Studies identify DNA regions linked to nicotine dependence

February 14 2007

Americans are bombarded with antismoking messages, yet at least 65 million of us continue to light up. Genetic factors play an important role in this continuing addiction to cigarettes, suggest scientists at Washington University School of Medicine in St. Louis.

In two studies in the January 2007 issue of *Human Molecular Genetics*, the scientists show that certain genetic variations can influence smoking behaviors and contribute to a person's risk for nicotine dependence.

The smoking-related genes identified normally facilitate communication between nerve cells in the brain. One gene in particular, the alpha-5 nicotinic cholinergic receptor (CHRNA5) gene, was a very strong indicator of risk for nicotine dependence. Individuals with a specific variation in the gene seemed to have a two-fold increase of developing nicotine dependence once exposed to cigarette smoking. CHRNA5 is from a class of receptors that plays a role in dopamine pathways in the brain, which are linked to a person's experience of pleasure.

The researchers also identified genes related to gamma aminobutyric acid (GABA) receptors, another set of proteins vital to nerve cell function. Both GABA and nicotinic receptors had been suspected of involvement in nicotine addiction, but these findings strengthen those suspicions.

The studies also identified a gene not previously known to be involved with nicotine dependence. Called the Neurexin 1 (NRXN1) gene, it

helps regulate the balance between excitatory mechanisms — those that increase communication between nerve cells — and inhibitory mechanisms — those that slow firing between nerve cells.

"An imbalance between excitatory and inhibitory activity in the brain may predispose people to addiction, such as alcoholism, drug dependence or nicotine dependence," says Laura Jean Bierut, M.D., associate professor of psychiatry and principal investigator of both studies. "The Neurexin gene we've identified is really a key factor in the balance between inhibition and excitatory activity in neurons."

Bierut suspects a large number of genes are involved in nicotine dependence, and she says understanding how they work may make it possible to develop new treatments for smoking cessation.

The research team analyzed data from almost 2,000 participants in two ongoing studies. One, called the Collaborative Genetic Study of Nicotine Dependence, is a U.S.-based sample that includes both addicted smokers and "social" smokers from St. Louis, Minneapolis and Detroit. The other is an Australian study of smokers of European ancestry called the Nicotine Addiction Genetics study.

The scientists combined two approaches for analyzing genetic information. One approach scanned the entire human genome for suspicious areas of DNA while the second approach closely examined specific target genes.

"The combination of these two approaches represents the most powerful and extensive study on nicotine dependence to date and is an important step in a large-scale, genetic examination of nicotine dependence," says Elias A. Zerhouni, M.D., the director of the National Institutes of Health, which funded the studies. "As more genomic variations are discovered that are associated with substance abuse, we can better

understand addictive disorders."

The researchers identified an area of DNA variation that seems to alter the function of a nicotinic receptor protein. That small variation makes a big difference in risk for nicotine dependence.

Current drug treatments for nicotine dependence continue to be only marginally successful, and Bierut believes using information about genetic traits to tailor medications to individuals could make them significantly more effective. "The type of variant you have at this particular receptor — the alpha-5 nicotinic receptor — may actually predict whether or not you will do well on nicotine replacement therapy," she says.

Proving that, however, will require more studies, and the researchers have launched a new project to study DNA in a sample of both low-level smokers and heavier smokers. They are also working with colleagues at the University of Colorado to develop a mouse with the same variant in the CHRNA5 gene that seems to increase the risk of nicotine dependence. That would allow them to compare the effects of nicotine in mice with and without the genetic variation.

Tobacco use, primarily through cigarette smoking, is a leading cause of death and disability. Each year, approximately 440,000 Americans die of smoking-related illnesses, and worldwide, deaths attributed to tobacco total about 5 million. Although the prevalence of cigarette smoking has decreased over the last 30 years in the United States, the rate of smoking cessation among adults has been slowing since the mid-1990s. In addition, adolescents continue to start smoking, with 21 percent of high school students reporting they have smoked a cigarette sometime in the last month.

More than half of the people who smoke at least five packs in their lives

— 100 cigarettes — go on to become nicotine dependent. But about 15 percent of people who smoke that amount won't develop any symptoms of nicotine dependence. "These people can give up smoking at any time," Bierut says. "They have no cravings. They smoke socially."

Earlier research suggested that smoking behaviors tend to cluster in families, and large studies of twins previously concluded that the clustering is partly related to genetic factors. An important aspect of these latest studies is that rather than comparing smokers to non-smokers, the researchers compared addicted smokers to non-addicted smokers.

"You're not at risk for nicotine dependence unless you've smoked," Bierut says. "You have to study smokers to identify the people who are at risk of becoming nicotine dependent versus those who smoke but can give it up at any time."

Bierut says it's important to find genetic factors related to nicotine dependence because so much of the population continues to smoke, in spite of the overwhelming evidence that it's harmful. And she believes some of the genes her research team has identified will help scientists to develop therapies for smokers who just can't seem to quit with existing treatments.

Source: Washington University School of Medicine