Condition: Fragile X syndrome

Inheritance:

X-linked.

Genetic etiology:

Expansion of a CGG triplet repeat in the promoter region of the *FMR1* gene on the X chromosome. Repeat number ranges from 6 – 40 in the general population. Affected individuals have more than 200 repeats, accompanied by methylation of the promoter, which leads to silencing of the gene. Individuals with 40-200 repeats do not display fragile X syndrome, but are at risk of further expansion during germ cell development, and are designated as having "premutations".

Frequency:

Approximately 1/5,000 males.

Clinical features:

Fragile X syndrome most often affects males, though some females may manifest signs due to nonrandom X chromosome inactivation. The phenotype includes developmental delay, behavioral problems, long, narrow facies, large head circumference, and macro-orchidism. Premutation females do not have these symptoms, but may experience premature ovarian failure. Some premutation males develop a syndrome of ataxia, tremor, and dementia in late adulthood.

Management:

Supportive care.

Genetic counseling:

Expansion to full mutation only occurs in the female germline; the likelihood is related to the size of the permutation allele. Premutation males will transmit the premutation allele to all of their daughters and non of their sons.

Human Genetics and Genomics, Fourth Edition. Bruce R. Korf and Mira B. Irons.