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"Using Transgenic Mouse Models to Track DNA Repeat Expansion of Friedriech's Ataxia Patients"

DNA repeat expansion disorders, also known as "trinucleotide repeat disorders," result from repeating sequences of DNA that cause disease as they progress past a threshold length. Such neurodegenerative disorders as Huntington's disease, myotonic dystrophy, and fragile X have been attributed to these expanding trinucleotide repeats. Friedriech ataxia (FRDA) is a progressive neurodegenerative disorder caused by GAA•TTC repeat expansion and specifically will be the focus of this research. Since FRDA is an autosomal recessive disorder, two inherited copies of the expanded frataxin (FXN) gene will lead to expressed symptoms of the phenotype. Patients will ordinarily exhibit a lack of reflexes and lower-body coordination, as well as speech difficulties, loss of sensation, and eventual heart disease.

Long sequences of GAA•TTC found in the first intron of the FXN gene affect proper transcription of the gene. Friedriech's patients have long repeats which hinder production of FXN. As a result, low levels of FXN mRNA transcript and frataxin proteins are characteristic of FRDA patients. Previous studies have indicated DNA mismatch repair (MMR) as a major player in repeat expansion. Sequences of repetitive nucleotide triplets are prone to forming loops by sticking to each other. Performing its usual function, MMR molecules "correct" these loops but will expand the repeating sequence in the process. While MMR is crucial for genome integrity elsewhere, the process facilitates the instability in DNA expansion. Research has identified the role of MMR molecule MLH3 in the expansion of GAA•TTC repeats in the FXN gene. Importantly, one isoform of MLH3 does not cause repeat expansion.

Of course, determining the exact location and speed of repeat expansion is a crucial step prior to any therapeutic solution. In this study, transgenic mouse models were used to track the length of repeats in the human FXN gene over time. Tissues from mice of different ages were analyzed to determine the extent of somatic expansion and to visualize the discrepancies between different tissues. As seen in these mouse models, the phenomenon of expansion is one that compounds over time, and thus an early delay or even a halt to expansion can be life changing for FRDA patients.