Long telomeres, the endcaps on DNA, not the fountain of youth once thought, and scientists may now know why

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In a study of 17 people from five families, Johns Hopkins Medicine researchers say they found that ultra-lengthy DNA endcaps called telomeres fail to provide the longevity presumed for such people. Instead, people with long telomeres tend to develop a range of benign

and cancerous tumors, as well as the age-related blood condition clonal hematopoiesis.

Reporting in the May 4 issue of the *New England Journal of Medicine*, the Johns Hopkins researchers say clonal hematopoiesis is common among this long-telomere group, and the blood condition combined with long telomeres may help mutations stick around longer in blood cells.

"Our findings challenge the idea that long telomeres protect against aging," says Mary Armanios, M.D., professor of oncology at the Johns Hopkins Kimmel Cancer Center, and professor of genetic medicine, molecular biology and genetics, and pathology at the Johns Hopkins University School of Medicine. "Rather than long telomeres protecting against aging, long telomeres allowed cells with mutations that arise with aging to be more durable."

Armanios directs the telomere center at the school of medicine. The center includes a laboratory-based service that provides telomere length testing for clinical diagnostics, a multidisciplinary clinic that serves people with telomere syndromes, and a group that conducts fundamental telomere research.

Long telomeres in cells grown in the lab have been shown to predict cellular longevity, but this study suggests that, in people, the longer-lived cells can cause problems, Armanios says. "Cells with very long telomeres accumulate mutations and appear to promote tumors and other types of growths that would otherwise be put in check by normal telomere shortening processes," she says.

Such tumors were found in 12 of the 17 people in the two-year Johns Hopkins study. Ranging in age from 7 to 83, the study participants experienced goiters (enlarged thyroid glands), various types of melanoma, lymphomas, other cancer types and uterine fibroids. Some of

the participants had more than one of these conditions. Four patients who died during the study had lymphoma, colon cancer, leukemia and a brain tumor.

All 17 people in the study had mutations in POT1, a telomere-linked gene. Normally, POT1 places a check on telomere lengthening, but its mutated form allows telomeres to be longer. Of the 17 study participants, the telomere length was measured for 13. All had telomeres that were 90% longer than those in the general population, and nine had telomeres longer than those in 99% of most people.

Six study participants showed signs of youthfulness. For example, all six, who were in their 70s, had delayed hair graying.

In addition to collecting information on the study participants' confirmed cancer diagnoses, the researchers looked closely at cells in their blood samples.

As people age, about 20% of those over age 70 have mutations in blood cells that are acquired over time, says Armanios. These mutations give blood cells a survival advantage and continue copying, making more of those cells and spreading the mutation. The duo of survival advantage and mutations in blood cells—clonal hematopoiesis of indeterminate potential—has been linked to various conditions including blood cancer and other cancers.

The Johns Hopkins researchers examined blood cells in study participants with long telomeres and some unaffected family members. Then, they generated a phylogenetic (evolutionary) tree to see how the clonal-hematopoiesis-related mutations evolved from inherited genomes.

Of the 12 study participants with mutations in the POT1 gene studied, eight (67%) had clonal hematopoiesis-related mutations—a rate much

higher than normally expected in older people, Armanios says. In 21 of their relatives, only two had clonal hematopoiesis-related mutations, which is the expected rate in the general population of older adults.

In a 66-year-old study participant's blood, the researchers found about 400 mutations per clone (blood cell type). The participant's younger relative, who has long telomeres and a POT1 mutation, had about 700 mutations per clone, even though the relative is 18 years younger.

Another study participant who has long telomeres and a POT1 mutation had some cells with as high as about 1,000 mutations per clone. According to the phylogenetic tree, the clonal hematopoiesis mutations in the study participant's blood cells likely began before they were 4 years old, and the long telomere length allowed the blood cell propagation since then, says Armanios.

The increase in blood cell mutations among the long telomere group may contribute to their increased risk for blood cancers, say the researchers.

During the two-year study, Armanios and her team also found that people with long telomeres had a slower rate of telomere shortening than people who had normal telomere length.

Armanios says she plans to examine the mutation rates in cells other than those in the blood in people with long telomeres. She and her team are working to combine a telomere length test with a phylogenetic tree that maps mutations in blood cell lines to assess blood health and risk for leukemia.

More information: Emily A. DeBoy et al, Familial Clonal Hematopoiesis in a Long Telomere Syndrome, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2300503

George Vassiliou et al, Telomere Length and Clonal Hematopoiesis, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMe2303022