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# Early intervention may hold key to treatment of Friedreich's ataxia

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Current treatments may be administered too late to target Friedreich's ataxia effectively. New research using a slow-onset frataxin knock-in/knockout mouse model showed significantly reduced levels of mitochondrial biosynthesis proteins and early mitochondrial deficiency in the cerebellar cortex, even at pre-symptomatic stages of development. This suggests that the progressive degeneration in mitochondrial function seen in individuals with Friedreich's ataxia is not only the mechanism causing the disease, but also a potential biomarker and therapeutic target.

New research published today in *Disease Models & Mechanisms* indicates that early intervention should be a key target in the development of new therapeutics for Friedreich's ataxia, as current treatments may be administered too late to target the disease effectively.

Around 1 in 50,000 people across the world are affected by Friedreich's ataxia, an autosomal recessive inherited disease that causes progressive damage to the nervous system. Friedreich's is the most common recessive ataxia (a lack of muscle control in voluntary movement) and results from deficient expression of the small mitochondrial protein frataxin. Mitochondria are the energy centres of the cell, relying on electron transport through a chain of enzymes that contain iron-sulphur clusters to produce the energy required for cell metabolism. Frataxin plays a vital role in this process by ensuring proper formation of the iron-sulphur clusters within the enzymes. In cells with reduced levels of frataxin, abnormal iron-sulphur cluster formation leads to decreased energy production and an accumulation of iron that induces cell-

damaging reactive oxygen species (ROS). Damage from excess ROS then causes the degeneration of nervous tissue in the spinal cord. Additionally, individuals with Friedreich's ataxia experience frequent fatigue resulting from cell metabolism defects. The usual initial symptom of the disorder is gait ataxia, a difficulty with walking that usually manifests in children between the ages of 5 and 15 years, although onset may occur in adulthood. The ataxia worsens over time and most individuals will ultimately require a wheelchair and assistance with daily tasks. Friedreich's ataxia is commonly accompanied by a range of heart defects, and is also associated with carbohydrate intolerance and diabetes.

## Identifying early deficiencies

Previous studies into Friedreich's ataxia have investigated the direct effect of frataxin deficiency on mitochondrial enzymes that contain iron-sulphur clusters, but with a focus on nerve cell mitochondrial defects once symptoms had already been detected and the disease diagnosed. More recently, the focus of research has shifted to the deficiencies in mitochondrial biogenesis and respiratory chain complexes that occur before any symptoms are evident. Dr David Lynch, lead author on the study published in *Disease Models & Mechanisms*, explains that furthering knowledge of the earliest stages of Friedreich's ataxia is essential, as their data suggest that the progressive degeneration in mitochondrial biogenesis leading to clinical disease is very slow. Lynch suggests that treatments developed to date may have failed because they didn't target the disease at an early enough stage, and that early intervention is likely to prove crucial to successful therapy.

## The advantages of slow progress

For their investigations, the team from the Children's Hospital of

Philadelphia, Weill Cornell Medical College, Queen's University Belfast and the University of Pennsylvania used a frataxin knock-in/knockout model mouse model that has been available for a number of years, but had previously been overlooked for Friedreich's ataxia research as the neurological phenotype is modest and has a slow onset. Lynch and the team, however, reasoned that a model that mirrored the slowly progressive nature of the disease might be more valid than the rapidly progressive mouse models more commonly used. Using this frataxin knock-in/knockout model, the researchers found significantly reduced levels of the mitochondrial biosynthesis master generator protein PGC-1α and biosynthesis pathway proteins Nrf1 and Tfam in mutant mice, even at pre-symptomatic stages of development. They also found evidence of reduced numbers of mitochondria and early mitochondrial deficiency in the cerebellar cortex. These results not only suggest early mitochondrial biogenesis deficits as a pathogenic mechanism, but also as a potential biomarker and therapeutic target in individuals with Friedreich's ataxia.

## An impact beyond Friedreich's ataxia

Mitochondrial biogenesis deficits are associated with a number of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease and stroke. This means that new discoveries relating to mitochondrial defects in the progression, pathology or treatment of any one of these diseases can potentially be broadly applied. Lynch says, "I think our results rationalise directed studies toward improving mitochondrial biogenesis as a long-term therapy in Friedreich's ataxia, and that the goals of therapy must include not only correcting iron-sulphur enzymes but also other mitochondrial dysfunction. This is a target, not only in Friedreich's ataxia, but also in Parkinson's disease, so it is likely that collaborative drug development can move forward."

**More information:** Hong Lin et al, Early cerebellar deficits in mitochondrial biogenesis and respiratory chain complexes in the KIKO mouse model of Friedreich ataxia, *Disease Models & Mechanisms* (2017). DOI: 10.1242/dmm.030502