Variations in telomere lengthening genes may predispose some people to papillary thyroid cancer

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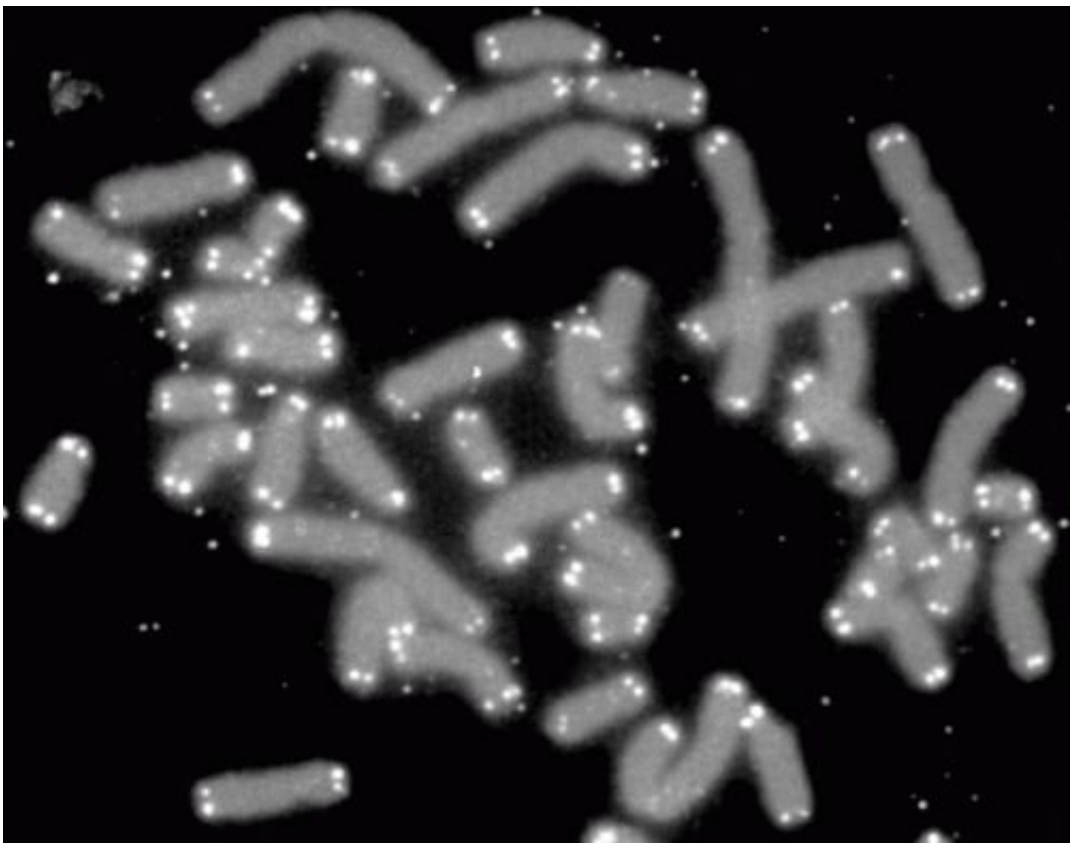

Human chromosomes (grey) capped by telomeres (white). Credit: PD-NASA; PD-USGOV-NASA

Johns Hopkins Medicine researchers say they have found that specific variations in three genes related to maintaining the length of

telomeres—the protective DNA endcaps on chromosomes—may explain up to 4.5% of papillary thyroid cancers. Papillary thyroid cancer is the most common form of thyroid cancer.

The findings, published online April 29 in *The American Journal of Human Genetics*, follow previous research results from the Johns Hopkins scientists that very long telomeres are linked to development of certain cancers.

"This study provides a better understanding of what may predispose some people to papillary thyroid cancer, including multiple individuals in families," says Mary Armanios, M.D., professor of oncology at the Johns Hopkins Kimmel Cancer Center, professor of genetic medicine, molecular biology and genetics, and pathology at the Johns Hopkins University School of Medicine, and director of the Telomere Center at Johns Hopkins.

"We now may be able to identify people who could benefit from closer monitoring for secondary cancers common among this population."

Of 18 people with variants in three telomere-related genes, 15 (83%) developed a second cancer. Most frequently, these cancers were melanoma, sarcoma and cancer of lymphocytes (such as lymphoma and multiple myeloma). Their family members, who carried the same gene variants, were also prone to papillary thyroid cancers as well as other malignancies.

However, Armanios cautions that more work is needed to understand how to interpret these sequence variants and the role of telomere length, and genetic counseling and testing is best reserved for people with papillary tumors and secondary cancers, and those with a family history of thyroid cancers.

Armanios adds, this research contributes to mounting evidence of the role of long telomeres and telomere lengthening as risk factors for development of cancer.

Thyroid cancer occurs in more than 40,000 people in the U.S. each year and is one of the top 10 cancers in women in the country. Early stage disease is nearly always treatable. Most (about 80%) of these cancers are papillary thyroid cancers.

Scientists have known that 5%–10% of papillary thyroid cancers are heritable in some families, and that people with the condition may be prone to developing other cancers.

The researchers say the findings suggest that a mechanism underlying this risk may be longer telomeres.

The scientists analyzed the genetic sequence of five genes related to telomere maintenance in 200 people with papillary thyroid cancer from 189 families who had volunteered to be included in a registry at the Ohio State University.

About one-quarter of the 200 people had hereditary thyroid cancer or secondary cancers to thyroid tumors, or were males who developed thyroid cancer at a young age. They found nine people from seven families (4.5% of the 200) had genetic variations in at least one of three genes (POT1, TINF2, or ACD) already linked to telomere maintenance.

Of the people with those gene variants, the scientists measured their telomere lengths and discovered that five of them had very long telomeres—longer than 90% of most people—and three had ultra-long telomeres—longer than 99% of the population.

In another group of 270 people with papillary thyroid cancer not

included in the hereditary cancer registry, four of the 270 (1.5%) had variants in those same three genes.

Researchers Emily DeBoy, Anna Nicosia, Sandya Liyanarachchi and Sheila Iyer from Johns Hopkins, and Manisha Shah, Matthew Ringel and Pamela Brock from the Ohio State University contributed to the study.

More information: Emily A. DeBoy et al, Telomere-lengthening germline variants predispose to a syndromic papillary thyroid cancer subtype, *The American Journal of Human Genetics* (2024). DOI: 10.1016/j.ajhg.2024.04.006

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