

NCI TOBACCO CONTROL MONOGRAPH SERIES

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Major Accomplishments and Directions for Future Research

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

MONOGRAPH TWENTY

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 (valid and homogeneous patterns) of smoking behavior and endophenotypes (measurable components along the pathway between the distal genotype and proximal condition of interest) 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—synthesize the expanding literature in the field and develop a scientific blueprint for the integration of genetic research into transdisciplinary studies of nicotine dependence. This monograph also contributes important, innovative, and new concepts and methodologies for behavioral genetics.

Continued research in behavioral genetics will enhance our understanding of the role of genetic variation on smoking behavior and nicotine use and dependence. The editors recommend that researchers planning the next generation of studies on nicotine dependence consider the following general strategies:

- Use a comprehensive approach to examine and report genotype-phenotype associations—for example, single-gene studies are discouraged unless they can be replicated and validated.

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- Examine the roles of genetics and the environment in a greater number and broader range of homogeneous groups of tobacco users.
- Avoid stigmatization of population subgroups by communicating research results carefully and including limitations of the work and the extent to which the results are reliable and can be generalized.
- Take a theoretically-based approach to nicotine dependence, specifying the relationships within and between phenotypic domains.
- Combine differing levels of analysis—for example, incorporate measured genetics into genetic latent growth curve models in extended twin design studies.
- Analyze phenotypes and endophenotypes that are considered to be risk factors for the adoption or maintenance of nicotine dependence in genome-based studies.
- Apply epigenetic methodologies to enhance the understanding of the impact of the environment on the differential expression of gene variants.

In developing this NCI monograph, the editors and authors accomplished several major “firsts” in the field of genetic research and nicotine dependence:

- First comprehensive review of the broadly relevant literature.
- First demonstration that differences in tobacco-use trajectories—from early adolescence to early mid-life—are related to both family history of smoking and nicotine dependence in adulthood.
- First demonstration that conjoint trajectories of tobacco and alcohol use in adolescents can be inherited.
- First identification of biobehavioral phenotypes that can be used in future genomic studies of adolescents and adults pre- and post-nicotine exposure.
- First demonstration that microcontextual effects on nicotine dependence can be assessed and are informative in genomic studies.
- First use of Bayesian analysis to determine the relative importance of several genes to variations in nicotine metabolism.

This NCI monograph makes a strong case for continued and expanded research of genetic influences on tobacco use. This research will be enhanced by new technological developments, such as whole-genome genotyping, epigenetics, proteomics, and metabolomics. Transdisciplinary research teams are needed to fully explore the complex interplay between genes and the environment in explaining tobacco use behavior. 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.