

Progressive neurodegenerative disorder linked to R-loop formation

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Researchers at UC Davis have identified a new feature of the genetic mutation responsible for the progressive neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS)—the formation of "R-loops," which they believe may be associated with the disorder's neurological symptoms, such as tremors, lack of balance, features of Parkinsonism, and cognitive decline.

The finding suggests that the R-loops may be potential targets for drug development, said Paul Hagerman, senior study author, professor in the Department of Biochemistry and Molecular Medicine and director of the UC Davis NeuroTherapeutics Research Institute. The study, "Transcription-associated R-loop Formation across the Human FMR1 CGG-repeat Region," is published today in the online journal *PLoS Genetics*.

An R-loop is formed when the messenger RNA being made at the gene reinserts itself into the DNA helix, displacing one strand of DNA, which creates the "loop." Such loops are known to be prone to damage, which can in turn lead to loss of cell function, particularly in neurons.

Hagerman and his collaborators discovered the R-loops while investigating mutations in the gene that causes FXTAS and other conditions associated with the fragile X mental retardation gene 1 (FMR1). R-loops are not unique to FXTAS and can occur in the promoter regions of many [genes](#).

"But in FXTAS, the R-loops are more numerous and much longer than they are in FMR1 genes that are not mutated," said Hagerman, a researcher who also is affiliated with the UC Davis MIND Institute. "

In FXTAS, the number of excessive CGG repeats and the length of the R-loops are correlated, Hagerman said.

"The longer the R-loops, the greater their likelihood of being damaged," he said.

Like other genes, FMR1 is composed of the molecules adenine, thymine, cytosine and guanine, commonly referred to by their abbreviations, A, C, G and T. In the promoter area of a mutated FMR1 gene a trio of these molecules, C-G-G, is repeated an excessive number of times. In healthy individuals without the FMR1 gene mutation, the total of C-G-G repeats ranges from six to 45. However, in patients with FXTAS, the number of C-G-G repeats can be 200 or more.

The excessive numbers of C-G-G repeats in the mutated FMR1 gene are so distinctive that they are the basis of a genetic test to determine whether a patient has FXTAS or one of the other fragile X-associated disorders caused by FMR1 mutations.

In addition to FXTAS, fragile X-associated disorders include fragile X syndrome, the most common form of intellectual disability in children, and fragile X-associated primary ovarian insufficiency (FXPOI). In fragile X syndrome, the number of C-C-G repeats exceeds 200. The FMR1 [gene mutation](#) in fragile X is regarded as "full mutation," while the mutation in FXTAS and FXPOI are referred to as "premutations", Hagerman said.

Although a higher than normal number of CGG repeats in the FMR1 gene characterizes both FXTAS and fragile X syndrome, the molecular

mechanisms that are disrupted in these disorders differ substantially, he pointed out.

In patients with fragile X syndrome, the abnormally high number of C-G-G repeats shuts down, or silences, the FMR1 gene. In FXTAS, the less dramatic increase in C-G-G repeats boost the gene's transcription of its DNA into overdrive, triggering the creation of excessively long R-loops that are toxic to neurons, he said.

Provided by UC Davis

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