

Friedreich ataxia: from genes to therapies?

Most cases are caused by a single mutation, paving the way for therapeutic advances for this fatal disease

Friedreich ataxia (FRDA), an autosomal recessive disease, is the commonest of the inherited ataxias, affecting around 1 in 30 000 people.¹ With an average age of onset of 10 years, those affected by this condition become wheelchair-bound on average 10 years after onset. The symptom that heralds onset in the vast majority of cases is increasing incoordination. Onset after 30 years of age is rare. Death ensues, on average, 36 years after disease onset and is largely due to hypertrophic cardiomyopathy.² Other sources of morbidity in FRDA include an increased incidence of diabetes mellitus, dysarthria, swallowing difficulties, scoliosis, optic atrophy, hearing loss and foot deformity.¹

FRDA is caused by mutations in the *FRDA* gene which encodes the protein frataxin. The pathogenic mutation is an expanded GAA triplet repeat in intron one of the *FRDA* gene in 98% of mutant alleles.¹ The other 2% are point mutations. The fact that one mutation accounts for the vast majority of FRDA means that there is a relatively simple diagnostic test available for this disease.

The genetic basis of FRDA was elucidated in 1996, and much has since been learnt about its pathogenesis. The first evidence of the role of frataxin came serendipitously, when the yeast equivalent of the *FRDA* gene (*yfh1*) was removed and increased levels of mitochondrial iron were detected.³ Human studies have confirmed that FRDA is indeed a disease of mitochondria. The accumulated evidence suggests that the marked reduction in frataxin results in decreased production of iron-sulfur cluster-containing proteins, which leads to deficiencies of some of the mitochondrial respiratory chain complexes and to secondary iron accumulation.² Oxidative damage has been strongly implicated, although recent evidence brings this into question.⁴

These genetic and molecular findings have led to a number of therapies being proposed for FRDA. Interventions to maximise quality of life are of paramount importance, while the quest to find disease-modifying therapies continues.

Hopes for the obvious prospect of iron chelation therapy have been tempered because none of the current iron chelators approved for clinical use preferentially reduce the levels of iron in mitochondria without also reducing cytosolic iron levels.⁵

Antioxidant therapy has shown the most promise. High-dose coenzyme Q10 and vitamin E has been shown to reverse the surrogate marker of reduced energy production in muscle magnetic resonance spectroscopy.⁶ Idebenone, an analogue of coenzyme Q10, reduces cardiac hypertrophy, although it has not been shown to relieve the neurological aspects of FRDA.⁷ A multicentre placebo controlled trial of idebenone is to start soon in the United States.

An antioxidant targeted at mitochondria, mitoquinone, has been developed in New Zealand.⁸ Because mitochondria have a very strong membrane potential of about 150 mV (positive outside, negative inside), the drug is concentrated in mitochondria about 500-fold compared with antioxidants without a mitochondrial-targeting moiety. Clinical trials of this agent are planned to commence this year.

Another approach that has promise is identifying agents that increase frataxin expression.⁹ The rationale for this approach is that all patients with FRDA produce low levels of normal frataxin, and, in experimental animal models, production of 25% of normal

levels is enough to prevent development of disease. Therefore, a 5–10 fold increase in frataxin production may be therapeutic for most patients, while lower levels of induction may still produce significant amelioration of the disease.² A small number of pharmacological agents have been screened thus far, causing up to a 2.5-fold induction in frataxin expression. It is hoped that high throughput screening of approved drugs and chemical libraries will lead to the identification of more effective and safe inducers.

A major challenge facing FRDA clinical investigation is the development of appropriate outcome measures for clinical trials.¹⁰ FRDA is rare, and its rate of progression is not predictable, but occurs in a step-wise fashion. Therefore, a multicentre approach is vital to enable development of scales to measure the effects of therapies so that pharmacological discoveries can be quickly translated to patient benefit.

The discovery of the underlying genetic mechanism for FRDA has led rapidly to better understanding of its pathogenesis. It is likely that this expanding knowledge will lead to therapies that slow the progression of, and ultimately cure, this fatal disease.

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- 1 Delatycki M, Williamson R, Forrest S. Friedreich ataxia: an overview. *J Med Genet* 2000; 37: 1-8.
- 2 Voncken M, Ioannou P, Delatycki MB. Friedreich ataxia — update on pathogenesis and possible therapies. *Neurogenetics* 2004; 5: 1-8.
- 3 Babcock M, Silva D, Oaks R, et al. Regulation of mitochondrial iron accumulation by Yfh 1p, a putative homolog of frataxin. *Science* 1997; 276: 1709-1712.
- 4 Seznec H, Simon D, Bouton C, et al. Friedreich ataxia: the oxidative stress paradox. *Hum Mol Genet* 2004 Dec 22; [Epub ahead of print].
- 5 Richardson DR. Friedreich's ataxia: iron chelators that target the mitochondrion as a therapeutic strategy? *Expert Opin Investig Drugs* 2003; 12: 235-245.
- 6 Lodi R, Hart PE, Rajagopalan B, et al. Antioxidant treatment improves in vivo cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. *Ann Neurol* 2001; 49: 590-596.
- 7 Mariotti C, Solari A, Torta D, et al. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; 60: 1676-1679.
- 8 Kelso GF, Porteous CM, Coulter CV, et al. Selective targeting of a redox-active ubiquinone to mitochondria within cells: antioxidant and antiapoptotic properties. *J Biol Chem* 2001; 276: 4588-4596.
- 9 Sarsero JP, Li L, Wardan H, et al. Upregulation of expression from the FRDA genomic locus for the therapy of Friedreich ataxia. *J Gene Med* 2003; 5: 72-81.
- 10 Lynch DR, Farmer JM, Balcer LJ, Wilson RB. Friedreich ataxia: effects of genetic understanding on clinical evaluation and therapy. *Arch Neurol* 2002; 59: 743-747. □