

Friedreich Ataxia Research and Prospects for Therapy Grazia Isaya, MD, PhD

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Outline

- •Friedreich Ataxia (FA)
- •Frataxin
- Frataxin and Iron-Sulfur Cluster Synthesis
- •FA Pathophysiology
- •Emerging Treatments for FA

Friedreich Ataxia (FRDA)

Autosomal recessive (~1:40,000)
Progressive ataxia
Hypertrophic cardiomyopathy (60%)
Diabetes mellitus (30%)
Muscle weakness, scoliosis







This is Keith. Keith has Friedreich's Ataxia.





Friedreich Ataxia: Molecular Basis



How is frataxin normally made?
What does frataxin normally do?
What happens when there is not enough frataxin the disease?



•What exactly is mitochondrial iron metabolism?

And how does Frataxin relate to this process?





Biological Fe-S Clusters



[2Fe-2S]²⁺ [2Fe-2S]⁺



[3Fe-4S]⁺ [3Fe-4S]⁰ [3Fe-4S]⁻ [3Fe-4S]²⁻



[4Fe-4S]³⁺ [4Fe-4S]²⁺ [4Fe-4S]⁺ [4Fe-4S]⁰



[8Fe-8S]⁵⁺ [8Fe-8S]⁴⁺ [8Fe-7S]³⁺ [8Fe-7S]²⁺

Structure

Oxidation state

Johnson et al. Annu Rev Bioche

Fe-S Cluster Synthesis in Prokaryotes



Marc Fontecave & Sandrine Ollagnier-de-Choudens Arch Biochem Biophys 2008

Fe-S Cluster Synthesis in Eukaryotes



Fe-S Cluster-Containing Enzymes



Frataxin promotes [2Fe-2S] Assembly on ISCU





•Frataxin deficiency causes progressive accumulation c cellular damage.

How can we stop this?



Other Approaches

•iPS Technology

•Gene Therapy

The promise of human induced pluripotent stem cells for research and therapy.



Nature Reviews | Molecular Cell Biolog

Nishikawa S, Goldstein RA, Nierras



Conclusions

FA results from low levels of the mitochondrial protein frataxin.

Frataxin plays an essential role in iron metabolism and in the protection from oxidative stress.

Emerging therapies target the negative effects of frataxin deficiency (e.g. ROS, toxic iron); they also target frataxin expression (e.g. HDAC inhibitors).

iPS technology for FA is also actively pursued in the research pipeline.

