Huntington's disease-causing DNA repeat mutations reversed in the lab

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[Please see video below] Graphic portrays the DNA repeat expansion mutation that causes Huntington's disease being reversed by a newly discovered molecule (shown here as "new intervention" starburst). Increasing number of repetitions of "FAT FAT FAT" represents worsening disease; reduced repetitions of "FAT FAT FAT" caused by the new intervention represent less severe disease. Credit: Osaka University

Neurodegenerative diseases, like Huntington's disease and myotonic dystrophy, are often referred to as DNA repeat diseases, named because

of long repeated sequences in the DNA of patients. Increasing repeat expansion length in the affected tissues contribute to earlier age of disease onset and worsen the progression and severity of the disease over time.

In an international study published in the February 14 online edition of *Nature Genetics*, scientists from The Hospital for Sick Children (SickKids), Canada, along with research teams from Osaka University, Japan, reveal the ability to reverse this repeat mutation length in the brains of a mouse model with Huntington's disease. The team discovered a compound that targets the unusual DNA structure and was shown to reverse repeat expansions with undetectable off-target effects.

First evidence of a molecule that induces in-vivo repeat contractions

Huntington's disease is one of more than 40 neurodegenerative diseases caused by DNA repeat expansion mutations in specific genes. The unusual DNA structures, called slipped-DNAs, are formed by the repeats, and levels of slipped-DNAs are greater in affected tissues that have longer repeat expansions, causing more severe mutations.

The study found evidence that the molecule compound called Naphthyridine-Azaquinolone (NA) can recognize slipped-DNAs and reverse the mutation—essentially causing a contraction of the expansion. In the lab, the research team was able to successfully reduce the repeat expansions in the brain of a Huntington's disease mouse model, as well as in cells extracted from tissues of individuals affected by Huntington's disease.

"We found that targeting the unusual slipped-DNA structures, which are critical to ongoing mutations in patient tissues, allowed us to reverse the size of repeat expansion mutations. Since longer expansions over time

are directly associated with more severe disease, our findings offer hope for the ability to delay the onset of Huntington's and slow its progression," says Dr. Christopher E. Pearson, SickKids senior scientist in genetics and genome biology, and principal investigator of the study.

Critical to the findings was that no off-target effects were detected anywhere else in the DNA, suggesting high specificity of the compound for the disease gene. This is important for any treatment, as off-target effects could be harmful.

"This is the first evidence for a small molecule that can induce contractions of disease-causing expansions in vivo in an affected brain region," says Dr. Masayuki Nakamori, Assistant Professor, Osaka University Graduate School of Medicine.

Potential future treatment option for individuals with Huntington's disease

The findings suggest that NA could be a possible drug therapy for individuals who inherit the disease from a parent. Applying this compound to cells or tissues with repeat expansions could both block the expansions and kick start contractions of the mutant genes.

"Consider the gene as a sentence that reads, 'THE CAT ATE THE FAT FAT RAT.' In repeat-associated diseases, the mutation would be 'THE CAT ATE THE FAT FAT FAT FAT FAT FAT FAT FAT RAT.' More FAT units lead to more severe disease. We are now able to reverse the disease-causing repeat mutation—in other words, we can reduce the number of 'FAT' units," says Pearson, who is also Professor in the Department of Molecular Genetics at the University of Toronto and holds a Tier 1 Canada Research Chair in Disease-Associated Genome Instability.

"Until now, we have only dreamed of finding a compound like this.

When we first began research into repeat expansions in the mid '90s, there were only three diseases known to be caused by them. Now, we know nearly 50 diseases are involved. Our finding reveals a new avenue by which Huntington's and other diseases, like myotonic dystrophy, could be treated by other compounds directed at the mutant repeats that are causing those diseases," says Pearson.

This study builds on a decade of collaborative research between the Canadian and Japanese researchers. The molecule NA was developed by Professor Kazuhiko Nakatani of the Institute of Scientific and Industrial Research, Osaka University, and his lab is working on compounds to target other disease repeats. Small molecules targeting other repeat sequences are also being developed by Nakatani's laboratory.

The article, "A slipped-CAG DNA-binding small molecule induces trinucleotide-repeat contractions in vivo," was published in *Nature Genetics*.

More information: Masayuki Nakamori et al. A slipped-CAG DNA-binding small molecule induces trinucleotide-repeat contractions in vivo, *Nature Genetics* (2020). DOI: 10.1038/s41588-019-0575-8

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