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Fragile X syndrome untangled: Emory geneticists learn mechanics, but no solution yet

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Building on earlier breakthroughs, Emory geneticists have deciphered the mechanics of a runaway gene responsible for impaired motor function later in life, particularly among men.

The defective gene can cause a degenerative neurological disorder in adults known as fragile X-associated tremor/ataxia syndrome, or FXTAS. It also is responsible for fragile X syndrome in children, the most common type of inherited mental retardation.

Scientists estimate that full-blown fragile X syndrome, the most common cause of autism, affects about one in 4,000 males and one in 8,000 females.

The latest research sheds no new light on potential treatments for fragile X syndrome. But the findings could ultimately point the way to new therapies for gene carriers who develop FXTAS. These sufferers show no mental impairment early in life but can develop tremors and memory loss later, on average after age 60.

The Emory geneticists found that certain cell transmitters, previously thought to be benign, have a toxic effect on a key protein associated with motor function.

"The depletion of that protein could be a cause of neurodegeneration," said Dr. Peng Jin, a researcher and professor at Emory University School of Medicine's Department of Human Genetics. Dr. Jin's findings are reported in today's edition of *Neuron*, a journal of neuroscience.

Another contributor to the research, Dr. Stephen T. Warren, helped isolate the gene responsible for fragile X syndrome in 1991, and Emory geneticists have since pioneered tests to diagnose the disorder.

The new research focused on the characteristics of the gene in carriers who are at risk of developing FXTAS later in life. Aside from tremors and memory loss, FXTAS produces other symptoms similar to Parkinson's disease — loss of balance, poor coordination and general slowness.

Earlier research has found that fragile X carriers and those with full-blown symptoms have a series of repeating DNA sequences in the errant gene. Normal range is below 55 repetitions, while abnormal exceeds 200.

Those carriers between the two ranges are at risk for developing FXTAS. Overall, about one in 800 men and one in 260 women carry the mutated gene. But men are at greater risk than women for developing FXTAS symptoms.

Jin's research found that cell transmitters in the fragile X gene, known as messenger RNA, play a toxic role in normal brain function, interfering with certain proteins.

Researchers are only just beginning to understand how these proteins work in the brain and influence the countless signals the brain transmits to the body.

In the case of the fragile X gene, researchers had previously believed that the messenger RNA were largely innocuous.

But Jin and his colleagues found that they neutralize a key protein in the brain associated with motor function called pur alpha.

In previous research in mice, lower levels of pur alpha produced tremors and Parkinson-like symptoms, leading Emory researchers to conclude that the protein plays an important role in motor function.

What then would account for the diminished levels of the protein in fragile X carriers? The Emory researchers theorize that the toxic effect of the messenger RNA is magnified because of the abnormally high numbers of the repeating DNA sequences, and the strands themselves are elongated.


The concentration of messenger RNA acts like a magnet, bonding to pur alpha and effectively blocking the protein's ability to properly influence motor skills.

Jin said future research will likely focus on treatments that could suppress the toxic effect of the messenger RNA, freeing up more of the pur alpha protein for normal brain function.

"If we can block the RNA-protein interaction, we might also be able to make this toxic RNA nontoxic," Jin said.

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