Frataxin

Frataxin is a protein that in humans is encoded by the FXN gene. It is located in the mitochondrion and Frataxin mRNA is mostly expressed in tissues with a high metabolic rate. The function of frataxin is not clear but it is involved in the assembly of iron-sulfur clusters.

Case series

Thomas-Black et al. investigated 62 genetically confirmed FRDA patients using an integrated approach as part of an observational cohort study. They included measurement of frataxin protein levels, clinical evaluation of visual and neurological function, optical coherence tomography to determine retinal nerve fiber layer thickness and macular layer volume, and volumetric brain MRI.

They demonstrated that frataxin level correlates with peripapillary retinal nerve fiber layer thickness and that retinal sectors differ in their degree of degeneration. They also showed that the retinal nerve fiber layer is thinner in FRDA patients than in controls and that this thinning is influenced by the AAO and GAA1. Furthermore, they show that the ganglion cell and inner plexiform layers are affected by FRDA. The MRI data indicate that there are borderline correlations between retinal layers and areas of the cortex involved in visual processing.

The study demonstrates the uneven distribution of axonopathy in the retinal nerve fiber layer and highlights the relative sparing of the papillomacular bundle and temporal sectors. They show that thinning of the retinal nerve fiber layer is associated with frataxin levels, supporting the use of the two biomarkers in future clinical trials design [1)]

Epigenetic silencing in Friedreich's ataxia (FRDA), induced by an expanded GAA triplet-repeat in intron 1 of the FXN gene, results in deficiency of the mitochondrial protein, frataxin. A lesser-known extramitochondrial isoform of frataxin detected in erythrocytes, frataxin-E, is encoded via an alternate transcript (FXN-E) originating in intron 1 that lacks a mitochondrial targeting sequence. We show that FXN-E is deficient in FRDA, including in patient-derived cell lines, iPS-derived proprioceptive neurons, and tissues from a humanized mouse model. In a series of FRDA patients, deficiency of frataxin-E protein correlated with the length of the expanded GAA triplet-repeat, and with repeat-induced DNA hypermethylation that occurs in close proximity to the intronic origin of FXN-E. CRISPR-induced epimodification to mimic DNA hypermethylation seen in FRDA reproduced FXN-E transcriptional deficiency. Deficiency of frataxin E is a consequence of FRDA-specific epigenetic silencing, and therapeutic strategies may need to address this deficiency [2)].

1)
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2)
Rodden LN, Gilliam KM, Lam C, Rojsajjakul T, Mesaros C, Dionisi C, Pook M, Pandolfo M, Lynch DR,

Blair IA, Bidichandani SI. DNA methylation in Friedreich ataxia silences expression of frataxin isoform E. Sci Rep. 2022 Mar 23;12(1):5031. doi: 10.1038/s41598-022-09002-5. PMID: 35322126.