How genes work together to shape how much you smoke

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Smoking harms nearly every organ in the body and causes many diseases. Credit: CDC/Debora Cartagena

Take a puff of nicotine for the first time, and your DNA plays an important role, alongside social and environmental factors, in shaping what happens next.

In recent years, scientists have identified thousands of genetic variants

believed to influence everything from when people first try smoking to how good that first cigarette feels to how often they light up and how hard it is to quit. Some variants influence how quickly we metabolize nicotine, while others underlie how sensitive we are to it. But little is known about how they interact with each other and with other genetic differences.

A new University of Colorado Boulder study sheds unprecedented light on these interactions and provides new insight on the most well-known smoking-related variant to date—commonly nicknamed "Mr. Big."

"We know that smoking is highly heritable, with genetic differences accounting for 40% to 75% of the differences in people's smoking behaviors," said Pamela Romero Villela, a Ph.D. student in the Department of Psychology and Neuroscience and first author of the study in the journal *Drug and Alcohol Dependence*.

"The more we can understand what those genes do and how they interact, the better equipped we will be to develop personalized approaches to helping people quit."

Beyond Mr. Big

About 22% adults worldwide use nicotine and smoking is linked to one in five deaths in the United States.

"A lot of people still smoke, and it is one of the hardest drugs to quit," said Romero Villela, a researcher with CU Boulder's Institute for Behavioral Genetics.

For the study, Romero Villela collaborated with Integrative Physiology Professor Marissa Ehringer, who has studied substance use disorders for more than 20 years.

They zeroed in on the single nucleotide polymorphism (SNP), or genetic variant, rs16969968, known as "Mr. Big" because it has been the mostly widely replicated genetic variant associated with smoking behaviors.

Mr. Big is located in a gene called CHRNA5F (nicotinic acetylcholine receptor 5) and influences how well nicotine binds to receptors in the brain. People with a certain version of Mr. Big, known as the AA version, are less sensitive to nicotine and have been shown to smoke more.

"It kind of numbs your response so in order for you to feel the same effect as someone who smoked one cigarette you might have to smoke almost one and a half cigarettes," said Romero Villela.

As their study reveals, the story does not end there.

A personalized approach

When analyzing genetic information from about 165,000 current or former smokers of European, South Asian, and Finnish descent, the team discovered genes and variants in a completely different region of the genome that appear to interact with Mr. Big in a way that influences smoking habits.

Notably, when people had the risk-boosting version of Mr. Big but also had a genetic variant called rs73586411, they smoked significantly less than expected.

"We basically found another variant that ameliorates the effect of Mr. Big," said Romero Villela.

More research is needed to understand just what the genes highlighted in the study do. (Interestingly, one called TMEM230 has previously been

associated with Parkinson's disease. Nicotine is known to blunt some symptoms of the disease).

The study authors imagine a day when people could be given a "polygenic risk score" which considers their gene variants and interactions to provide personalized recommendations for quitting. For instance, preliminary studies have already suggested that people with high-risk genotypes in the CHRNA5 region may benefit more from medications targeting nicotinic receptors.

Eventually, if researchers could determine what a variant does to dull the craving to smoke, they might be able to develop medications that mimic that action.

Bigger picture, the authors hope the study inspires more research looking not just at individual genes but also how genetic variants work together.

"Genes don't operate in a vacuum," said Ehringer. "If our ultimate goal is more personalized medicine, we have to understand these interactions better."

More information: Pamela N. Romero Villela et al, Loci on chromosome 20 interact with rs16969968 to influence cigarettes per day in European ancestry individuals, *Drug and Alcohol Dependence* (2024). DOI: 10.1016/j.drugalcdep.2024.111126

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