

# If your first cigarette gave you a buzz and you now smoke, a gene may be to blame

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Anyone who has ever tried smoking probably remembers that first cigarette vividly. For some, it brought a wave of nausea or a nasty coughing fit. For others, those first puffs also came with a rush of pleasure or "buzz."

Now, a new study links those first experiences with smoking, and the likelihood that a person is currently a smoker, to a particular genetic variation. The finding may help explain the path that leads from that first cigarette to lifelong smoking.

The new finding also adds to growing suspicion surrounding the role of a particular nicotine-receptor gene in smoking-related behaviors and in lung cancer. Other researchers have already linked variations in the same genetic region to smokers' level of dependence on nicotine, to the number of cigarettes smoked per day and to a far higher risk of lung cancer — the ultimate outcome of a lifetime of smoking.

In a paper published online today in the journal *Addiction*, a multi-university collaborative team of researchers specializing in statistical genetics, gene analysis, and trait analysis reports an association between a variant in the CHRNA5 nicotine receptor gene, initial smoking experiences, and current smoking patterns.

The genetic and smoking data come from 435 volunteers. Those who never smoked had tried at least one cigarette but no more than 100 cigarettes in their lives, and never formed a smoking habit. The regular

smokers had smoked at least five cigarettes a day for at least the past five years.

The regular smokers in the study were far more likely than the never-smokers to have the less common rs16969968 form of the CHRNA5 gene, in which just one base-pair in the gene sequence was different from the more common form. This kind of genetic variation is called a single nucleotide polymorphism or SNP.

Smokers were also eight times as likely to report that their first cigarettes gave them a pleasurable buzz.

"It appears that for people who have a certain genetic makeup, the initial physical reaction to smoking can play a significant role in determining what happens next," says senior author and project leader, Ovide Pomerleau, a professor of psychiatry at the University of Michigan Medical School and founder of the U-M Nicotine Research Laboratory.

"If cigarette smoking is sustained, nicotine addiction can occur in a few days to a few months," he adds. "The finding of a genetic association with pleasurable early smoking experiences may help explain how people get addicted — and, of course, once addicted, many will keep smoking for the rest of their lives."

The researchers point out that the genetic variant explains only a portion of human smoking behavior, and that a more complete explanation of why people smoke and why they can't quit will require much more information about how genes interact with social influences and other environmental factors.

Pomerleau predicts that the ability to link behavioral patterns in smoking to individual genotypes will need extensive information concerning behavior, genes, and the environmental context — as well as

bioinformatic tools to bring it all together. "Understanding the genetics of complex disorders such as nicotine addiction will require much more research on key traits," he says.

The team notes that the CHRNA5 relationships appear to be strong and that practical applications from this research include new genetic tests for smoking risk and the development of medications that target smoking-risk genes.

Pomerleau states that the new paper builds on findings reported last year by fellow author Laura Bierut, in which a whole-genome study found that the same single nucleotide polymorphism, rs16969968, of the CHRNA5 gene was associated with smokers' level of nicotine dependence.

He also notes that, this year, three papers published independently of one another demonstrated that variations in the same gene, and related genes, greatly increase the risk of lung cancer.

Taking into account its links to increased liking of initial smoking, stronger likelihood of getting addicted to nicotine, and greater probability of developing lung cancer, this genetic variant may well constitute a "triple whammy" for smoking-related disease, he says.

A mechanism for explaining increased disease risk, proposed by one of the cancer genetics researchers, is the possibility that certain chemicals, for instance N-nitrosonornicotine in tobacco smoke, act on nicotine receptors in the lung to produce cancer-causing changes – a process known as tumorigenesis.

The new findings linking first smoking experiences, smoking habits, and genetic variation build on previous research by Ovide Pomerleau and Cynthia Pomerleau, Ph.D., at U-M. In studies conducted over a 10-year

span, they documented a link between nicotine-dependent smoking and positive first smoking experiences.

Source: University of Michigan

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