

Major Conclusions

**PHENOTYPES AND
ENDOPHENOTYPES:
FOUNDATIONS FOR GENETIC
STUDIES OF NICOTINE USE
AND DEPENDENCE**
MONOGRAPH TWENTY

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Although tobacco use in the United States has steadily declined since the 1980s, an estimated 45 million people in the United States still smoke. Worldwide millions of people die each year from illnesses caused by tobacco use. Tobacco use behavior is dependent on complex genetic and environmental influences and interactions that are currently not well understood. Identifying phenotypes (observable traits determined by groups of genes) and endophenotypes (traits that are found more often in individuals with a condition than in the general population) for smoking behavior may help guide future research, tailor treatments for individual smokers more effectively, and enhance existing public health policy in tobacco prevention and control.

The National Cancer Institute (NCI) presents *Phenotypes and Endophenotypes: Foundations for Genetic Studies of Nicotine Use and Dependence*, the 20th monograph in the NCI Tobacco Control Monograph Series. This monograph reviews the scientific foundation for genetic studies of nicotine use and dependence. The authors and editors—representing a wide range of expertise in the fields of psychology, psychiatry, behavioral pharmacology, neurobiology, epidemiology, statistical genetics, and bioinformatics—reviewed and analyzed the growing body of research findings in the field to develop a scientific plan for incorporating genetic research into crossdisciplinary studies of nicotine dependence. This monograph provides important, innovative, and new concepts and methodologies for behavioral genetics.

Major conclusions from the monograph are:

1. At every level of analysis (theoretical, animal, child, and adult), good candidate endophenotypes are available for inclusion in future genomic studies of nicotine dependence.

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2. Results from the animal and human domains implicate the importance of nicotinic acetylcholine receptors in nicotine self-administration, reward, and dependence.
 3. Developmentally, there is evidence from latent class growth analysis and growth mixture modeling in unrelated and related adolescents that familial and/or genetic factors play a role in trajectories of tobacco use that vary in age of onset, level, and chronicity of use, as well as in the extent to which tobacco and alcohol use co-occur.
 4. In children and adults, there are neuropsychological, electrophysiological, and behavioral laboratory measures characterized in other research contexts that are or may be heritable and may shed light on mechanisms that promote risk for initiation and maintenance of nicotine dependence.
 5. Along with more refined definitions of nicotine dependence at the epidemiological level and an increased number of options at the phenotypic level, several technological developments will be important to the next generation of studies of nicotine dependence, such as whole-genome genotyping, epigenetics, proteomics, and metabolomics. Complementing these technologies are methodological advances including Bayesian statistics, behavioral ontologies, identification of developmental trajectories, and real-time measurement of environmental antecedents to nicotine dependence.

This NCI monograph makes a strong case for continued and expanded research of genetic influences on tobacco use. A better understanding of the role of genetic susceptibility may help the public health community enhance already effective public policies for tobacco prevention and control. Placed into the context of what is known to already work, the knowledge gained from genetic studies may play an important role in the future development of environmental and policy interventions.

About the NCI Tobacco Control Monograph Series

The NCI began the Tobacco Control Monograph Series in 1991 to provide ongoing and timely information about emerging issues in tobacco prevention and control. The monographs are available at no cost in print and electronically via the Web.

For More Information

For more information or to order this monograph, go to <http://www.cancercontrol.cancer.gov/tcrb/monographs/20/index.html>, or call the NCI Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) and ask for NIH Publication No. 09-6366.