Large-scale study explores link between smoking and DNA changes across six racial and ethnic groups

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Smoking changes the way genes are expressed, which later contributes to the development of lung cancer and other smoking-related illnesses. But

the link between epigenetics (the study of mechanisms that impact gene expression) and smoking is not fully understood, especially in terms of differences across racial and ethnic groups.

"We know that smoking affects people differently based on their race and ethnicity, but identifying epigenetic signatures of smoking would help us better predict risk for smoking-related diseases," said Brian Huang, Ph.D., an assistant professor in the department of population and public health sciences at the Keck School of Medicine of USC and first author of the new study.

In a National Institutes of Health-funded effort, researchers from the Keck School of Medicine analyzed the link between smoking and DNA methylation, a specific type of epigenetic change that can alter a number of biological processes. The study included data from 2,728 people across six distinct racial and ethnic groups. Researchers found 408 DNA methylation markers (known as "CpG sites") related to smoking, including two that differed depending on race or ethnicity. The results were published in the American Journal of Human Genetics.

Most past research on smoking and epigenetics has looked at just one or two racial groups at a time, making the new effort one of the largest multiethnic studies yet. In addition, the researchers quantified smoking by calculating participants' total nicotine equivalents (TNEs), a biological measure of nicotine uptake that measures levels of nicotine and several other metabolites of cigarette smoke with a urine sample. That enabled a more accurate calculation of smoking dose compared to much of the existing research, which relies on self-reported measures.

"This study gives us some additional information about the mechanism by which smoking can affect health, and how that could differ across various populations," Huang said. "Ultimately, that can lead to better prediction, early detection and treatment for smoking-related

conditions."

Insights from the epigenome

The research team conducted their primary analysis using data from the Multiethnic Cohort Study, a collaboration between USC and the University of Hawaii that includes African Americans, European Americans, Japanese Americans, Latinos and Native Hawaiians. Using biological samples from 1,994 participants, the researchers determined each person's smoking dose (by measuring TNEs), as well as the levels of DNA methylation at CpG sites across the genome (through an epigenome-wide association study, or EWAS).

Across the epigenome, smoking was linked to DNA methylation at 408 sites. That total includes 45 new sites that were not identified in previous studies that relied on self-reports of smoking behavior.

"This gives us an indication that TNEs can provide more information beyond what we already know from self-reported measures of smoking," Huang said.

Of the 408 sites identified, two carried a significant risk difference depending on race or ethnicity. One site on the gene CYTH1 only showed changes in African American people who smoked; another site on MYO1G was more strongly linked with epigenetic changes in Latinos who smoked, compared to other racial and ethnic groups. Those genes perform functions that relate to cancer progression and other disease processes.

The new insights could improve scientists' understanding of why some populations face a higher lung cancer risk than others, Huang said. African Americans who smoke face a higher risk of lung cancer than non-Hispanic whites who smoke, while people of Hispanic origin may

face a lower risk.

To further confirm their findings, Huang and his team collected TNE and DNA methylation data from two other groups of participants: 340 people in the Singapore Chinese Health Study and 394 people in the Southern Community Cohort Study. The researchers identified many of the same CpG sites found in the Multiethnic Cohort Study, including the sites most strongly associated with TNEs. That provides evidence that the strongest epigenetic markers of smoking are consistent across multiple racial and ethnic groups, Huang said.

Better prediction of disease risk

In their next study, the researchers will conduct an EWAS of DNA methylation and lung cancer risk: How do epigenetic changes increase a person's risk for lung cancer?

"By conducting these joint studies, we can understand the mechanism by which DNA methylation acts as a mediator between smoking and lung cancer, which can in turn improve our ability to predict lung cancer risk," Huang said.

He and his team also have research underway to study epigenetic changes associated with additional biomarkers of smoking, including biological levels of cadmium, a heavy metal found in cigarette smoke.

More information: Brian Z. Huang et al, Epigenome-wide association study of total nicotine equivalents in multiethnic current smokers from three prospective cohorts, *The American Journal of Human Genetics* (2024). DOI: 10.1016/j.ajhg.2024.01.012