Fragile X

Genetics

-FMR-1 (FMRP, Fragile X Mental Retardation Protein, Xq27.3)

-X-linked triplet repeat, CGG repeat expansion in the 5’ UTR

-Normal alleles ~5-44

-Intermediate alleles ~ 45-54: 14% of intermediate alleles are unstable and may expand into premutation when transmitted by the mother; not known to expand to full mutation

-Premutation alleles ~55-200: no fragile X syndrome, but increased risk for FXTAS/POI; 56 is smallest repeat known to expand to full mutation in single transmission; not hypermethylated

-Full-mutation alleles > 200 CGG repeats: 100s – 1000s repeats typical; hypermethylation of the FMR1 promoter

Clinical findings/Dysmorphic features

1) Fragile X syndrome:

-FMR1 full mutation or LoF variant; moderate ID in affected males/ID in affected females

-Males with FMR1 full mutation accompanied by aberrant methylation: typical facial features (long face, prominent forehead, large ears, prominent jaw), connective tissue findings (joint laxity), large testes after puberty, behavioral abnormalities (ASD)

2) Fragile X-associated tremor/ataxia syndrome (FXTAS):

-In males (and some females) with FMR1 premutation

-Characterized by late-onset, progressive cerebellar ataxia and intention tremor

3) FMR1-related primary ovarian insufficiency (POI):

-Age at cessation of menses <40 years; in approx. 20% of females with FMR1 premutation

Etiology

-16 to 25:100,000 males affected with fragile X syndrome

Pathogenesis

->200 repeats lead to silencing by methylation --> FMRP is RNA-binding protein that forms a messenger ribonucleoprotein complex --> associates with polysomes --> inhibitor of translation --> regulates protein synthesis dendrites --> in fragile X: translation of certain messages may be exaggerated because the normal inhibition provided by FMRP is absent

-FXTAS and POI resulting from FMR1 premutations may be manifestations of RNA-mediated toxicity due to increased FMR1 expression

Genetic testing/diagnosis

- >99% with increased number of CGG trinucleotide repeats (typically >200) --> aberrant methylation of FMR1 promoter; del and SNVs variants can also cause fragile X syndrome

-PCR for the CGG trinucleotide repeat --> high sensitivity for normal and lower premutation range (≤100 to 120 repeats); less sensitive to larger premutations; fails to amplify full mutations

-Southern blot analysis detects all FMR1 alleles including normal, larger-sized premutations, and full mutations and in addition determines methylation status of the FMR1 promoter region

-Methylation can be assessed by PCR-based methods independent of the of CGG repeats

Others

-CGG repeats expand exclusively during transmission from female carriers

-Risk for expansion depends on number of CGG repeats and presence of AGG triplets