

Heavy Smoking May Be a Genetic Thing

By Cole Petrochko, Associate Staff Writer, MedPage Today

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Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner

Patients who start smoking at a younger age appear to have a genetic susceptibility to heavy smoking as adults, researchers found.

In a meta-analysis, smokers who started at age 16 or younger and had at least one mutation in a nonsynonymous single-nucleotide polymorphism in *CHRNA5* -- rs16969968 -- had a significantly greater risk for heavy smoking in adulthood than those who started smoking later (OR 1.45, 95% CI 1.36 to 1.55, $P=0.01$), according to Laura Bierut, MD, of Washington University School of Medicine in St. Louis, Mo., and colleagues.

"The finding of a stronger genetic risk in early-onset smokers supports public health interventions to reduce adolescent smoking," they wrote in the Aug. 6 issue of *Archives of General Psychiatry*.

The results are supported by earlier studies in animal models showing that "the developing adolescent brain [is] particularly vulnerable to addictive effects of nicotine and by human studies suggesting that adolescent neurodevelopment is a particularly vulnerable period for the development of addiction," the authors explained.

The researchers analyzed a sample of 33,348 ever-smokers from 43 studies and stratified participants into early-onset -- those who started smoking at 16 or younger -- and late-onset smokers or those who started after age 16.

Additionally, participants had presence of the rs16969968 genotype, or an analogous SNP called rs1051730, measured against heavy and light smoking status.

The analogous gene was included, the authors wrote, because it provided "statistically equivalent results and there is biological evidence that rs16969968 alters receptor function."

"An unresolved issue is whether rs16969968 plays a role in the heightened susceptibility to nicotine dependence in early-onset smokers," they added.

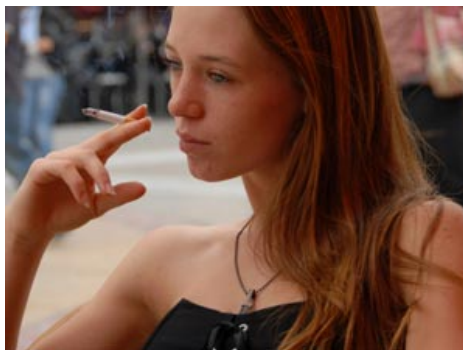
Heavy smoking status was defined as more than 20 cigarettes per day, while light smoking was defined as 10 or fewer cigarettes per day, with moderate smoking status excluded from the analysis.

They found that the overall risk for heavy smoking in participants who initiated smoking early was significant at an odds ratio of 2.63 (95% CI 2.49 to 2.78, $P<0.001$).

They also reported that early-onset smoker participants with mutated AG or AA alleles -- versus wild-type GG alleles -- of the rs16969968 genotype had a 1.45 and 2.10, respectively, increased OR for heavy smoking (95% CI 1.36 to 1.55 and 1.97 to 2.25).

In late-onset smokers with the same genetic mutations, the OR was 1.27 (95% CI 1.21 to 1.33) for those with an AG allele ($P=0.01$).

Bierut and colleagues added that because early-onset smoking was a strong risk for smoking in later life and that age of smoking onset is a heritable characteristic, "we must consider the possibility that a shared genetic factor could lead to early-onset smoking and heavy smoking in adulthood" but that



Action Points

Patients who start smoking at a younger age appear to have a genetic susceptibility to heavy smoking as adults.

Point out that smokers who started at age 16 or younger and had at least one mutation in the rs16969968 gene had a significantly greater risk for heavy smoking in adulthood.

there did not seem to be a shared genetic factor between early-onset smoking and heavy smoking ($P=0.77$ for association).

"Accordingly, early use may not cause greater vulnerability to addiction; instead, early use and vulnerability to addiction may have a shared etiology," they wrote.

The authors noted that their study was limited by a number of factors, including heterogeneity of samples with differential assessment of measures, inconsistent genetic markers between studies, and lack of external modifiers to smoking behavior, such as parental monitoring and peer smoking.

They also noted that future research could investigate the interactions of these external modifiers and their associations with cigarettes smoked per day with a genetic component.

Bierut and two co-authors served as consultants for Pfizer.

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Bierut LJ, et al "Increased genetic vulnerability to smoking at CHRNA5 in early-onset smokers" *Arch Gen Psychiatry* 2012; 69(8): 854-861.

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