Ataxia-telangiectasia

Genetics

-ATM on 11q22.3

-AR (carriers with 4x increased risk for cancer and coronary artery disease)

-Amish founder mutation: c.1564\_1565delAG

Clinical findings/Dysmorphic features

-Progressive gait and truncal ataxia with onset between 1-4yo and progressively slurred speech

-Oculomotor apraxia (inability to follow an object across visual fields)

-Choreoathetosis (occurrence of involuntary movements, combination of chorea and athetosis)

-Telangiectasias of the conjunctivae (tissue that lines inside of eyelids and covers the sclera)

-Immunodeficiency and increased risk for malignancy (particularly leukemia and lymphoma)

Etiology

-Prevalence in the US: 1:40,000-1:100,000 live births

Pathogenesis

-ATM is activated by double-stranded DNA breaks --> coordinates cell-cycle checkpoints prior to repair, attaches near damage sites, recruits other repair proteins to damaged sites

-Most mutations LOF

Genetic testing/diagnosis

-Sequence analysis of ATM first, followed by gene-targeted deletion/duplication analysis if only one variant is found --> 90% sequence analysis, 1-2% deletion/duplication

-Targeted analysis for ATM pathogenic variants in specific populations, i.e. Amish

Others

-Most common cause of progressive cerebellar ataxia in childhood in most countries with low coefficients of inbreeding

-Individuals with AT are sensitive to ionizing radiation!

-Elevated AFP in blood