Duchenne & Becker Muscular Dystrophy

Genetics

-Gene: DMD (Dystrophin; Xp21.2)

-XLR, 1/3 de novo, 2/3 inherited

Clinical findings/Dysmorphic features

-DMD: onset <5 years; progressive symmetrical muscular weakness; delayed motor milestones; waddling gait and difficulty climbing stairs, running, jumping, standing up from a squatting; calf hypertrophy, wheelchair by age 12; dilated cardiomyopathy in almost all individuals >18y; few survive beyond the 3rd decade --> respiratory complications, progressive cardiomyopathy

-BMD: later onset; less severe; wheelchair after age 16 years; weakness of quadriceps may be only sign; activity induced cramping; preservation of neck flexor muscles (vs.DMD)

-DMD-associated dilated cardiomyopathy (left ventricular dilation and congestive heart failure); heterozygous females are at increased risk for DCM

Etiology

-DMD: 1 in 3,500 males; BMD: 1 in 30,000 males

Pathogenesis

-Dystrophin binds actin and other membrane proteins; mutations causing lack of dystrophin expression --> DMD; mutations causing abnormal quality or quantity of dystrophin --> BMD

Genetic testing/diagnosis

-Increase in serum concentration of creatine phosphokinase (CK); CK 10x nl in DMD, 5x nl in BMD (unreliable test for carrier females; tends to decrease with age)

-Multiplex PCR: DMD exon del (65% DMD, 85% BMD); Southern or qPCR for gene duplication (6% DMD); DMD seq for small del/ins or SNVs (30% DMD); MLPA or gene-targeted microarray

Others

-Pseudohypertrophy; Gowers’ Maneuver

-80% of het females no symptoms, but: Turner syndrome (45,X), skewed X-inactivation (balanced X-autosome translocation), UPD for X (from carrier mother or BMD father), compound heterozygosity for 2 DMD variants (carrier mother and BMD father)

-Germline mosaicism: risk is estimated to be ~10-15% (rr ~7%)

-Therapy: exon skipping, stop-readthrough, Crispr/Cas