Antiviral protein causes genetic changes implicated in Huntington's disease progression

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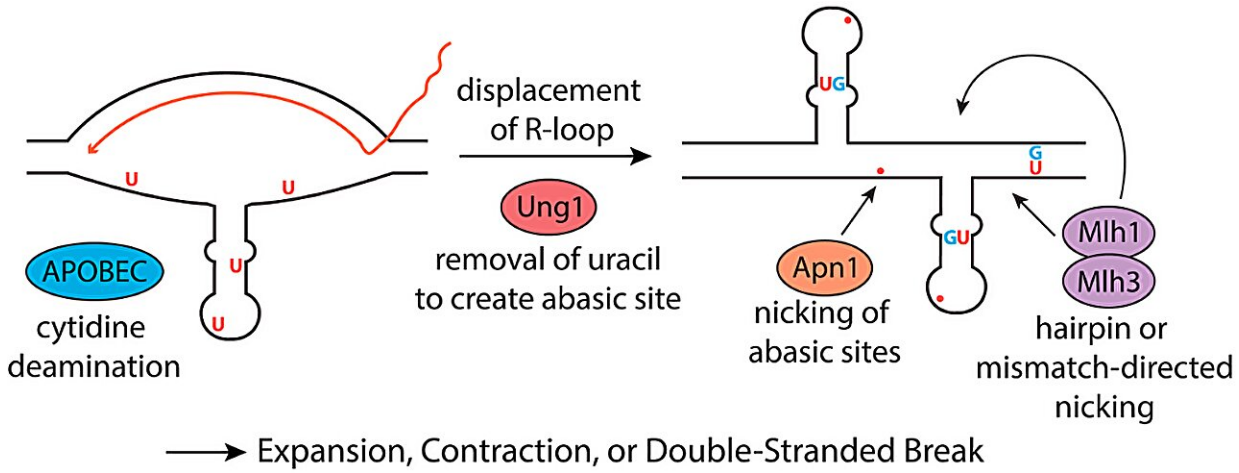

Model for how APOBECs deaminate cytidines within a CAG/CTG repeat tract by targeting ssDNA within hairpin loops and bulges. Credit: *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2408179122

People genetically susceptible to Huntington's disease often see their movement, mood, and cognition decline slowly over time. The cause is related to expansion of repeating DNA units, in which specific strings of genetic code—in this case, a series of cytosine-adenine-guanine nucleotides, or CAG, on one strand of the DNA and cytosine-thymine-guanine, or CTG, on the complementary strand—begin to repeat over

and over, expanding to as many as 40 to 120 copies.

The extended copies create kinks in the DNA, making it more susceptible to breakage and replication errors. When cells attempt to fix the breaks, repeat expansions occur, which leads to loss of essential protein functions, and the impairment and death of nerve cells.

Research from the laboratory of Catherine Freudenreich, professor and department chair of biology, has now revealed a possible molecular mechanism explaining how the DNA repeats are broken and then expanded in the Huntington's disease gene. Freudenreich and her research team report the results in a new study published in the *Proceedings of the National Academy of Sciences*.

The cause, they find, may be natural proteins of the immune system that normally target viruses by damaging their DNA. The proteins are called Apolipoprotein B mRNA editing catalytic proteins, or APOBECs.

APOBECs are part of a first response team of proteins used to fight off viral infection until the adaptive part of the immune system can generate antibodies and killer T cells. They work by clipping off an amine group (one nitrogen connected to three hydrogens) from cytosine nucleotides in single stranded virus DNA, mutating the genetic code and ultimately rendering viral genes useless.

But in the case of people with Huntington's disease, some of these helper proteins may be attacking and destabilizing not viruses but the patients' own DNA.

This happens in parts of human DNA that are susceptible to reshaping into single stranded loops, such as some DNA segments of the huntingtin gene, which codes for a protein important for many neurological functions. When an APOBEC deaminates parts of that gene containing

the CAG/CTG sequence, it increases the error rate of DNA repair enzymes, causing them to insert multiple CAG/CTGs where there should only be one. This happens repeatedly until the CAG/CTG repeats expand enough to interfere with the function of the huntingtin gene.

There are 11 types of natural APOBECs in humans, so Freudenreich's research team inserted single APOBEC types into yeast to isolate and study the effects of each one. APOBEC3A was found to have the most pronounced effect, causing DNA repeat expansion in a CAG/CTG tract, with a lesser role for APOBEC3B.

Her collaborator Steve Roberts, an associate professor at the University of Vermont, examined publicly available protein expression data from brain tissue samples from deceased Huntington's disease patients and found an unusually high presence of the APOBEC3A enzyme, supporting a causal link.

"The level is even higher than in breast cancer cells, where APOBECs are known to play a role," says Freudenreich. "This means that APOBECs are in the right place to cause trouble, and that makes them really intriguing candidates for disease initiation."

The researchers found additional evidence for other proteins that may be helping APOBECs induce the DNA repeat expansions.

Freudenreich and her collaborators will continue to explore this pathway's role in Huntington's disease, as well as whether APOBEC inhibitors could damp down their activity. The work also raises questions about the role of viral infections in triggering Huntington's disease, perhaps by increasing the presence of APOBECs in the brain environment.

More information: Rebecca E. Brown et al, APOBEC3A deaminates

CTG hairpin loops to promote fragility and instability of expanded CAG/CTG repeats, *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2408179122