Friedreich ataxia (FRDA), an autosomal recessive disease, is the commonest of the inherited ataxias, affecting around 1 in 30,000 people. 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. Other sources of morbidity in FRDA include an increased incidence of diabetes mellitus, dysarthria, swallowing difficulties, scoliosis, optic atrophy, hearing loss and foot deformity.

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. 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. 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. Oxidative damage has been strongly implicated, although recent evidence brings this into question.

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.

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. Idebenone, an analogue of coenzyme Q10, reduces cardiac hypertrophy, although it has not been shown to relieve the neurological aspects of FRDA. A multicentre placebo controlled trial of idebenone is to commence this year.

Another approach that has promise is identifying agents that increase frataxin expression. 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. 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. 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.

Martin B Delatycki
Director, Bruce Lefroy Centre for Genetic Health Research
Murdoch Childrens Research Institute, Melbourne, VIC, and
Associate Professor, Department of Paediatrics, University of Melbourne
martin.delatycki@ghsv.org.au

Panos A Ioannou
Head, Cell and Gene Therapy Group
Murdoch Childrens Research Institute, Melbourne, VIC, and
Associate Professor, Department of Paediatrics, University of Melbourne

Andrew J Churchyard
Neurologist, Monash Institute for Neurological Disease
Monash Medical Centre, Melbourne, VIC

5 Richardson DR. Friedreich’s ataxia: iron chelators that target the mitochondrion as a therapeutic strategy? Expert Opin Investig Drugs 2003; 12: 235-245.