Friedreich Ataxia

Genetics

-Gene: FRDA (Frataxin, 9q13)

-AR; GAA triplet repeat expansion in FRDA intron 1

Clinical findings/Dysmorphic features

-Progressive degeneration of the dorsal root ganglia, posterior columns, corticospinal tracts, dorsal spinocerebellar tracts of the spinal cord and cerebellum

-Progressive limb and gait ataxia (slurred speech, stumbling, falling, incoordination) < 25 yrs; absent tendon reflexes in the lower extremities

-Within 5 years of disease onset: dysarthria, areflexia, pyramidal weakness of legs, extensor plantar responses; distal loss of joint position and vibration sense

-Scoliosis, pes cavus, optic nerve atrophy, hypertrophic cardiomyopathy

Etiology

-1 in 50,000; carrier frequency: 1:60-1:100

Pathogenesis

-Frataxin is predominantly located in mitochondria

-Carboxy-terminal region is highly conserved and is target for pathogenic missense variants

-Frataxin binds iron and is required for synthesis of iron-sulfur clusters --> synthesis of enzymes in the respiratory chain complexes I–III and aconitase

-GAA repeat results in transcriptional silencing of FXN: 1) epigenetic silencing in the sequence flanking the expanded GAA repeat and near the FXN promoter; 2) formation of one or more abnormal DNA structures, which interferes with transcriptional elongation

Genetic testing/diagnosis

-GAA triplet repeat expansion in FRDA intron 1 (96% homozygous): normal 5-33, premutation 34-65, disease causing: 66-1700 repeats; some comphet for expansion and path variant

-Electrophysiologic evidence of axonal sensory neuropathy