Scientists identify gene mutations in smoking-related cancers

July 25 2017

African-Americans typically have worse outcomes from smoking-related cancers than Caucasians, but the reasons for this remain elusive. However, scientists at Wake Forest Baptist Medical Center have taken a big step toward solving this puzzle.The scientists found that African-American patients had an increased mutation rate in several genes, including the best known in tobacco-related tumors, TP53. The findings are published in the current online issue of the journal *Theranostics*.

"We know TP53 mutation happens in 55 percent of all cancer patients," said the study's lead author, Wei Zhang, Ph.D., Hanes and Willis Family Professor in Cancer at Wake Forest School of Medicine, part of Wake Forest Baptist. "In our study, we found that the African-American population had close to a 70 percent mutation rate.

"This data suggests that increases in TP53 mutation in African-Americans may be responsible for the observed resistance to chemotherapy and a poorer prognosis overall."The trial at Wake Forest Baptist enrolled 431 cancer patients from March 2015 to May 2016. The majority of the patients had advanced tobacco-related cancers - lung, colorectal and bladder - and 13.5 percent were African-American.

Tumors from study participants were sequenced to identify mutations and genetic alterations associated with smoking and/or African-American ancestry. The proportion of smokers was similar among African-American and Caucasian participants. Scientists validated their findings through the Cancer Genome Atlas dataset that includes 2,821

cases with known smoking status.

Both the Wake Forest Baptist and Cancer Genome Atlas cohorts revealed a significantly increased mutation rate in the TP53 gene in the African-American groups studied. The researchers also found that a number of genes - including those that repair DNA damage and remodel chromatin - mutated at higher frequencies in the African-American cancer patients.

Additionally, the Wake Forest Baptist team identified other genes that were highly mutated in current and former smokers, regardless of race.

"These results provide strong evidence that genomic instability is a fundamental hallmark of cancer and the events underlying the regulation of genome stability are centered on interactions with environmental factors and lifestyle, such as smoking," Zhang said.

Due to the relatively small number of participants in the Wake Forest Baptist study, the findings need further validation in a larger trial, Zhang said.

However, he added, this study provides an understanding of the molecular basis of smoking-related cancers and how doctors can use this information to treat patients by knowing what genes to target with drugs. The essence of precision oncology is to match mutational information with drugs that have shown therapeutic efficacy in targeting the mutated protein.

"These exciting findings uncover new genetic information related to smoking that may lead to the development of novel diagnostic and therapeutic options for patients," said the study's co-corresponding author, Boris Pasche, M.D., Ph.D., director of the Comprehensive Cancer Center at Wake Forest Baptist.

Provided by Wake Forest University Baptist Medical Center