Identifying rare genetic variants that increase risk for lung cancer

March 18 2021, by Molly Chiu

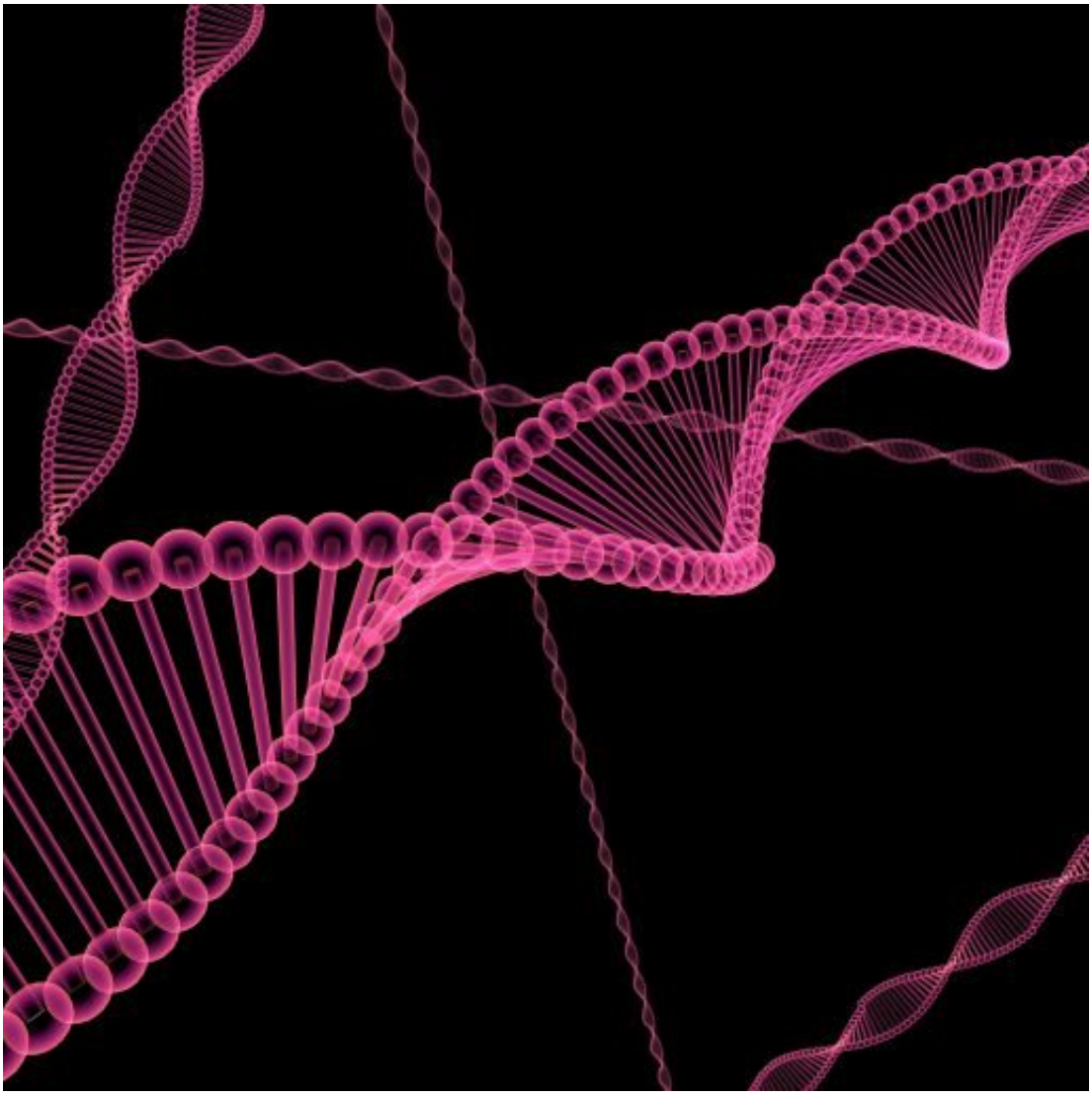

Illustration of the DNA double helix. The newly discovered genetic variants are involved in mechanisms of DNA repair. Credit: Peggy&Marco

Lung cancer is the leading cause of cancer death in the U.S. for both men and women. While risk for this disease can be influenced by environmental and lifestyle factors like smoking, studies estimate that 18% of lung cancer cases are due to inherited genetic variants. New research led by Baylor College of Medicine investigates how genetic variants contribute to increased risk of lung cancer.

The researchers performed whole exome sequencing on germline (inherited) DNA from eight large-scale datasets, including 1,045 patients with a family history of lung cancer or early-onset cancer. Those groups are more likely to harbor genetic risk variants. The analysis also included 885 control cases.

"We were looking for variants that have a relatively high impact on risk but occur at relatively low frequency," said Dr. Chris Amos, corresponding author of the study, professor of medicine—epidemiology and population sciences and director of the Institute for Clinical and Translational Research (ICTR) at Baylor. "If a variant occurs at low frequency, you have to look at many different large data sources to validate the variant. These results can be replicated in many different European populations."

The researchers identified 25 new rare pathogenic variants associated with lung cancer susceptibility and validated five of those variants. Of those five, two variants involved genes with known connections to lung cancer risk, ATM and MPZL2. Three variants involved novel lung cancer susceptibility genes, POMC, STAU2 and MLNR. According to co-first author of the study, Dr. Yanhong Liu, exome sequencing allowed the researchers to identify more variants that impact proteins and cell function.

Investigating the contribution of insertions or

deletions

"Mutations of DNA where sections are either inserted or deleted have been understudied compared to single nucleotide variants, but they are also very important because they can result in truncated proteins," said Liu, assistant professor of medicine—epidemiology and population sciences and member of the Dan L Duncan Comprehensive Cancer Center at Baylor. "Of the 25 candidate variants we identified, two-thirds of them are insertions or deletions."

In order to further understand the effect of these candidate variants on cellular functions, the Baylor researchers applied endogenous DNA damage assays, which test for replications of certain types of mutations in DNA. They hypothesized that lung cancer risk genes lead to an increased level of endogenous DNA damage in cells, leading to genomic instability and ultimately causing cancer.

"Many studies have looked at lung cancer risk genes, but the function of those genes has not been well understood. In our study, we found that dysregulation or mutations in these candidate genes showed increased DNA damage, suggesting that their potential cancer-causing role might be due to genome instability at the DNA level," said Dr. Jun Xia, co-first author of the study and postdoctoral associate in the Department of Molecular and Human Genetics and ICTR at Baylor.

The analysis showed that POMC, MLNR and ATM variants led to increased levels of DNA damage. ATM is known to be a critical first responder to DNA damage, and several ATM variants are linked to increased susceptibility for multiple cancers. According to Amos, understanding which variants cause increased DNA damage could be key to unlocking treatments for these cancers.

"We know from breast cancer that PARP inhibitors, drugs that prevent

DNA repair, work in people with inherited BRCA1 and BRCA2 mutations because those cells already have some DNA damage due to the inherited mutation. If you disable PARP, the cancer cells can't repair DNA damage and won't survive," said Amos, member of the Dan L Duncan Comprehensive Cancer Center at Baylor and CPRIT Scholar. "It's possible that people with inherited ATM mutations causing them to develop lung cancer may respond to those PARP inhibitors as well, and that is something that needs to be studied further."

The results are published in the journal, *NPJ Precision Oncology*.

More information: Yanhong Liu et al, Rare deleterious germline variants and risk of lung cancer, *npj Precision Oncology* (2021). DOI: 10.1038/s41698-021-00146-7

Provided by Baylor College of Medicine