

Lay summary

Friedreich's ataxia (FRDA) is the most frequent inherited form of ataxia in humans. The most common FRDA symptoms include muscle weakness and loss of coordination, vision impairment and hearing loss, heart muscle abnormalities, scoliosis, and diabetes. The first symptoms can usually be noticed between the ages of 5 and 15 and they progressively worsen with time. Cardiac failure is the primary cause of death in FRDA patients.

The underlying cause of FRDA is a genetic mutation in the *Frataxin* gene. The consequence of this mutation is a significant decrease in the production of a protein called frataxin. Frataxin plays crucial roles in delivering and redistributing iron between different compartments of human cells. Iron is an essential microelement, indispensable for several vital processes, including energy production. Both iron deficiency as well as iron overload are extremely harmful to the human body. One of the major consequences of insufficient levels of frataxin in FRDA is altered localization of iron in cells – accumulation in some parts and deficiency in the other compartments. Consequently, a short supply of frataxin, especially in the nervous system and heart, leads to malfunction and premature death of these neurons and cardiac cells.

Deficiency of frataxin also leads to significant changes in the genetic program of affected cells: many genes become more active and others become less active. This is also the case for a group of small molecules termed microRNAs, which regulate the activity of other genes. In this way, deficiency of frataxin causes a change from the normal pattern in which many genes in the cell are turned on or turned off. We will study the changes in the activity of microRNAs in FRDA, and analyze how these abnormalities affect the activity of genes which are responsible for the localization and amount of iron in neuronal and heart cells of patients with Friedreich's ataxia. Our primary goal is to define the relationship between miRNA molecules and iron availability. We will also uncover the pattern of detectable microRNA molecules that is specific to FRDA. This "microRNA signature" characteristic of FRDA will help to evaluate the effectiveness of therapeutic approaches intended to increase activity of the frataxin gene or to regulate distribution of iron in neurons and cardiac cells of FRDA patients. Misregulated microRNAs as well as genes under their control may also become new targets for therapy in FRDA.

Importantly, we will conduct these studies in neuronal and cardiac cells. To develop these model cells we will apply recent advances in stem cell research to convert human skin cells into neuronal and cardiac cells. This will allow us to carry out experiments in cell types that are highly affected in Friedreich's ataxia, and whose damage is responsible for many of the disease symptoms. Additionally, we will take advantage of recent technological developments and create "corrected" neuronal and cardiac cells that are free of the mutation that causes FRDA. We will use specific molecular scissors, termed engineered nucleases, to create these corrected cells. In the future, this technique may be used for regenerative medicine approaches to treat or prevent progression of several human disorders.

These studies are intended to advance our knowledge about the molecular basis of FRDA, define the role of iron in progression of this disease and apply this knowledge towards the development of new therapeutic strategies for this debilitating disease.