Mitochondrial DNA-Associated Leigh Syndrome and NARP

Genetics

-Genes: MT-ATP6 (~50% Leigh syndrome; >50% NARP); MT-ND5; MT-ND3; MT-ND6

-If nuclear: mostly AR

Clinical findings/Dysmorphic features

-Spectrum: progressive neurodegenerative disorders due to anomalies of mt energy generation

-Leigh syndrome: onset between 3 and 12mths (often following viral infection); decompensation (often with elevated lactate levels in blood/CSF) during an intercurrent illness --> psychomotor retardation/regression; neurologic features include hypotonia, spasticity, movement disorders (including chorea), cerebellar ataxia, peripheral neuropathy, basal ganglia + brainstem MRI abnormalities in Leigh syndrome; extraneurologic manifestations may include hypertrophic cardiomyopathy; 50% of affected individuals die by 3 years (respiratory or cardiac failure)

-NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa): proximal neurogenic muscle weakness with sensory neuropathy, ataxia, pigmentary retinopathy; onset of symptoms, particularly ataxia and learning difficulties, often in early childhood; can be stable for years, but may suffer episodic deterioration (associated with viral illness)

Etiology

-Prevalence is likely to be 1:30,000 to 1:40,000; no data on prevalence of NARP

Pathogenesis

-Caused by mutations in more than 75 different genes; most in nuclear DNA, some in mtDNA

-Pathogenic variants fall into 2 classes: 1) tRNA --> decreased mitochondrial protein synthesis; 2) Protein-coding mtDNA genes --> decreased activity of respiratory chain complex

-m.8993T>G, p.Leu156Arg in subunit 6 of the mt ATP synthase --> ATP synthase (or complex V) uses the proton gradient generated by respiratory chain complexes I to IV to drive ATP synthesis --> impaired proton translocation and inhibition of ATP synthesis

Genetic testing/diagnosis

-Diagnosis: progressive neurologic disease with motor and intellectual DD, signs of brain stem/basal ganglia disease, raised lactate in blood/CSF, and any one of the following:

--> Characteristic features on brain imaging/typical neuropathologic changes/typical neuropathology in a similarly affected sibling

-Identification of a pathogenic variant in one of 14 mitochondrial genes confirms diagnosis: targeted seq 2 common MT-ATP6 variants, concurrently with del/dup on leukocyte DNA --> mt genome sequencing next

-MT-ATP6: Seq 95%; InDel 5%; most common: m.8993T>G