DNA (driver of nicotine addiction)

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Cigarette smoking is the largest preventable source of death and disability in the USA, contributing to ~ 400,000 deaths annually. Despite widespread knowledge of the health dangers, ~ 1 in 8 American adults is a habitual heavy smoker.

For several decades, scientists have known that most of the risk for habitual heavy smoking (smoking a pack each day) is largely influenced by genetics. This conclusion comes from the study of identical and fraternal twins from Scandinavia, North America, Australia and (more recently) China. It has been estimated that ~ 2/3 of the risk to become a heavy habitual smoker is genetic. This does not imply that this genetic risk is due to a single gene. It is known that many genes are involved, each one contributing a small amount of risk.

Finding the individual genes is a considerable challenge, but worth the effort, because it is hoped that the genes conveying risk for heavy smoking could be used to develop new medicines to help people quit. The development of new medicines to help people quit is particularly important, because the existing medications, including nicotine replacement ('the patch' or gum), bupropion and varenicline are effective in the short-term (several months) for a minority of heavy smokers.

This paper describes the results of a genetic study of 14,000 people, from the USA and Europe, whose smoking histories were known. DNA samples from ~ 6000 people were analyzed at ~ 500,000 known variations in the human genome to determine whether any of these variations predicted cigarettes per day during the period of heaviest smoking for these individuals. The results implicated variations in two genes, both producing brain proteins to which nicotine binds in generating its addicting effects. These two proteins (are their genes) are termed the alpha 3 and alpha 5 nicotinic receptor subunits, so-called because they form (with other nicotinic receptor subunits) binding sites for nicotine on certain brain cells which are known to be activated during the process of addiction.

A second population of ~ 8000 people (whose smoking histories were known) was analyzed in a similar manner, the result again suggesting that variations in these two genes increased risk for heavy smoking. Taken together, these two studies provide convincing proof that variations in the alpha 3 and alpha 5 nicotinic receptor subunit genes play a significant role in risk for nicotine addiction. A previously published paper, using similar methods, also supports this conclusion.

These results suggest two important research activities. First, and foremost, the alpha 3 and alpha 5 nicotinic receptor subunits will be made targets for new smoking cessation medication development programs by pharmaceutical companies. Second, the implicated DNA variants can be used to determine whether they predict ability to quit using the one of the currently available smoking cessation medicines. This "personalized medicine" approach might allow for more efficient and productive use of those medicines, until improved ones can be created.

Source: Molecular Psychiatry