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Genetics might determine which smokers get hooked, research says

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Researchers have identified genetic risk factors that may accelerate a teen's progression to becoming a lifelong heavy smoker.

The team of scientists from the U.S., the U.K. and New Zealand examined earlier studies by other research teams to develop a genetic risk profile for heavy smoking. Then they looked at their own long-term study of 1,000 New Zealanders from birth to age 38 to identify whether individuals at high genetic risk got hooked on cigarettes more quickly as teens and whether, as adults, they had a harder time quitting.

Study participants who had the high-risk genetic profile were found to be more likely to convert to daily smoking as teenagers and then progress more rapidly to heavy smoking (a pack a day or more). When assessed at age 38, the higher-risk individuals had smoked heavily for more years, had more often developed nicotine dependence and were more likely to have failed in attempts to quit smoking.

"Genetic risk accelerated the development of smoking behavior," said Daniel Belsky, a post-doctoral research fellow at Duke University's Center for the Study of Aging and Human Development and the Duke Institute for Genome Sciences & Policy. "Teens at a high genetic risk transitioned quickly from trying cigarettes to becoming regular, heavy smokers."

A person's genetic risk profile did not predict whether he or she would try cigarettes. But for those who did try cigarettes, having a high-risk

genetic profile predicted increased likelihood of heavy smoking and nicotine dependence.

The findings appear March 27 in *JAMA Psychiatry*. They were supported by multiple grants from the U.S. National Institutes of Health, as well as the U.K. Medical Research Council and the New Zealand Health Research Council.

The Duke researchers developed a new "genetic risk score" for the study by examining prior genome-wide associations (GWAS) of adult smokers. These studies scanned the entire genomes of tens of thousands of smokers to identify variants that were more common in the heaviest smokers. The variants they identified were located in and around genes that affect how the brain responds to nicotine and how nicotine is metabolized, but it is not yet known how the specific variants affect gene function.

It makes sense that the genes on which the group based their risk score are involved in nicotine metabolism and sensitivity, said Jed Rose, a Duke nicotine addiction researcher who was not involved in this study. "Addictions are a learned behavior and it requires reinforcement through neural pathways."

In their first step, the researchers found the genetic risk score they developed was able to predict heavy smoking among individuals in two large databases created by other researchers.

Then they turned to their New Zealand sample of 880 individuals of European descent to see whether the genetic risk score predicted who initiated smoking, who progressed to heavy smoking, and who developed nicotine dependence and experienced relapse after quitting.

Genetic risk was not related to whether a person tried smoking, which 70

percent of the sample had. One reason for this was that so-called "chippers"—smokers who consume cigarettes only on weekends or smoke only one or two per day—had even lower genetic risk than nonsmokers.

Genetic risk was related to the development of smoking problems. Among teens who tried cigarettes, those with a high-risk genetic profile were 24 percent more likely to become daily smokers by age 15 and 43 percent more likely to become pack-a-day smokers by age 18.

As adults, those with high-risk genetic profiles were 27 percent more likely to become nicotine dependent and 22 percent more likely to fail in their attempts at quitting. By age 38, a study participant with high-risk genetic profile had smoked about 7,300 more cigarettes (one "pack-year") than the average smoker.

Study participants who did not become regular, heavy smokers during their teens appeared to be "immune" to genetic risk for adult smoking problems. "The effects of genetic risk seem to be limited to people who start smoking as teens," said Belsky. "This suggests there may be something special about nicotine exposure in the adolescent brain, with respect to these genetic variants."

"Adolescence is indeed a period of high risk for nicotine addiction," said Denise Kandel, a professor of sociomedical sciences in psychiatry at Columbia University, who was not involved in this study. "The results illustrate why adolescence is of crucial importance for the development and targeting of prevention and intervention efforts. How this genetic risk affects brain functions, which in turn affect reactions to nicotine, remains to be determined."

The risk factor the team developed "may not be sensitive or specific enough to be a clinical test, but it may have public health uses," said

Rose, who is the director of the Duke Center for Smoking Cessation and co-developer of the nicotine patch.

"Public health policies that make it harder for teens to become regular smokers should continue to be a focus in antismoking efforts," Belsky said.

More information: "Polygenic Risk and the Developmental Progression to Heavy, Persistent Smoking and Nicotine Dependence," Daniel W. Belsky, Terrie E. Moffitt, et al. *JAMA Psychiatry*, March 27, 2013. DOI: 10.1001/jamapsychiatry.2013.736

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