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Scientists find another clue to the origins of degenerative diseases

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For years, researchers in genome stability have observed that several neurodegenerative diseases—including Huntington's disease—are associated with cell-killing proteins that are created during expansion of a CAG/CTG trinucleotide repeat.

In research published in the March 17 online edition of the journal *PLoS Genetics*, Tufts University biologist Catherine Freudenreich, and then-graduate student Rangapriya Sundararajan show that cell death in yeast can also result from the process by which the cell repairs damage that occurs within a repeated CAG/CTG sequence.

The findings provide additional insight into the causes of some neurodegenerative diseases. "This represents a new way in which the expanded repeats may be causing cell death that leads to the disease," says Freudenreich. , associate professor of biology at the School of Arts and Sciences at Tufts University "The expanded DNA in and of itself can be toxic to cells."

Scientists have observed that Huntington's disease, myotonic dystrophy and multiple subtypes of spinal cerebella ataxia are caused when the number of repeats at the disease locus exceeds a stability threshold.

For Huntington's disease, the threshold is 38 to 40 repeats. Myotonic dystrophy results when there are close to 200 repeats.

When these expanded repeats occur, the abnormal DNA is copied

faithfully into ribonucleic acid, the chemical cousin of DNA. In myotonic dystrophy the errant RNA has a toxic effect because it grabs onto and holds hostage certain proteins, preventing them from carrying out the myriad functions that are vital to the cell.

In Huntington's disease and the ataxias, the RNA serves as a blueprint for an abnormal protein that contains an excessive amount of an amino acid called glutamine.

In her experiment, Freudenreich found a cause of cell death that arises from a DNA checkpoint response.

She started with a piece of human DNA that was cloned from a myotonic dystrophy patient. It contained CAG/CTG repeats of 70 and 155. She then placed the tract within a yeast chromosome.

Multiple types of DNA damage can occur at an expanded trinucleotide repeat. Damage of this magnitude triggers checkpoint proteins that respond like genomic firefighters to the emergency.

In normal circumstances these proteins halt the cell growth cycle until the damage is repaired.

In Freudenreich's study, the cell damage activated the Rad53 checkpoint kinase. But here, the protein arrested cell growth for an abnormally long period of time without repairing the damage. This often resulted in cell death.

In cases where the cell did manage to recover and keep dividing, the researchers observed an increased frequency of repeat expansions. "The cells that were having trouble growing and dividing due to the expanded repeat accumulated additional expansions. It became a vicious loop," says Freudenreich. She adds, "It will be important in the future to

determine if this phenomenon is contributing to the cell death that causes the human diseases."

Myotonic dystrophy is an inherited condition that affects muscles and other body systems. It is the most common form of adult onset muscular dystrophy, with progressive muscle wasting as well as a variety of other symptoms.

Huntington's disease is a genetic disease involving degeneration of the central nervous system, leading to uncontrolled muscle movements, emotional instability and dementia. Folk musician and songwriter Woody Guthrie died from complications of the disease in 1967.

More information: Sundararajan R, Freudenreich CH (2011) Expanded CAG/CTG Repeat DNA Induces a Checkpoint Response That Impacts Cell Proliferation in Saccharomyces cerevisiae. *PLoS Genet* 7(3): e1001339. doi:10.1371/journal.pgen.1001339

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