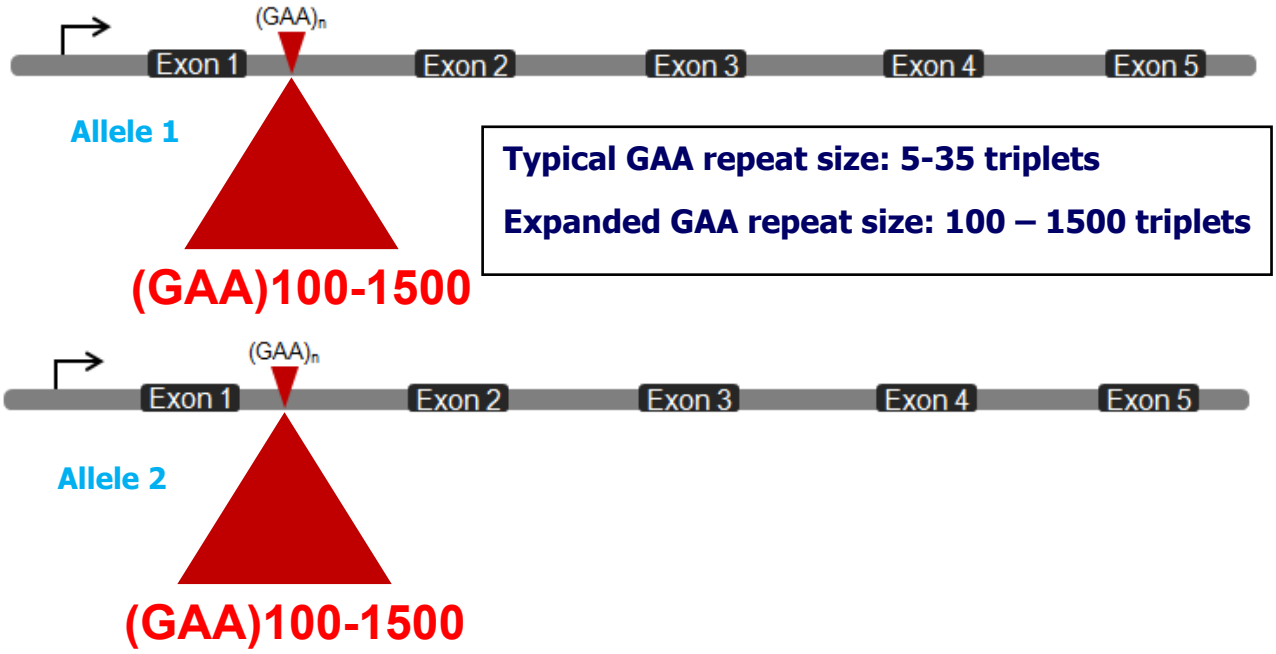
Genetics and Genetic Testing for Friedreich's Ataxia (FA)

Each person carries two copies of many of their genes, and the DNA sequence of each gene copy is called an **allele**. Each allele in a child is inherited from Mom or Dad. For the *FXN* gene, both alleles must contain a mutation for a person to be affected with FA (recessive inheritance).

The majority, 96%, of people affected by FA have a **GAA trinucleotide repeat expansion** in the first intron of each allele of the *FXN* gene.



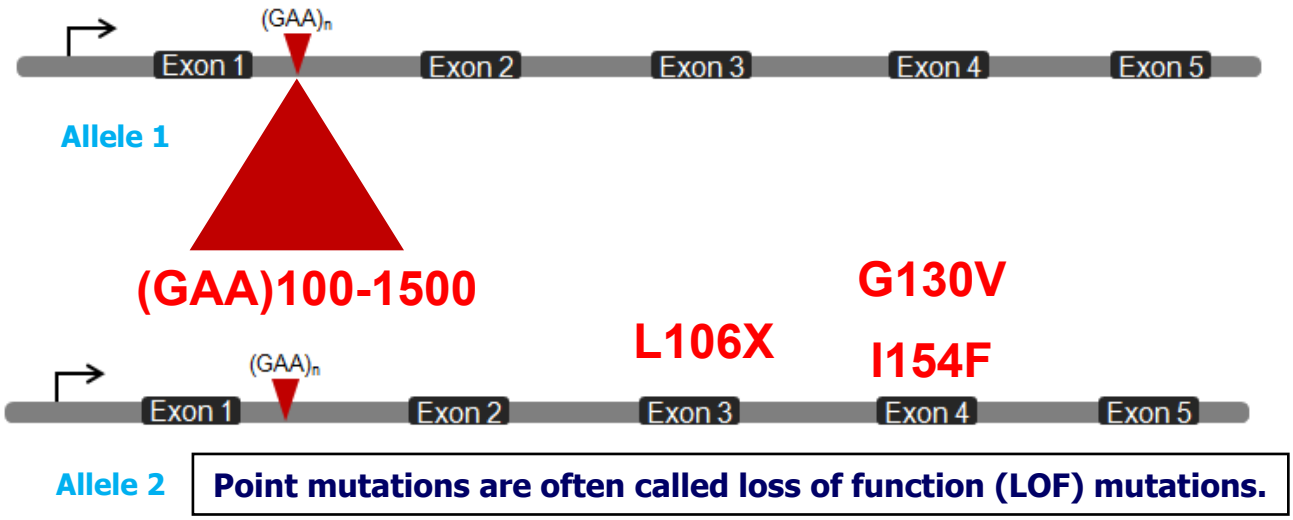
The GAA trinucleotide repeat expansion is analyzed by PCR and Southern Blot, although there are other technologies to detect the repeat expansion.

It is important to know that large GAA repeat expansions that cause FA cannot reliably be detected by:

- Gene sequencing
- Whole exome sequencing (WES)
- Whole genome sequencing (WGS)

If your physician feels strongly about the possible diagnosis of FA compared to other neurological conditions, it is cost effective to first test for the GAA repeat expansion.

The majority of people affected with FA have at least one allele with a GAA repeat expansion in intron 1. For some people, 3-4%, the second allele has a **point mutation**.



Point mutations are often called loss of function (LOF) mutations.

There are common point mutations that have been identified in people affected with FA, including L106X, L106S, G130V, I154F, R165C, W155R, and G137V; however, it is expected that a point mutation can occur anywhere within the *FXN* gene. When analyzing for point mutations, it is important that full gene sequencing be performed rather than an analysis only for specific point mutations.

In a small number of people affected with FA, likely less than 1%, the second allele has a **full or partial *FXN* gene deletion**, meaning that a copy of the *FXN* gene is completely missing or that some exons of the *FXN* gene are missing. Currently*, FARA is not aware of a commercial lab performing *FXN* gene deletion analysis. Laboratories consider deletions rare causes of FA, and the analysis requires a specific technology to reliably detect gene deletions.

When your physician orders genetic testing for FA, there are several ways the testing could be ordered and performed:

1. GAA repeat expansion analysis only.
2. GAA repeat expansion analysis plus full *FXN* gene sequencing (concurrently).
3. GAA repeat expansion analysis first with reflex testing to full *FXN* gene sequencing if only one allele has a GAA repeat expansion.

GAA repeat expansion analysis is less expensive than full *FXN* gene sequencing; therefore, many physicians perform Step 1 (above) first because it has the highest likelihood, 96%, of identifying the genetic cause of FA.

Please note: The above information describes most FA genetic diagnoses. There are cases where the causative mutation is *not* identified on both alleles and frataxin protein level might be measured to confirm the FA diagnosis. Genetic testing continuously evolves, and this information will be periodically updated.

*As of 8.19.2019