

NEWS

# Molecular mechanisms: Fragile X premutation proves toxic

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Vision loss: The protein expressed by a mutant form of the fragile X gene severely damages fly eyes (left).

A mild form of the fragile X mutation produces an unusual protein that may trigger fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disorder, according to a study published 8 May in *Neuron*<sup>1</sup>.

Fragile X syndrome is caused by more than 200 repeats of three nucleotides (CGG) located just before the coding region of the **FMR1** gene. These repeats shut off FMR1's expression, preventing its translation into messenger RNA (mRNA) and then into protein.

Unexpectedly, a premutation of FMR1, which has 55 to 200 repeats, boosts production of FMR1 mRNA. This can lead to FXTAS, which is characterized by memory loss and tremors. Researchers have speculated that in people with FXTAS, this **mRNA may itself be toxic**. Postmortem studies have also found clumps of protein in the brains of individuals who had FXTAS, although it was not clear how these clumps were related to the FMR1 mutation<sup>2</sup>.

In the new study, researchers found that in people with the premutation, CGG repeats of various sizes themselves are translated. When large enough, the resulting protein, called FMRpolyG, may accumulate into toxic, insoluble clumps that the cell's disposal machinery has difficulty clearing away.

The researchers found clumps that contain this protein in postmortem brains from three people who had FXTAS but none of five controls.

They also engineered fruit flies and cultured mammalian cells that express this CGG repeat region. The resulting clumps cause the flies' eyes to degenerate, and they kill mammalian cells.

Stimulating production of this protein in fruit flies boosts the toxic effects, and dampening its production does the opposite. This confirms that it is the protein and not the untranslated mRNA that does the damage, the researchers say.

## References:

1: **Todd P.K.** *et al. Neuron* **78**, 440-455 (2013) [PubMed](#)

2: Iwahashi C.K. *et al. Brain* **129**, 256-271 (2006) [PubMed](#)