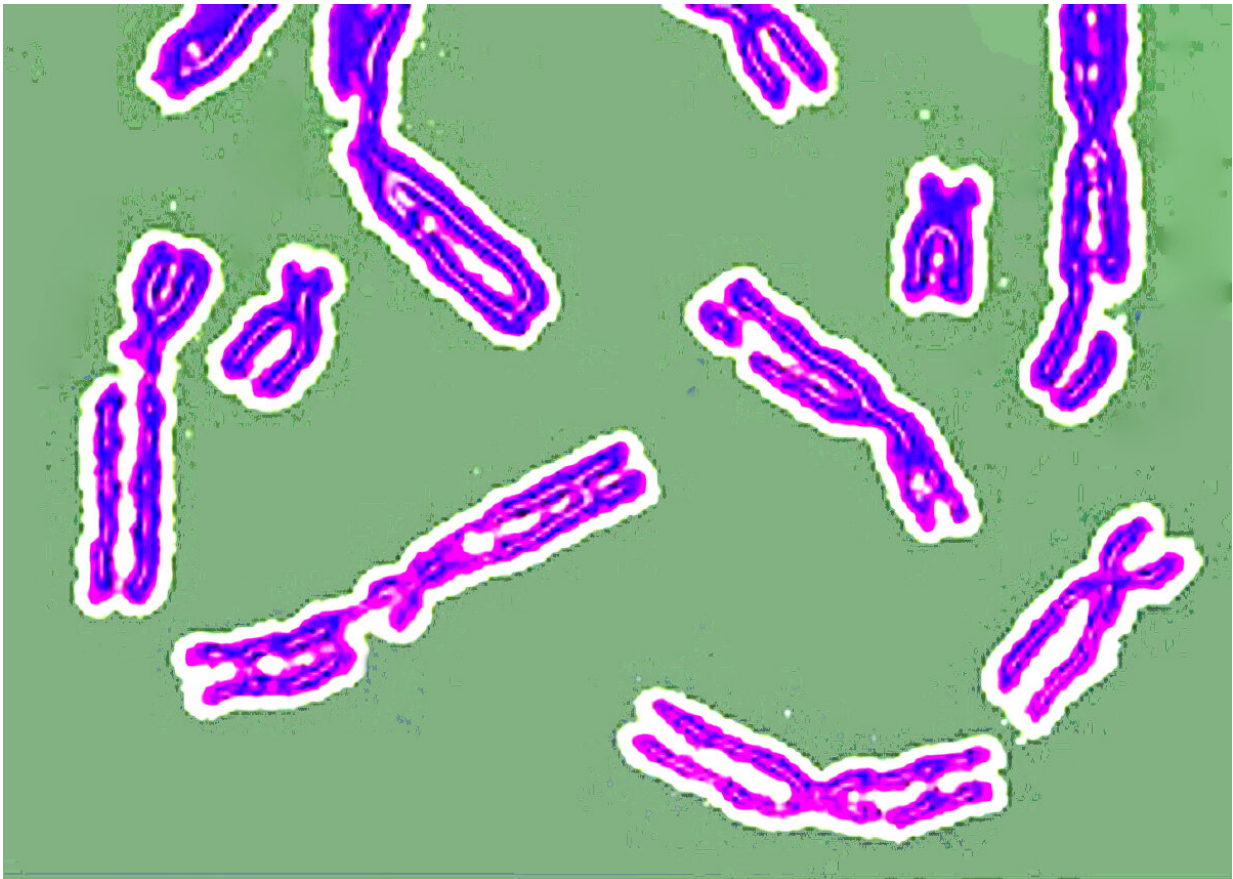


How DNA repair can go wrong and lead to disease

May 10 2023



DNA repair mechanisms can contribute to chromosome breakage at certain DNA sequences. Credit: Wikimedia Commons (Modified; no author stated)
Link: <https://commons.wikimedia.org/wiki/File:Brokechromo.jpg>

We often come to an understanding of what causes a disease. We know, for example, that cancers are caused by mutations at critical locations in the genome, resulting in loss of control of cell growth. We know that the onset of Huntington's disease, and other diseases that lead to muscle wasting and loss of coordination and balance, are linked to the expansion of short, repeated DNA sequences.

What we don't know is how these genetic events come about. In a study published in the journal *Nature Communications*, Catherine Freudenreich, professor and chair of the Department of Biology at Tufts, and her team of researchers uncovered mechanisms by which the natural process of DNA repair fails and mutations arise, opening up potential paths for understanding the origins of many diseases and the development of therapies to treat them.

"DNA breaks and repair events occur thousands of times per day in each of us," said Freudenreich. "Most of the time, repair works the way it should. But we now have a better understanding of how things can go wrong, and we can apply this knowledge to new therapeutic strategies."

Erica Polleys, a postdoctoral researcher in the Freudenreich Lab, focused on the gene repeats found in Huntington's disease—a long repetition of 60 or more copies of the sequence cytosine-adenine-guanine, or CAG, on one strand of the DNA and cytosine-thymine-guanine, or CTG, on the complementary strand.

"We've engineered yeast to have a CAG repeat sequence, because their cells are similar to [human cells](#) in many ways and they are easy to work with," said Polleys, "We can use simple model organisms to uncover how cells deal with repairing breaks and errors near repetitive sequences and use that knowledge to get an understanding of how human diseases like Huntington's disease or cancers develop."

It has been widely understood that DNA repeats can form structures that branch away from the linear chain of DNA, much like a cord or a hose will form branching twists if wound too tightly. These branches form barriers to natural replication and repair and introduce errors in the genome.

Freudenreich and Polley's examination of the mechanisms of DNA repair near Huntington's disease-like repeats revealed that repeats would expand or contract in number depending on which strand of the double stranded DNA was being repaired.

When the CAG side of the strand was being removed during a repair, the repeats contracted, and the DNA was at risk of large deletions, often fatal to the cell. When its complementary CTG strand was being removed and repaired, the repeats expanded, but only by one or two copies at a time. The researchers hypothesize that this is how the repeats accumulate in neurons of Huntington's disease patients.

A key observation was that DNA breaks near expanded repeats occurred a lot more frequently when the repeats were exposed as a single strand of DNA, something that occurs during many repair processes. This "fragile site" can lead to deletion of a nearby important gene, which can kill the cell, or result in diseases like cancer.

DNA fragility can happen near other sequences that make the DNA form branched twists. Genomic analysis could reveal more mutation hotspots that lead to cancer, or the accumulation of repair errors that lead to many conditions of aging.

Observing changes in repeat length provided more detail about what was happening, but not how it was happening. The Tufts team picked apart the repair mechanism further, deleting some proteins to see how they affected the fragility of the yeast genome.

Removal of one protein led to a faster recruitment of other proteins that untwist the DNA, leading to more successful repairs. A second protein was found that may help stabilize the DNA as it is being repaired, like fitting a sleeve over a hose to prevent it from twisting up.

The researchers point to the human equivalent of these yeast proteins, with the possibility that their inhibition or enhancement could lead to safer DNA repair and replication in patients with cancer or DNA repeat diseases, like Huntington's, myotonic dystrophy, and Friedrich's ataxia.

More information: Erica J. Polleys et al, Structure-forming CAG/CTG repeats interfere with gap repair to cause repeat expansions and chromosome breaks, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-37901-2](https://doi.org/10.1038/s41467-023-37901-2)

Provided by Tufts University

Citation: How DNA repair can go wrong and lead to disease (2023, May 10) retrieved 25 April 2024 from <https://phys.org/news/2023-05-dna-wrong-disease.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.