to iron accumulation and mitochondrial abnormalities with consequent oxidant damage. The clinical spectrum of Friedreich ataxia has also expanded with the recognition of broader phenotypic features, including the absence of classical Friedreich ataxia features, later age at onset, and spasticity instead of ataxia. Although no proven therapy is yet available, antioxidants are a potential method for therapeutic intervention.

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Friedreich ataxia (FRDA) is a progressive neurodegenerative disorder with a prevalence of about 1 in 50000 individuals, making it the most common early-onset hereditary ataxia. Although sometimes viewed as a form of cerebellar disease, the major pathological abnormalities are located outside the cerebellum.¹ Degeneration of the large fiber dorsal root ganglion neurons and their axons in the dorsal columns gives rise to loss of proprioception and a severe sensory ataxia. The spinocerebellar tracts are also affected, along with a few other nuclei (including the dentate nucleus of the cerebellum) within the central nervous system. Other clinical manifestations include cardiomyopathy, scoliosis, and diabetes mellitus. In recent years, the discovery of the disease-related gene, its mutation, and its gene product have provided a genetic basis for redefinition of the illness and new insight into the pathophysiological mechanisms of this disease.² This review will describe how these discoveries have affected the clinical diagnosis and evaluation of FRDA and discuss the proposed pathophysiological

mechanisms and potential therapies of this disease.

GENETIC BASIS OF FRDA

The major genetic mutation of FRDA is the presence of an expanded GAA trinucleotide repeat in the first intron of both alleles of a novel gene (X25 or FRDA) encoding the protein "frataxin." Normal alleles have fewer than 33 consecutive GAA repeats in the gene, whereas abnormal alleles carry 66 to 1500 GAA repeats.² Although 95% of people with FRDA have this abnormality, about 5% carry a point mutation in the gene on one allele in association with an expanded repeat on the opposite allele.²⁻⁶ This intronic trinucleotide repeat leads to the disruption of transcription and the almost complete absence of frataxin. The length of the smaller repeat correlates with the severity of the disease phenotype as assessed by age at onset of the disease, suggesting that in shorter (but still pathologic) repeats, a small amount of residual frataxin synthesis occurs (reviewed by Patel and Isaya⁷). The disease-causing point mutations also decrease frataxin levels, presumably by creating abnormalities of protein stability, targeting, or function. Thus, the basic genetic mechanism of FRDA is felt to be a decrease in functional frataxin.

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PATHOPHYSIOLOGICAL UNDERSTANDING FROM THE GENE DISCOVERY

Much of what we have learned about frataxin comes from studies of the yeast frataxin homologue, YFH1p. Both frataxin and YFH1p localize to mitochondria at the matrix side of the inner mitochondrial membrane. Frataxin can substitute for YFH1p in yeast, indicating that the 2 proteins are functional, as well as structural, homologues. In yeast, loss of frataxin leads to mitochondrial iron accumulation (reviewed by Patel and Isaya⁷). The mitochondrial iron overload is associated with cytoplasmic iron depletion, induction of plasma-membrane iron uptake proteins, decreased activities of iron-sulfur cluster enzymes, sensitivity to oxidants, loss of mitochondrial DNA, and impaired respiration. However, the exact role of frataxin in mitochondrial dysfunction is not yet clear. The yeast protein YFH1p may act as an iron ligand in the mitochondrial matrix. Isolated YFH1p binds Fe²⁺ (iron) and keeps it in a reduced and available form, protects other biomolecules from iron-induced oxidant damage, and can provide Fe²⁺ for heme synthesis *in vitro*. Thus, the function of YFH1p (and, by extension, frataxin) may be to bind Fe²⁺ and decrease the rate of oxidation to Fe³⁺. This would promote mitochondrial iron export, or use for iron-sulfur cluster or heme synthesis, and prevent iron-induced free radical formation.

DEVELOPMENT OF MODEL SYSTEMS: CELLULAR AND ANIMAL

Confirmation of the role of frataxin in mitochondrial function requires extension of the biochemical findings to higher animals such as mice, replication in tissue culture paradigms, and demonstration of similar findings in tissue from patients with FRDA. Iron deposits have been noted in the hearts of patients with FRDA, and more recent experiments have demonstrated signs of oxidant damage, decreased activities of iron-sulfur cluster enzymes, and loss of mitochondrial DNA in cardiac tissue from patients with FRDA.⁷ Thus, the basic biochemical features derived from *in vitro* studies are present in human tissue from biopsy or autopsy. Genetically engineered whole-animal models also appear to replicate some features of FRDA. A homozygous null (knockout) mouse lacking frataxin has been made, but these animals die before birth, indicating that at least some frataxin function is necessary for survival.⁸ Tissue-specific knockout mice develop phenotypic changes that overlap with FRDA, including hypertrophic cardiomyopathy and selective degeneration of the large fiber sensory afferents; however, they also develop changes (spongiform cerebral cortical degeneration) not characteristic of FRDA.⁹ Overall, their phenotype is somewhat more severe than that of FRDA.

Primary cell cultures provide an alternative model for FRDA. Cultured fibroblasts and lymphocytes from patients with FRDA accumulate mitochondrial iron and are sensitive to oxidant stress.⁷ Therefore, cell culture models correspond well with pathological findings from patients and with mouse models and may be useful for screening compounds for possible therapeutic agents.

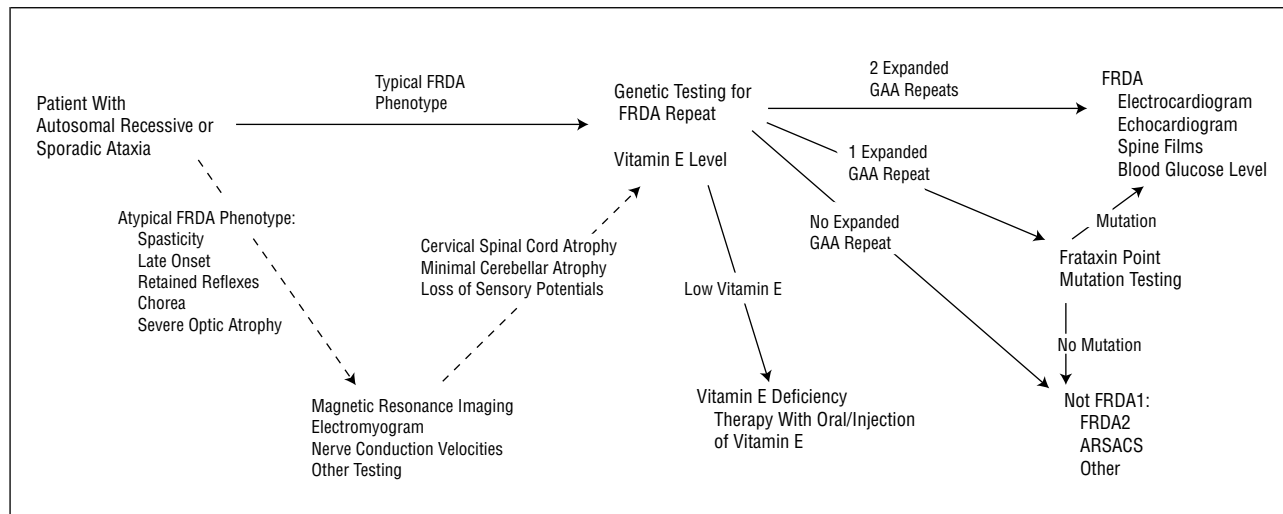
EFFECT OF GENOTYPE ON DIAGNOSTIC POSSIBILITIES

The clinical phenotype of FRDA was well defined before genetic testing, based on the examination of a large number of individuals.¹ The clinical definition of FRDA includes autosomal recessive inheritance, onset before age 25 years (and usually much earlier), progressive gait and limb ataxia, absent lower extremity reflexes, and extensor plantar responses. Electrophysiologically, FRDA is associated with absent or markedly reduced sensory nerve action potentials with normal motor nerve conduction velocities, and imaging findings of the brain are usually normal early in the disease.¹⁰ Cervical spine magnetic resonance imaging frequently reveals atrophy. Most patients also have dysarthria, complete areflexia, pyramidal weakness of the legs, loss of vibration and proprioception sensation, scoliosis, and an electrocardiogram with abnormal results. Less common features include nystagmus, optic atrophy, sensorineural hearing loss, distal motor atrophy, pes cavus, and diabetes mellitus.

The clinical spectrum of FRDA has expanded noticeably through the use of molecular diagnosis, now available in some form at several commercial laboratories. Many patients with atypical features for FRDA (such as severe optic atrophy) have genetically confirmed disease.⁴ Conversely, the classic features of FRDA may not be present in patients with genetically confirmed disease.¹¹ Patients with FRDA may retain reflexes and may present at substantially later ages than defined previously.^{12,13} This has led to the recognition of a number of variant presentations, including diffuse chorea, spastic paraparesis, and sensory neuronopathy.^{14,15}

Patients with these atypical or variant features are more likely to carry slightly different genotypes as well. Such individuals are more likely to be among the 2% to 5% of patients harboring a point mutation on one allele. In general, C terminal point mutations cause patients to be severely affected and have more classical phenotypes, whereas N terminal point mutations result in less severe abnormalities.⁶ However, there are exceptions to this generalization.⁴ Alternatively, patients with these atypical features (particularly spastic paraparesis) may carry expanded GAA repeats that are longer than the normal range but not into the range associated with childhood onset.^{12,15} Patients with atypical clinical features for FRDA but with appropriate family histories thus deserve testing for FRDA in some situations (**Figure**). However, in such cases, the laboratory performing the testing must be capable of testing for point mutations to confirm the diagnosis. The carrier frequency in the population for FRDA is about 1:100 (based on an incidence of 1:40 000). Thus, some individuals with other neurodegenerative disorders unrelated to frataxin will coincidentally appear to be carriers for FRDA when assessed for the expanded GAA repeat of FRDA. This is the same result seen in patients with FRDA who carry point mutations and a single expanded allele. Confirmation of a variant type of FRDA in this situation requires identification of a point mutation on the opposite allele.

Although the genotypic changes are helpful for confirmation of disease, they do not provide complete ex-



Conceptual paradigm for use of Friedreich ataxia (FRDA) diagnostic testing when evaluating a patient with an unknown ataxia. The ideal method for evaluation will vary based on the availability of genetic testing and other diagnostic testing for any individual patient. ARSACS indicates autosomal recessive spastic ataxia of Charlevoix-Saguenay.

planations for differences in disease phenotype. The presence of cardiomyopathy is associated with longer GAA repeat length, but not all patients with long GAA repeat lengths develop cardiomyopathy.¹⁴ In FRDA, the length of the shorter GAA repeat correlates with age at onset,¹¹ but the correlation is not high enough (0.7-0.8) to predict reliably the age at onset or phenotype in an individual patient. Substantial differences in age at onset have been noted within a single generation of families and between families.¹⁶ This is illustrated by the Acadian variant of FRDA.¹⁷ Patients with this variant progress more slowly and are, overall, less severely affected than patients with the classical phenotype. However, these individuals share the same expanded GAA repeat found in others with classical FRDA, and, as yet, no differences within the FRDA gene explain the variation. This suggests that influences outside the FRDA gene may lead to the milder clinical course.

A second group of patients has also been identified through genetic testing: those who appear to have FRDA clinically but who carry no expanded alleles.^{18,19} Theoretically, testing for the expanded GAA repeat may miss the 0.05% of people with FRDA who harbor 2 point mutations. No patient with 2 point mutations has yet been described. In addition, several families have been characterized with the phenotype of FRDA whose disease is linked to a different genetic locus (*FRDA2*).²⁰ More likely, the individuals who test entirely negative for FRDA expansions have other less common diseases. A variety of disorders clinically overlap with FRDA, either in the presence of a primarily sensory ataxia or in the age at onset. There are many defined diagnostic possibilities for these individuals, a few of which deserve special mention due to recent developments:

1. *Ataxia with vitamin E deficiency*: This inherited disorder was initially described both genetically as a subgroup of patients with FRDA linked to a separate genetic locus and by the discovery of an FRDA phenotype associated with low levels of vitamin E. The phenotype of ataxia with vitamin E deficiency is

essentially identical to that of FRDA, with the exception of retinopathy in a few patients.²¹ More important, it represents the major treatable disorder overlapping with FRDA. Patients with ataxia with vitamin E deficiency stabilize and may improve following vitamin E treatment, which must be lifelong.

2. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)*: This genetically distinct disorder is found in individuals from a specific region of Quebec, Canada, thus overlapping with the population at risk for FRDA. However, as the name implies, spasticity is seen in this disorder, distinguishing it from classical FRDA, and cerebellar atrophy is found pathologically and on imaging studies. Genetically, the disease is defined by mutations in a novel protein on chromosome 13.²² A similar disorder inherited in an autosomal recessive pattern in Tunisians has been mapped to the same region of chromosome 13.²³
3. *Posterior column ataxia with retinal pigmentary changes*: This unique disorder, which is localized to chromosome 1q31-32, is distinguished from FRDA by the retinal changes.²⁴
4. *Early-onset cerebellar atrophy with retained reflexes*²⁵: This disorder likely constitutes a heterogeneous syndrome including individuals who overlap clinically with all of the above groups and atypical FRDA but in whom no definitive genetic or biochemical diagnosis can be confirmed.

On occasion, individuals with Charcot-Marie-Tooth disease or mitochondrial disorders may resemble patients with FRDA. The signs and symptoms of FRDA are reminiscent of the mitochondrial encephalomyopathies with peripheral neuropathy, ataxia, hearing loss, diabetes mellitus, and cardiac disease. In addition, rare patients with FRDA develop paroxysmal features characteristic of mitochondrial disorders.²⁶ However, in spite of their pathophysiological similarity, FRDA and mitochondrial disorders are usually readily distinguishable on clinical grounds.

GENETIC COUNSELING

The availability of genetic testing for FRDA has clarified some issues in genetic counseling of patients with ataxia, while introducing challenges in other ways. The standard genetic testing offered by commercial laboratories measures the GAA repeat length on both alleles. This testing offers a 95% to 98% detection rate, which makes it useful for confirming diagnoses and carrier testing. Patients with FRDA can constitute a significant proportion of patients with apparently sporadic ataxia due to autosomal recessive inheritance, even in the adult-onset population.¹⁸ Genetic testing allows these individuals to be given a firm diagnosis. Genetic testing also identifies carriers of FRDA among individuals at increased risk based on family history and among spouses of carriers or affected individuals. The general population carrier frequency is roughly 1 in 100 persons. As with many trinucleotide repeat disorders, genetic counseling for individuals who are carriers for repeat lengths at the shorter end of the pathologic range can be more complex. In addition, the relatively small number of independent patients with point mutations makes prediction of the exact phenotype in these cases very difficult. Although carrier testing can improve overall risk assessment, it cannot always define the phenotype.

THERAPY: PRESENT AND FUTURE

At present there is no clearly effective protective pharmacological therapy for FRDA. Citalopram hydrobromide, amantadine hydrochloride, and serotonin derivatives have shown minimal to no benefit as symptomatic therapy in small trials.²⁷⁻²⁹ However, comprehensive care of the patient with FRDA is not passive, particularly with the potential for more novel therapies in the tangible future. Aggressive surveillance for progressive cardiomyopathy, arrhythmias, scoliosis, and diabetes mellitus can markedly improve the life span and quality of life of the patient. Such care is also crucial for maintaining function for future therapeutic approaches.

The overlapping phenotypes of vitamin E deficiency and FRDA and the biochemical studies on frataxin have led to investigations designed to develop antioxidant therapy in FRDA. Noninvasive measures of patients support the link to antioxidants as a potential therapy.³¹ Phosphorous 31-labeled magnetic resonance spectroscopy has demonstrated that mitochondrial adenosine triphosphate production is decreased in the skeletal muscles of patients with FRDA.^{30,31} Urinary measurement of 8-hydroxy-2'-deoxyguanosine and plasma malondialdehyde, markers of reactive oxygen species production, are elevated in patients with FRDA and may be useful as surrogate markers of pathophysiological characteristics in patients with FRDA.^{32,33}

These findings have expanded antioxidant therapy in FRDA. Using markers of disease activity (such as cardiac ejection fraction) as outcome measures, FRDA has been treated with some success in an unblinded fashion with a coenzyme Q analogue (idebenone), but a more recent study using a shorter duration of therapy did not reveal any beneficial effect.^{34,35} The successful study demonstrated a decrease in cardiac hypertrophy, suggesting

a capacity for repair of damaged heart muscle cells. Other cardiac surrogate markers improve with high doses of the antioxidant coenzyme Q and vitamin E.³¹ Further trials will be needed to define the specific features of disease that respond to antioxidants, as well as the appropriate doses and lengths of therapies.

However, many difficulties may be present in the performance of such trials. With the availability of many antioxidants on a nonprescription basis, the widespread use of these well-tolerated dietary agents may complicate a placebo-controlled trial. Although the ease of administering such antioxidants suggests little benefit to a systematic examination of their usefulness in FRDA, other factors demonstrate the need for such an analysis. Antioxidants are readily available, but they are not necessarily inexpensive. In addition, although no adverse effects are commonly reported in moderate duration use, the long-term effects are not known. Finally, it is possible that use of multiple antioxidants is counterproductive. In one in vitro model of FRDA, coenzyme Q improved iron-sulfur-containing enzyme activities, vitamin E had no effect, and ascorbate worsened enzymatic activities.³⁶ These results demonstrate the need for a systematic understanding of the usefulness of dietary antioxidants in disorders such as FRDA.

CLINICAL OUTCOME MEASURES IN FRDA

Although initial therapeutic trials are now being conducted for FRDA largely using surrogate markers of disease activity, more systematic trials will require the use of clinical outcome measures. Successful use of agents, particularly those with significant adverse effects, requires a demonstration of effects on patient outcome, not simply an improvement in surrogate markers. Although magnetic resonance spectroscopy measures correlate with triplet repeat length, they do not clearly correlate with disease progression.^{30,37} In addition, the expense and technical expertise needed for performance of ³¹P-magnetic resonance spectroscopy may make it impractical for large-scale clinical trials. Echocardiography detects disease effects on the heart but provides no information on neurological features. At present, no adequate measure has been identified or validated in a large cohort of patients with FRDA. Clinical outcome measures must be easy to administer and sensitive to change over time. The ideal scale for FRDA would be sensitive and yet capture the entire clinical neurological spectrum of the disease. The most sensitive clinical outcome measures for multiple sclerosis now reflect simple performance measures rather than traditional neurological examinations or disability scales. Although the pathophysiological characteristics of multiple sclerosis are distinct from those of FRDA, both lead to progressive dysfunction of multiple neurological systems with variable phenotypes. Future measures of FRDA might use a similar design to that of the Multiple Sclerosis Functional Composite,³⁸ and development of analogous measures must represent an avenue for clinical research in FRDA if therapeutic trials are eventually to become effective.

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