Genetics linked to smoking dependency, addiction

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WASHINGTON – Scientists say they have pinpointed a genetic link that makes people more likely to get hooked on tobacco, causing them to smoke more cigarettes, making it harder to quit, and leading more often to deadly lung cancer.

The discovery by three separate teams of scientists makes the strongest case so far for the biological underpinnings of the addiction of smoking and sheds light on how genetics and cigarettes join forces to cause cancer, experts said. The findings also lay the groundwork for more tailored quit-smoking treatments.

"This is kind of a double whammy gene," said Christopher Amos, a professor of epidemiology at the M.D. Anderson Cancer Center in Houston and author of one of the studies. "It also makes you more likely to be dependent on smoking and less likely to quit smoking."

A smoker who inherits this genetic variation from both parents has an 80 percent greater chance of lung cancer than a smoker without the variants, the researchers reported. And that same smoker on average lights up two extra cigarettes a day and has a much harder time quitting than smokers who don't have these genetic differences.

The three studies, funded by governments in the U.S. and Europe, is being published Thursday in the journals *Nature* and *Nature Genetics*.

The scientists surveyed genetic markers in more than 35,000 people in Europe, Canada and the United States, zeroing in on the same set of genetic differences. They aren't quite sure if what they found is a set of variations in one gene or in three closely connected genes. But they said the result is the same: These genetic quirks increase the risk of addiction and lung cancer.

The studies' authors disagreed on whether the set of variants directly increased the risk of lung cancer or did so indirectly by causing more smoking that led to the cancer.

The genetic variations, which encode nicotine receptors on cells, could eventually help explain some of the mysteries of chain smoking, nicotine addiction and lung cancer that can't be chalked up to environmental factors, brain biology and statistics, experts said. These oddities include why there are 100-year-old smokers who don't get cancer and people who light up an occasional cigarette and don't get hooked.

In the last 40 years, the rate of adult Americans smoking has been cut from 42 percent in 1965 to less than 21 percent now.

The studies show on average the consequences of the set of variations in the alphabet of genetic code that people inherit from each parent:

Smokers who get the set of variants from only one parent see a risk of lung cancer that is about one-third higher than people without any variants. They also smoke about one more cigarette a day on average than other smokers. This group makes up about 45 percent of the population studied.

Smokers who inherit the variants from both parents have almost a one in four chance of developing lung cancer. Their risk is between 70 and 80 percent higher than the cancer risk of other smokers without the genetic variants. They smoke on average of two extra cigarettes a day, and have a 45 percent higher risk of peripheral artery disease. This group accounts for about one in nine people of European descent.

Smokers who don't have the variants are still more than 10 times more likely to get lung cancer than nonsmokers. Smokers without the variant overall have about a 14 percent risk of getting lung cancer. By comparison the risk of lung cancer for people who have never smoked is less than 1 percent, said another study author, Paul Brennan of the International Agency for Research on Cancer in Lyon, France.

Brennan's study also found that lung cancer risk for nonsmokers with the variants was higher than for those without the variants. However, his small sample size of nonsmokers requires further study. Amos' study didn't find increased lung cancer risk for people with the set of variants who have never smoked.

But Kari Stefansson, lead author of the largest of the three studies and chief executive of deCode Genetics of Iceland, said the increased lung cancer risk was indirect, and that the variant caused more addiction and more smoking.