Charcot Marie Tooth Disease

Genetics

-CMT1 (AD): 70-80%: 1.5Mb dup of PMP22 on 17p11.2 (CMT1A); 5-10%: MPZ variant (CMT1B)

-CMT2 (AD): MFN2, MPZ, HSPB1, KIF1B, LMNA

-CMT intermediate form (AD): DNM2, YARS

-CMT4 (AR): 11 genes known: GDAP1 (CMT4A), MTMR2 (CMT4B1), SBF2 (CMT4B2), SBF1 (CMT4B3), SH3TC2 (CMT4C), NDRG1 (CMT4D), EGR2 (CMT4E), PRX (CMT4F), HK1 (CMT4G), FGD4 (CMT4H), FIG4 (CMT4J)

-CMTX; XLD: 90% with GJB1 (mainly sequence variants)

Clinical findings/Dysmorphic features

-CMT affects the peripheral nerves (both motor and sensory nerves)

-CMT1 (50% of all CMTs): demyelinating peripheral neuropathy; distal muscle weakness and atrophy; sensory loss; slow nerve conduction velocity; often associated with pes cavus and bilateral foot drop; onset 5-25 years

-CMT2 (20-40% of all CMTs): axonal (non-demyelinating) peripheral neuropathy; distal muscle weakness and atrophy; mild sensory loss; normal or near-normal nerve conduction velocities; clinically similar to CMT1; typically less severe; peripheral nerves not enlarged or hypertrophic; subtypes of CMT2 are clinically similar --> distinguished only by molecular genetic findings

-CMT intermediate form (rare): combination of myelinopathy and axonopathy

-CMT4 (rare): either myelinopathy or axonopathy; progressive motor and sensory axonal and demyelination; typical CMT phenotype of distal muscle weakness and atrophy associated with sensory loss and, frequently, pes cavus foot deformity

-CMTX (10-20% of all CMTs): moderate to severe motor and sensory neuropathy in affected males; usually mild to no symptoms in carrier females; SNHL and CNS symptoms may also occur

Etiology

-1 in 3300 worldwide

Pathogenesis

-Abnormal peripheral myelination

Genetic testing/diagnosis

-Nerve conduction studies, nerve biopsy

-Gene sequencing, deletion/duplication analysis