THE FRAGILE X MUTATION

Fragile X syndrome is caused by an expansion of CGG nucleotide repeats in the \textit{FMR1} gene at the end of the long arms of the X chromosome. To identify the mutation, researchers culture cells in media deficient in folic acid, which causes the ends of the X chromosome to appear as though they are about to break off. Before molecular testing, this was the only way to see the mutation.

The \textit{FMR1} gene encodes the fragile X mental retardation protein (FMRP), which regulates gene expression and protein translation in the brain. FMRP is important for maintaining synaptic plasticity and the ability to make new neurons. Levels of FMRP associated with disease severity in patients with FXS.

\textbf{Premutation:} The \textit{FMR1} gene has 55 to 200 CGG repeats that are not methylated. Premutations with fewer than 120 CGG repeats typically lead to normal FMRP levels; more repeats lead to lowered FMRP production, though this doesn’t necessarily translate to more severe disease. Premutations of any number of repeats can result in higher \textit{FMR1} mRNA levels, which can cause problems for the individual even if FMRP protein levels are normal. Collectively these problems are referred to as fragile X-associated disorders; they include fragile X-associated tremor/ataxia syndrome (FXTAS), primary ovarian insufficiency (FXPOI), and neuropsychiatric problems.

\textbf{Full mutation:} The \textit{FMR1} gene has more than 200 repeats of the nucleotides CGG that are heavily methylated. Males completely lack FMRP, while females typically have some protein produced from the \textit{FMR1} gene on the healthy X chromosome. Individuals carrying a copy of the full mutation present with FXS.