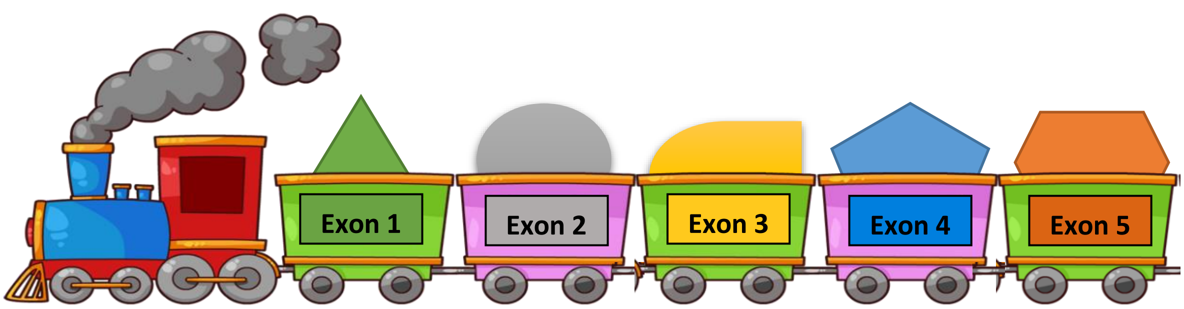
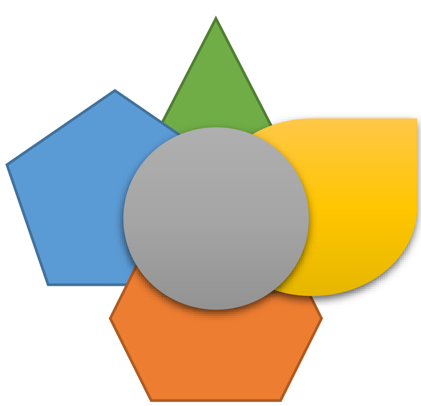
Genetic basis of Friedreich's ataxia

The ***FXN* gene** has five genetic segments. The segments, called exons, together code for the **frataxin protein** (shown below). Every person has two copies of the *FXN* gene, and every copy of the *FXN* gene has a GAA trinucleotide repeat in intron 1 (area between exon 1 and exon 2). The number of GAA trinucleotide repeats influences whether the gene functions normally to produce sufficient frataxin protein or whether the gene is silenced with very little frataxin protein produced. Frataxin protein contributes to energy production in mitochondria to keep cells functioning properly. When frataxin protein is too low in mitochondria of the cells, the person develops symptoms of Friedreich's ataxia.

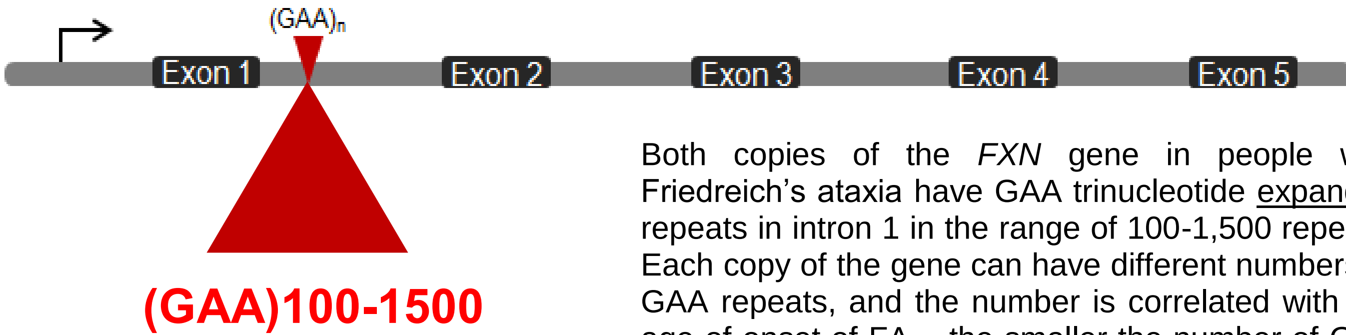
The metaphor for *FXN* gene function is a train with five compartments. The train engine functions to make sure all the segments (exons) of the *FXN* gene are made for adequate frataxin protein production.



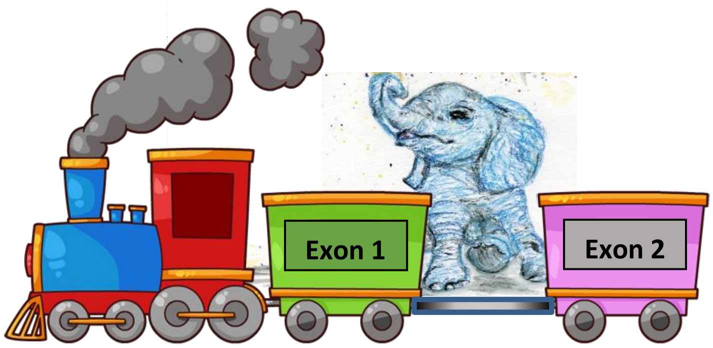


Frataxin protein

The five compartments make different portions of the frataxin protein.

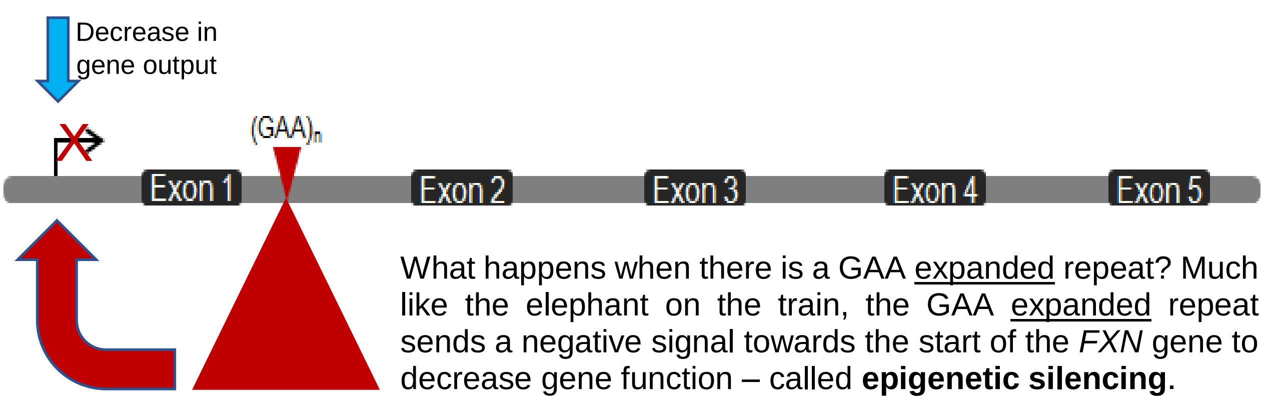


Both copies of the *FXN* gene in people with Friedreich's ataxia have GAA trinucleotide expanded repeats in intron 1 in the range of 100-1,500 repeats. Each copy of the gene can have different numbers of GAA repeats, and the number is correlated with the age of onset of FA – the smaller the number of GAA repeats, the later the age of onset of FA.



A GAA repeat expansion is like an elephant sitting on the train between the first and second compartments.

What harm comes from an elephant sitting on the train? The elephant sends a negative signal (shown here as a muddy substance) towards the engine of the train causing it to decrease its ability to function at peak capacity.



What happens when there is a GAA expanded repeat? Much like the elephant on the train, the GAA expanded repeat sends a negative signal towards the start of the *FXN* gene to decrease gene function – called **epigenetic silencing**.

Research studies are being performed to find ways to re-activate the *FXN* gene by overcoming the epigenetic silencing. Two methods being tested are **HDAC inhibitors** (BioMarin Pharmaceutical) and **oligonucleotides** (David Corey's lab, UT Southwestern). Both strategies are designed to reduce the amount of the negative (epigenetic silencing) signal; HDAC inhibitors are designed to clean up the negative signal, and oligonucleotides are designed to specifically prevent the formation of the negative signal.