Rett syndrome

Genetics

-Gene: MECP2 (MECP2, Xq28)

-XLD; pathogenic variant in a male is presumed to most often be lethal (surviving males: severe neonatal encephalopathy; manic-depressive psychosis, pyramidal signs, Parkinsonian, macro-orchidism)

->99% are simplex cases (i.e. single occurrence in family), resulting from de novo variant

Clinical findings/Dysmorphic features

-Spectrum in females: classic Rett, variant Rett, mild LD

1) Classic:

-Normal psychomotor development during first 6 - 18 months --> short period of developmental stagnation --> rapid regression in language and motor skills --> followed by long-term stability

-Repetitive, stereotypic hand movements replace purposeful hand use

-Additional findings: fits of screaming, autistic features, panic attacks, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, acquired microcephaly

2) Variant:

-Clinically suspected but molecularly unconfirmed Angelman syndrome

-Intellectual disability with spasticity/tremor, mild LD, rarely autism

Etiology

-Prevalence of Rett syndrome in females: 1:8,500 by age 15 years

Pathogenesis

-MECP2 binds methylated CpG islands

-Decreased of LoF --> Disruption of regulated gene expression during development

-Ubiquitously expressed but predominantly neurologic phenotype --> brain tissues more vulnerable or tissue-specific differences in MECP2 expression (alternate transcripts, differentially expressed in brain during development)

Genetic testing/diagnosis

-Sequencing of exons 1-4, followed by deletion/duplication if sequencing is normal

-Testing of both parents for the identified sequence variation if VUS

-Sequencing of MECP2 in classic Rett: 80%, In/Del: 8%

Others

-Germline mosaicism described

-MECP2 microduplication syndrome (0.3 to 2.3 Mb) --> infantile hypotonia, severe ID, absence of speech, progressive spasticity, recurrent respiratory infections, seizures

-Phase I and II: administration of tri-peptide form of insulin-like growth factor, rhIGF-1 (mecasermin)