Mitochondrial DNA Deletion Syndromes

Genetics

-mtDNA large-scale deletion ranging from 1.1 to 10 kb

Clinical findings/Dysmorphic features

1) Kearns-Sayre syndrome (KSS): progressive multisystem disorder; onset < 20y; pigmentary retinopathy; progressive external ophthalmoplegia (paralysis/weakness of the eye muscles); additional features: cerebellar ataxia, impaired intellect, SNHL, ptosis, oropharyngeal and esophageal dysfunction, exercise intolerance, muscle weakness, endocrinopathy

2) Pearson syndrome: sideroblastic anemia and exocrine pancreas dysfunction; may be fatal in infancy without appropriate hematologic management; (pancreatic failure, sideroblastic anemia, and pancytopenia)l typically lethal in infancy

3) Progressive external ophthalmoplegia (PEO): ptosis, ophthalmoplegia, oropharyngeal weakness, variably severe proximal limb weakness with exercise intolerance.

4) Rarely, a mtDNA deletion can manifest as Leigh syndrome

Etiology

-Adults with single large-scale mtDNA deletions: 1.5:100,000 individuals

Pathogenesis

-Even smallest mtDNA deletion cover several tRNA genes --> "deleted" mtDNA is normally transcribed --> transcript is not translated because essential tRNAs are missingfor protein syn.

-Larger deletions also remove mRNAs required for synthesizing the mtDNA-encoded subunits of respiratory chain complexes I, III, IV, or V --> impaired mitochondrial energy production.

Genetic testing/diagnosis

-Deletion/duplication analysis of mtDNA: 100% of KSS; 100% of PEO; <5% of Leigh syndrome

-Common deletion m.8470\_13446del4977 present in 30% of KSS individuals

Others

-Almost always de novo: mtDNA deletions in mother's oocytes during germline development or in embryo during embryogenesis  
-Homologous recomb. or slipped mispairing (i.e., unequal crossing over) as origin of deletions