Amyotrophic lateral sclerosis

Genetics

-ALS/FTD --> C9orf72, 23-30%, AD; ALS1 --> SOD1, 20%, AD; ALS6 --> FUS/TLS, 4%, AD; AD (AR: ALS2 and SPG20)

Clinical findings/Dysmorphic features

-Progressive neurodegenerative disease involving upper motor neurons (UMN, located within brain and brainstem; send axons down the spinal cord to innervate with LMN) and lower motor neurons (LMN, located within ventral horn of spinal cord, send axons towards the periphery to innervate skeletal muscles)

-UMN signs: hyperreflexia, extensor plantar response, increased muscle tone, weakness in a topographic representation

-LMN signs: weakness, muscle wasting, hyporeflexia, muscle cramps, fasciculations (small, local, involuntary muscle contraction and relaxation, may be visible under the skin)

-Asymmetric focal weakness of extremities (stumbling or poor handgrip) or bulbar findings (dysarthria, dysphagia)

-Mean onset is 56y with no known family history; 46y with >1 one family member (familial ALS)

-Disease duration ~ 3years (death from compromise of the respiratory muscles)

Etiology

-Prevalence is 4-8:100,000

Pathogenesis

-Toxic gain of function, not enzyme deficiency (SOD1 prevents oxidative damage to cells)

Genetic testing/diagnosis

-SOD1 mutation (20% familial, 3% sporadic ALS; 50% have p.Ala4Val in exon 1 mutation)

-Multigene panel

Others

-Steven Hawkins diseases

-An increased number of GGGGCC (G4C2) hexanucleotide repeats in C9ORF72 can cause ALS