

General Overview

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 (measurable components along the pathway between genes and the 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—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.

The monograph is organized into six parts:

- **Part 1—Overview**, provides background context for research in genetic and gene-environment factors in tobacco use. It focuses on phenotypes and endophenotypes that may link genes and behavior and be a basis for future genetic studies. In addition, conceptual, theoretical, and methodological considerations in the further study of nicotine dependence are examined.

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- **Part 2—Theoretical Considerations**, examines the theoretical basis for constructs that may link heritable genetic traits with observable measures of nicotine dependence. These include phenotypes representing a causal path between specific genetic actions and measures of nicotine dependence, as well as endophenotypes measuring indirect influences, such as those found before nicotine exposure. This part examines theoretical issues in establishing nicotine-dependence phenotypes as well as studies of human and animal behavior.
- **Part 3—Developmental Trajectories of Tobacco Use and Their Relation to Tobacco Dependence**, examines issues in the study of trajectories of tobacco use and their future potential as a basis for genetic studies of nicotine dependence. Chapters include a literature review of developmental trajectories of cigarette smoking between adolescence and adulthood, genetic modeling issues in the study of smoking trajectories and behavior, and the relationship of these with other trajectories such as alcohol use or substance abuse.
- **Part 4—Endophenotypes**. Endophenotypes serve as intermediary measures that have the potential to provide a link between genes, smoking behaviors, and nicotine dependence. Endophenotypes may help serve as a basis for future studies to identify genetic liability markers for nicotine dependence. This part discusses the evidence base for several candidate endophenotypes for nicotine dependence at or before initial exposure to nicotine as well as for endophenotypes for nicotine dependence in chronic smokers.
- **Part 5—Epidemiological and Methodological Considerations**, examines epidemiological and methodological issues related to the future of genetic studies of nicotine dependence. These issues include the use of epidemiologically-based phenotypes for tobacco use; a potential etiological architecture for genetic and environmental influences on smoking phenotypes; and the hierarchical modeling of gene-gene joint action.
- **Part 6—Future Directions**, comments on how continued research in the area of genetics may influence future understanding of the pathways responsible for nicotine dependence, the role genetic variation plays in its initial acquisition and maintenance. It also provides summaries and recommendations from each of the parts of the monograph and concludes with several cross-cutting suggestions for future work in this area.

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.