## Fragile X syndrome

Fragile X syndrome (FXS) is the most common form of inherited mental retardation. An X-chromosome-linked disease, FXS is more prevalent and its symptoms are more severe (see box, "Symptoms of fragile X syndrome") in the male population (1:2000) than in the female population (1:4000). In 1991, Stephen Warren and colleagues at the Howard Hughes Medical Institute (Chevy Chase, MD) identified mutations in a gene (*FMR1*) located on the X chromosome of individuals with the disease. Unlike most disease-associated mutations, however, the FXS mutation resides in the gene-expression control region and takes the form of highly repetitive stretches of the nucleotide triplet CGG (Figure 1). Normally, this triplet repeats 5–54 times, whereas in "premutation" individuals, this sequence repeats 50–200 times. In FXS-affected or "full mutation" individuals, however, the repeat occurs more than 200 times.

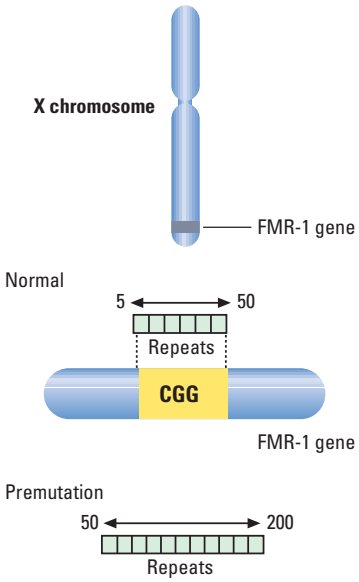


**Figure 1.** Schematic of FMR1 gene responsible for fragile X syndrome.

In the case of *FMR1*, the extreme number of CGG repeats causes excessive cytosine methylation in the promotor region of the gene such that *FMR1* is not transcribed at sufficient levels. The lack of *FMR1* mRNA leads to an equivalent or more severe lack of the protein encoded by the gene—the fragile X mental retardation 1 protein, or FMRP. FMRP is found predominantly in the cellular cytoplasm but can also translocate to the nucleus. Several research groups have shown that FMRP can bind to mRNA, but it preferentially binds to mRNA isolated from brain tissue.

In 1999, Warren's group used antibodies to isolate other mRNA-bound proteins that might interact with FMRP. Among the proteins associated with FMRP, the researchers found two that belong to the same family of proteins as FMRP, as well as nucleolin and a protein involved in mRNA unwinding during translation (Figure 2). This indicated a possible role for FMRP in translation control.

In early 2002, Peter Carlen and colleagues at the Toronto Western Hospital (Ontario) linked *FMR1* in mice to the function of the GluR1 protein, a neurotransmitter involved in learning. The researchers found reduced levels of GluR1 protein in brain tissue from mice that lacked *FMR1*, which resulted in an inability of the tissue to potentiate applied electrical signals—an in vitro model for learning.

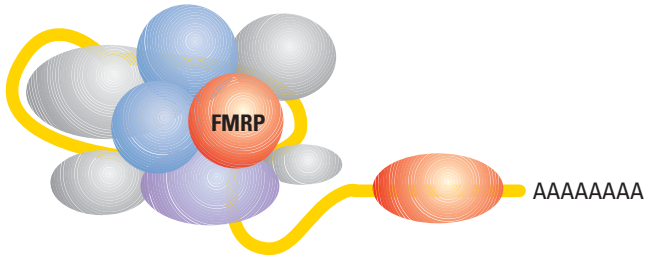


**Figure 2.** Schematic of a protein–mRNA translation complex involving FMRP.

Other studies have similarly located FMRP at the neuronal synapse, and its deletion has been shown to alter synaptic plasticity, which is associated with learning and memory.

Also in 2002, Haruhiko Siomi and colleagues at the University of Tokushima (Japan) purified a dFMR1 complex from *Drosophila* cell lysates that contained two ribosomal proteins. But they also found a third protein that is involved in RNA interference (RNAi), a cellular mechanism that inhibits infections and might be involved in mRNA degradation and therefore post-transcriptional gene control. Although the fly homologue of FMRP did not seem to be essential for RNAi-mediated mRNA degradation, it might play a secondary role. This finding might have serendipitously led researchers to the real cause of FXS, a defect in RNAi activity in neurons.

Unfortunately for people with FXS, there are still as many questions as there are answers. The complexity of the symptoms and the unknown pathogenesis of the syndrome complicate FXS treatment, because a palliative effect on one symptom can often worsen other symptoms. That being said, stimulants, selective serotonin reuptake inhibitors, anticonvulsants, and antipsychotics have all been used to attack some of the symptoms associated with FXS. But as concluded at a National Institute of Mental Health (Bethesda, MD) conference on FXS, "There is [still] a critical need for controlled studies of pharmacological and behavioral treatment approaches for the behavioral and psychiatric manifestations of FXS."

—RANDALL C. WILLIS

### Symptoms of fragile X syndrome

Researchers suggest that behavioral impairments rather than cognitive dysfunction limit the possible achievements of people with FXS. These impairments include

- autism,
- hyperarousal and hyperactivity,
- attention deficits,
- anxiety,
- soothing repetitive behavior,
- irritability,
- aggression, and
- extreme sensitivity to sensory stimuli.

(Source: Mental Health Aspects of Fragile X Syndrome: Treatment Research Perspectives. Available at www.nimh.nih.gov/research/fragilex.cfm.)