# Scientists show how mutation causes incurable premature aging disease

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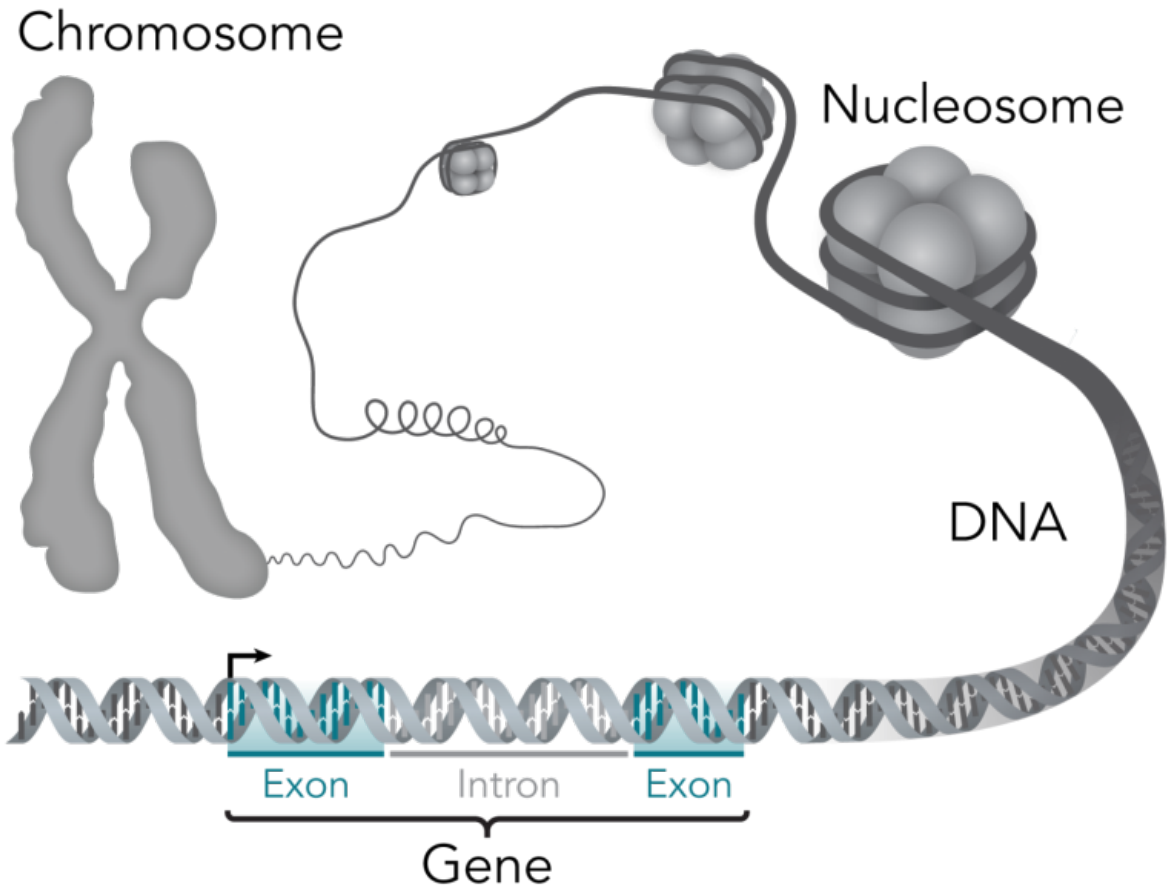


This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

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Scientists have demonstrated how a mutation in a specific protein in stem cells causes an incurable premature aging disease called dyskeratosis congenita, and were able to introduce the mutation into cultured human cells using gene editing technology.

The study findings provide a drug target for the disease, said lead study author Jayakrishnan Nandakumar, assistant professor of molecular, cellular and developmental biology at the University of Michigan.

The mutation compromises the function of an enzyme known as telomerase, which fuels stem cell division, he said. Stem cells must divide to repair old tissue.

This mutation, which occurs in the telomere protein TPP1, causes stem cells to slow or stop dividing in people with this rare, incurable disease. This can cause tissue breakdown, premature aging, bone marrow failure, cancer and even death.

Nandakumar and his U-M colleagues are believed to be the first to use genome editing technology called CRISPR/CAS9 to introduce a dyskeratosis congenita mutation into human cells.

This gene editing technology is often described as a pair of molecular scissors, because it cuts DNA in precise locations to allow for additions, deletions and replacements of DNA near the cut. The acronyms stand for Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated (CAS9).

The patient relevant to the study had one mutant gene, but also one

normal TPP1 gene, yet still suffered from the disease. Nandakumar's group wanted to know if introducing one copy of the mutant TPP1 gene into cultured human cells using the CRISPR/CAS9 gene editing technology would compromise telomerase function in those cells, too.

It did, which meant that the mutation caused the disease.

"We envision that correcting the mutation in the stem cells of the patient will reverse the cellular symptoms of the disease, if and when such technology becomes available," Nandakumar said.

Understanding how the TPP1 mutation works also has implications for treating cancer patients, he said. This is because while the TPP1 mutation inhibits stem cell division in people with dyskeratosis congenita, normal TPP1 fuels cell division in people with cancer.

The study, "Structural and functional consequences of a disease mutation in the telomere protein TPP1," appears online in the *Proceedings of the National Academy of Sciences* the week of Oct. 31.

**More information:** Structural and functional consequences of a disease mutation in the telomere protein TPP1, *Proceedings of the National Academy of Sciences*, www.pnas.org/cgi/doi/10.1073/pnas.1605685113

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