Medical Xpress

Genetic variation cuts bladder cancer risk, protects chromosome tips

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A common genetic variation links to both bladder cancer risk and to the length of protective caps found on the ends of chromosomes, scientists at The University of Texas MD Anderson Cancer Center reported today at the AACR 102nd Annual Meeting.

These endings or tips, called telomeres, guard against chromosomal damage and genomic instability that can lead to cancer and other diseases.

"We found a single point of variation in the genome strongly associated with a 19 percent decrease in bladder cancer risk. The same variant also is linked to longer telomeres, which accounts for part of the overall reduction in risk," said first author Jian Gu, Ph.D., assistant professor in MD Anderson's Department of Epidemiology.

Telomere length diminishes with age, Gu said, and short telomeres are associated with age-related diseases such as stroke, Alzheimer's disease, diabetes, cardiovascular disease and cancer.

Previous studies separately tied telomere length either to cancer risk or to genetic variation. The paper by Gu and colleagues is the first to make both connections.

"Understanding the complex genetic regulation of telomere length and its relation to the causes of bladder and other types of cancer will help develop therapies or lifestyle changes to reduce cancer risk," said senior

author Xifeng Wu, M.D., Ph.D., professor and chair of MD Anderson's Department of Epidemiology.

Wu and colleagues in 2003 were the first to show that short telomeres increase the risk of bladder, lung, kidney and head and neck cancers in a human epidemiological study.

Start with 300,000 SNPs

The new findings were presented by Gu at the AACR annual meeting and simultaneously published in *Cancer Prevention Research*, an AACR journal.

AACR President Elizabeth Blackburn, Ph.D., the Morris Herzstein professor of biology and physiology at the University of California San Francisco, won the Nobel Prize for Medicine or Physiology in 2009 for her role in the discovery of telomeres and the enzyme telomerase. She wrote an editorial in Cancer Prevention Research and appeared with Gu at a news conference Saturday to discuss the importance of the study results.

Researchers first conducted a genome-wide association study to identify genetic variations associated with telomere length. They analyzed more than 300,000 single nucleotide polymorphisms (SNPs), common points of variation in the genome, in 459 healthy controls.

This narrowed the field to 15,120 SNPs, which were then validated in 1,160 healthy controls in two independent populations. They selected the top four SNPs that were associated with telomere length across all three populations for the bladder cancer association study.

Then there was one

The team evaluated the association of these four sites with the risk of bladder cancer in a case-control study of 969 patients and 946 controls. Only one, a SNP on chromosome 14 known as rs398652, was associated with bladder cancer risk.

Since the SNP was associated with both telomere length and bladder cancer risk, the team conducted a mediation analysis to determine whether the effect on telomere length caused some of the risk reduction. Telomere length accounted for 14 percent of the SNP's effect on bladder cancer.

"We think the remaining portion of the SNP effect on bladder cancer may be caused by inflammation or immune response," Gu said. "But understanding the remainder of the risk will require more basic research." Rs398652 is nearest to a gene on chromosome 14 called PELI2, which is involved in the inflammatory and immune response.

Follow up studies will focus on whether this SNP is associated with other types of cancer, particularly those affected by telomere length such as lung, kidney and esophageal cancer, Gu said, as well as the biological mechanisms by which the SNP affects telomere length.

Provided by University of Texas M. D. Anderson Cancer Center

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