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Researchers probe genetic underpinnings of nicotine addiction

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A new study from the Abramson Cancer Center and Department of Psychiatry in the University of Pennsylvania School of Medicine shows that smokers who carry a particular version of a gene for an enzyme that regulates dopamine in the brain may suffer from concentration problems and other cognitive deficits when abstaining from nicotine – a problem that puts them at risk for relapse during attempts to quit smoking. The findings, newly published in the journal *Molecular Psychiatry*, pave the way to identify novel medications to treat nicotine addiction.

"These findings also provide an important step toward personalized therapy for nicotine addiction by clarifying the role of inherited genetic variation in smoking abstinence symptoms that promote relapse," says senior author Caryn Lerman, PhD, the Mary W. Calkins Professor in Penn's Department of Psychiatry and Scientific Director of Penn's Abramson Cancer Center.

"The new data identify a novel brain-behavior mechanism that plays a role in nicotine dependence and relapse during quitting attempts," says lead author James Loughead, PhD, assistant professor in the Department of Psychiatry. Loughead and Lerman studied groups of smokers with different inherited variations in a gene which influences levels of dopamine in the prefrontal cortex, the part of the brain that governs working memory and complex decision-making. Spurred by their previous findings that carriers of the catechol-O-methyltransferase (COMT) val gene variant are more susceptible to smoking relapse, the Penn researchers set out to learn if smokers with this genetic background

would be more likely to exhibit altered brain function and cognitive deficits during periods of abstinence from smoking.

"Inability to concentrate after quitting is reported by many patients, and this leads them to smoke to reduce these impairments," Loughead says.

In this study, 33 smokers underwent functional magnetic resonance imaging (fMRI) during periods of both abstinence from smoking and while smoking as usual. During the brain scans, subjects were asked to hold in their minds a series of complex geometric figures. Subjects were also asked to complete a withdrawal symptoms checklist and a questionnaire about their smoking urges. Results showed that smokers with the COMT val/val genotype suffered greater deficits in working memory and brain function when they had refrained from smoking for 14 or more hours, compared to their performance on this task when they had been smoking as usual. This group also exhibited significant increases in withdrawal symptoms during the abstinence challenge session, compared to the other two genotype groups in the study.

These indicators often play a role in the reasons why smokers relapse, and therefore, may lead to the development of personalized therapy to treat smokers who carry this gene variant – a group that is also less responsive to existing therapies for smoking cessation. One method may be to offer carriers of this gene targeted therapies with drugs like COMT inhibitors, some of which have been shown to increase working memory in healthy volunteers.

"Given the prevalence of smoking in the population, translating these findings for medication development could have a significant clinical and public health impact," Lerman says.

Source: University of Pennsylvania