Myotonic dystrophy type I

Genetics

-DMPK (Myotonin-protein kinase; 19q13.32)

-AD

Clinical findings/Dysmorphic features

-Multisystem disorder of skeletal and smooth muscle, eyes, heart, endocrine system, CNS

-Mild (50-150 repeats): cataract (clouding of lens) + mild myotonia (sustained muscle tensing)

-Classic (100-1000 repeats): muscle weakness/wasting, myotonia, cataract, arrhythmia; grip myotonia (inability to quickly release a hand grip)

-Congenital (>2000 repeats): hypotonia and severe generalized weakness at birth; often with respiratory insufficiency and early death, ID is common

Etiology

-Worldwide: 1:20,000

Pathogenesis

-DMPK is serine-threonine kinase --> interact with members of the Rho- GTPases --> substrates include myogenin, the beta-subunit of the L-type calcium channels

-Due to gain of function RNA mechanism --> CUG repeats attract many RNA splicing proteins --> alter alternative splicing of other genes, including the CL-channel --> myotonia

Genetic testing/diagnosis

-No DPMK SNVs, deletions or insertions reported, only CTG repeat expansion in the 3' untranslated region of DMPK

-Abnormal repeat can reach several thousand, particularly in individuals with congenital DM1

-PCR (detects repeats up to ~100), southern blot (detect repeats>100)

Others

-DM2: myotonia (90%) and muscle dysfunction (weakness, pain, stiffness; 82%), less commonly by cardiac conduction defects, iridescent posterior subcapsular cataracts; CNBP (ZNF9); intron 1 contains a complex repeat motif, (TG)n(TCTG)n(CCTG)n; expansion of the CCTG repeat 75 - 11,000 (mean 5000)