Genetic Research on Addiction

Ethics, the Law, and Public Health

EDITED BY AUDREY R. CHAPMAN

CAMBRIDGE Medicine

CAMBRIDGE more information - www.cambridge.org/9781107653344

Genetic Research on Addiction

Ethics, the Law, and Public Health

Genetic Research on Addiction

Ethics, the Law, and Public Health

Edited by

Audrey R. Chapman
Healey Professor of Medical Ethics and Humanities,
Department of Community Medicine and Health Care,
University of Connecticut School of Medicine,
Farmington, CT, USA

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town,
Singapore, São Paulo, Delhi, Mexico City

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9781107653344

First published 2012

Printed in the United Kingdom at the University Press, Cambridge

A catalogue record for this publication is available from the British Library

Library of Congress Cataloguing in Publication data
Genetic research on addiction : ethics, the law, and public health / edited by Audrey R. Chapman.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-107-65334-4 (hardback)
I. Chapman, Audrey R.
[DNLM: 1. Genetic Research–ethics. 2. Substance-Related Disorders–genetics.
3. Human Experimentation–ethics. 4. Informed Consent. 5. Public Policy. WM 270]
616.02′7–dc23
2012014544

ISBN 978-1-107-65334-4 Hardback

Contents

Contributors

Peter J. Adams
Associate Professor of Social and Community Health, University of Auckland, Auckland, New Zealand

Paul Appelbaum
Elizabeth K. Dollard Professor of Psychiatry, Medicine & Law and Director, Division of Law, Ethics & Psychiatry, Department of Psychiatry, Columbia University, New York, NY, USA

Thomas F. Babor
Physicians Health Services Chair in Community Medicine and Public Health, Professor, and Chair, Department of Community Medicine and Healthcare, University of Connecticut Medical School, Farmington, CT, USA

Adrian Carter
National Health and Medical Research Council (NHMRC) Post-Doctoral Research Fellow, University of Melbourne and Honorary Research Fellow, University of Queensland Centre for Clinical Research in New Zealand, New Zealand

Audrey R. Chapman
Healey Memorial Chair of Medical Ethics and Humanities and Professor of Community Medicine and Healthcare, University of Connecticut School of Medicine, Farmington, CT, USA

Karen L. Dugosh
Quantitative Psychologist, Section on Law and Ethics Research, Treatment Research Institute on the Organization and Management of Addiction Treatment, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

David S. Festinger
Director, Section on Law and Ethics Research, Treatment Research Institute on the Organization and Management of Addiction Treatment, and Adjunct Professor of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Carl Erik Fisher
Resident in the Department of Psychiatry at Columbia University, New York, NY, USA

Amy Gaviglio
Research Project Coordinator, Department of Health Behavior and Health Education, University of Michigan, Ann Arbor, MI, USA

Alicia Giordimaina
Genetic Counselor in the Minnesota Department of Public Health, MN, USA

Wayne Hall
Professor and National Health and Medical Research Council Australia Fellow, University of Queensland Centre for Clinical Research; and Visiting Fellow at the Queensland Brain Institute, Queensland, Australia

Deborah Hasin
Professor of Clinical Epidemiology, Department of Psychiatry, College of Physicians and Surgeons and Mailman School of Public Health, Columbia University, New York, NY, USA

Toby Jayaratne
Assistant Research Scientist, Department of Health Behavior and Health Education, University of Michigan, Ann Arbor, MI, USA

Jonathan M. Kaplan
Associate Professor of Philosophy, Oregon State University, Corvallis, OR, USA

Zita Lazzarini
Associate Professor of Health Law, Department of Community Medicine and Healthcare, University of Connecticut, Farmington, CT, USA

Bruce G. Link
Professor of Epidemiology, Mailman School of Public Health and Professor of Sociomedical Sciences, Department of Psychiatry, Columbia University, New York, NY, USA

Rebecca Mathews
Senior Research Assistant, University of Queensland Centre for Clinical Research, Queensland, Australia

Thomas J. McMahon
Associate Professor, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Jo C. Phelan
Associate Professor of Sociomedical Science, Mailman School of Public Health, Columbia University, New York, NY, USA

David B. Resnik
Bioethicist and Institutional Review Board Chair, National Institute of Environmental Health, National Institutes of Health, Bethesda, MD, USA

Katherine Robaina
Research Assistant, Department of Community Medicine, University of Connecticut School of Medicine, Farmington, CT, USA

Mark A. Rothstein
Herbert F. Boehl Chair of Law and Medicine and Director, Institute of Bioethics, Health Policy, and Law, University of Louisville Medical School, Louisville, KY, USA

Preface

This volume has a dual focus: identifying the ethical issues and requirements related to carrying out genetically based research on addiction and specifying the ethical, legal, and public policy implications of the interpretation, translation, and application of this research. It is hoped that the book will contribute to more ethically sensitive research and more socially responsible policies.

A motivating factor in the development of the volume was the desire to fill an important gap in the literature. It has been thought that a better understanding of the genetic contributions to addiction could lead to more effective drugs to assist in cessation of alcohol and drug use with fewer adverse side effects and that genotyping could better match patients to existing pharmacological treatments for addiction. These hopes have fueled medical investment in this field of research. Like other types of behavioral genetics research, the manner in which genetics research associated with addiction is conducted, interpreted to the public, and then translated into clinical practice and policy initiatives raises important ethical, social, and legal issues. Given the sensitivity of genetic research, its potential for stigmatization, its implications beyond the individual subject for the family and in some cases a broader community of membership, there is a need to guard against genetic research being misunderstood and misused. Yet there has been little literature exploring the ethical requirements of this research and its implications for public policy.

A grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the US National Institutes of Health awarded to the Alcohol Research Center of University of Connecticut Health Center, for "Dissemination, and Educational Activities Related to Alcohol Research," afforded me the time to work on this volume. I have also had financial assistance from the Alcohol Research Center for the preparation of the volume. I would like to thank Professor Victor Hesselbrock, the Scientific Director of the Alcohol Research Center, for his support.

I would like to take this opportunity to thank other people who assisted with the development of this volume. I am grateful to Professor Thomas Babor, the Chairman of the Department of Community Medicine and Health Care at the University of Connecticut Health Center, who generously gave of his time and expertise. The role of the contributing authors of the chapters in the volume is obvious. Without their time and effort it would not have been possible to prepare and develop a multi-disciplinary volume incorporating a wide range of expertise. I would like especially to thank Jonathan M. Kaplan and Adrian Carter for their participation in the process of drafting the guidelines. I am also appreciative of the assistance of Joanna Chamberlin, my editor at Cambridge University Press, and Dr. Matthew Davies of Out of House Publishing Solutions who oversaw the copyediting, typesetting, and proofreading of the volume.

Section 1 Introduction

Chapter 1

Introduction to the volume

Audrey R. Chapman

The misuse of alcohol and illicit drugs inflicts a major toll on individual users, their families, and the wider society. Addictive disorders contribute to excess morbidity and mortality and are economically costly. They also disproportionately affect people in the prime of life (Merikangas and Risch, 2003). The World Health Organization (WHO) divides the adverse effects of alcohol, opioids, and other psychoactive substances into four categories: chronic health effects (such as the toxic effect of alcohol in producing liver cirrhosis); the acute or short-term biological health effects of the substance (such as the effects of drug and alcohol overdose); the adverse social consequences of substance use (such as criminal activity to obtain access); and chronic social problems (such as the impact on family life) (WHO, 2004: 10–11). In addition, alcohol and drug consumption is associated with widespread psychosocial consequences, including violence, absenteeism in the workplace, and child neglect and abuse (WHO, 2011: 24). WHO estimates that alcohol ranks eighth among global risk factors for death and is the third leading global risk factor for disease and disability (WHO, 2011: 34). Of the ten leading risk factors of avoidable burden of ill-health, tobacco was fourth and alcohol fifth in 2000 (WHO, 2004: 16–17). Alcohol-related disability is a condition that affects more than 12% of the population in the United States at some point in their life. The majority of individuals with alcohol dependence (AD) – about three-quarters – never receive treatment (Heilig et al., 2011: 670–671).

Dependence on psychoactive substances has long been thought to have a biological basis, as suggested by observations of its prevalence in some families. The breaking of the genetic code in the 1960s and the inception of the Human Genome Project to sequence the human genome in 1990 have spurred efforts to identify the genetic basis of predispositions to drug and alcohol dependence. Given the high costs and difficulties in successfully treating addiction (Sellman, 2009), there has been interest in discovering more effective approaches to treatment. It has been thought that a better understanding of the genetic contribution of addiction could lead to more effective drugs to assist in cessation of drug use with fewer adverse side effects. Relatedly, it is assumed that genotyping could also better match patients to existing pharmacological treatments for addiction (Hall et al., 2002: 1482). This volume briefly describes such scientific research as well as current progress in identifying the genetic contributions to AD and other forms of addiction.

Like other behavioral genetics research, the manner in which genetics research associated with addiction is conducted, interpreted to the public, and then translated into clinical practice and policy initiatives raises important ethical, social, and legal issues. This volume

Genetic Research on Addiction, ed. Audrey R. Chapman. Published by Cambridge University Press.

has a dual focus: identifying the ethical issues and requirements related to carrying out genetically based research on addiction and specifying the ethical, legal, and public policy implications of the interpretation, translation, and application of this research. There are four sections in the volume. Section 1 consists of this introduction and two other chapters, one an overview of genetic research on AD and the other on the promises and risks for participants in studies. Section 2 addresses research issues, both human subject protection issues in genetically focused addiction research and issues related to seeking or accepting support for addiction research from industry. Section 3 explores ethical and policy issues in translating addiction research for public understanding and into public policy. The concluding chapter, which constitutes Section 4, uses the key issues raised in the volume and the recommendations made by the various chapter authors to develop guidelines for research and its policy applications.

Conceptualizing addiction

Criteria for addiction

To start at the beginning, what is addiction? According to one dictionary definition, addiction is the "compulsive need for the use of a habit-forming substance (like heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physical symptoms upon withdrawal" (Merriam-Webster Dictionary). Addiction is often used interchangeably with the terms "substance dependence" or the "dependence syndrome." Although, as noted below, there is ongoing debate among philosophers, ethicists, public health specialists, scientists, and the general public about the conception of addiction, there is considerable consensus about the criteria for identifying someone who is addicted. As noted from the descriptions below, the two major medical classifications of dependence have considerable overlap. Both emphasize a strong desire or sense of compulsion to take the substance in question and difficulties in controlling the pattern of use and its termination, despite clear evidence of overtly harmful consequences.

The *International Classification of Mental and Behavioral Disorders*, 10th revision, usually referred to as the ICD-10, was endorsed by the 43rd World Health Assembly in 1990 and came into use in 1994. The ICD-10 lists six criteria for substance dependence, some of which are measurable in biological terms whereas others are not. To be diagnosable as "dependent," three or more of the following must have been experienced or exhibited together at some time during the previous year:

1. strong desire or sense of compulsion to take the substance
2. difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use
3. physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
4. evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects

6. persistance with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to heavy substance use, or drug-related impairment of cognitive functioning (WHO, 2004: 13).

The second major source of criteria for identifying substance dependence is the fourth edition of the *Diagnostic and Statistical Manual* (DSM-IV) of the American Psychiatric Association. According to the DSM-IV, substance dependence is "a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period":

1. tolerance, as defined by either of the following:
   a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. markedly diminished effect with continued use of the same amount of the substance
2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance
   b. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use
5. a great deal of time is spent in activities necessary to obtain the substance
6. important social, occupational, or recreational activities are given up or reduced because of substance use
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (American Psychiatric Association, 1994).

Conceptions of addiction

There are currently two major approaches to conceptualizing addiction, both of which were developed primarily in reference to patterns of opioid drug misuse and not AD. Presumably the conception would apply to AD, as well as nicotine addiction. The traditional and popular understanding of addiction, sometimes labeled as the moral model, presents addiction as an issue of moral impropriety based on a choice that individuals voluntarily make and for which they should be held responsible. By contrast, the more recently developed medical model holds that addiction is primarily a psychiatric or brain disorder that requires treatment. Some researchers propose a third psychological approach. Chapter 13 by Toby Jayaratne, Alicia Giordimaina, and Amy Gaviglio in this volume, for example, discusses the tendency for some individuals with a propensity for AD to attempt to decrease the threat this poses to their self-esteem by employing genetic explanations as a psychological coping tactic. There are more- and less-nuanced proponents of each of these models, as well as a small number of analysts who take the position that addiction is both a disease and a moral condition (Cochrane, 2007). Conceptions of addiction have implications for how society should treat addicts and whether addicts are considered to have the capability to exercise rational or responsible agency – for example, to make an autonomous decision to participate in a genetic research study of addiction.

The dominant moral model of addiction holds that addicts knowingly and willingly choose to use drugs or alcohol without regard for the adverse consequences for themselves and others. According to this view, the choice that individuals make to use psychoactive substances springs from a weak will. Some adherents of this position recognize that in a minority of cases the decision to use harmful substances develops into an addictive pattern. Others believe that addiction is just an excuse for continuing to use drugs while avoiding responsibility for the consequences of doing so (Carter et al., 2009: 25). This perspective is sometimes also referred to as the "skeptical" view, because it discounts the relevance of biogenetic mechanisms and recent neuroscience research as well as the need for medical treatment for addiction. According to one proponent, "addiction is no more a treatable medical problem than is unemployment, lack of coping skills, or degraded communities and despairing lives…More treatment will not win our badly misguided war on drugs. It will only distract our attention from the real issues in addiction" (Peele, 1990). Many of those who subscribe to this approach to addiction contend that most addicts have the capacity to stop drug use on their own (Peele, 2004, cited in Carter et al., 2009: 25). Some of those who argue that addiction is best conceptualized as a moral condition rather than a compulsion requiring medical treatment base their views on the fact that drug seeking and drug taking involve a series of actions that require rational planning; they therefore draw the conclusion that addicts rationally decide to continue to use drugs. Others worry that medicalization might encourage drug use or lead addicted persons to fatalism about their condition (Hyman, 2007: 8–9). The common belief that drug use is a voluntary choice that results in significant personal and social harm has led most societies to adopt punitive laws to discourage drug use and to impose significant penalties for purchase and use of illegal substances or if addicts engage in harmful or illegal acts while under the influence of an addictive substance.

There are conceptions of addiction that share many of the premises of the moral model while not explicitly presenting addiction as a moral issue. Bennet Foddy and Julian Savulescu (2007) offer a self-labeled reductive account that characterizes addiction as pleasure-seeking, individually based action that is rationally decided by its user. In their account, addictive desires differ from other desires for pleasure more in degree than in kind: they are especially strong; they occur in a particular context that triggers anticipation; and they are socially unacceptable because they threaten the welfare of the individual or challenge social norms. Foddy and Savulescu also compare addiction to substances with physical dependency syndromes and the addiction to other biological sources of pleasure such as sugar, sex, eating, or water. Like advocates of the moral model, they reject the view of addiction as a disease. For them pleasure is a healthy, necessary part of an individual's life. When it becomes excessive and out of control it may be considered to be a poor choice, but not a disease. They argue that very few addicts suffer brain damage that impairs their judgment, and for the most part, the changes in an addict's brain are comparable to those of a normal person when they engage in any normal rewarding activity (Foddy and Savulescu, 2010: 6). They relegate the concept of addiction to being nothing more than "an illiberal term invented to describe those who seek pleasure in a way that expresses our social disapproval" (Foddy and Savulescu, 2010: 20). Instead their "liberal account" of addiction advocates that the pleasure of addiction can be conceptualized as a legitimate human good and can be part of an autonomous, and even rational, life plan (Foddy and Savulescu, 2010: 19–20).

By contrast, the medical or disease model of addiction, informed by neuroscience research and brain-imaging studies, presents an addict's drug-seeking behavior as the direct result of changes in the structure and function of the brain caused by chronic substance

use. Neurobiological research, particularly brain scans, suggests that chronic substance use can produce long-term disruptions of neurocognitive circuits involved in motivation and attention, decision making, and the ability to inhibit impulses. These alterations then increase cravings, impair appreciation of the consequences of substance use, and make it more difficult to resist urges to use the substance in question (Carter et al., 2009: 25–26). Some proponents of the medical model explicitly conceptualize addiction as a brain disease. The "chronic and relapsing brain disease" model of addiction put forward by Alan Leshner (1997) uses evidence that prolonged substance use causes pervasive and long-term changes in brain function to explain why an addicted person is vulnerable to relapse even after protracted periods of abstinence.

Acknowledging that the science is still in its early stages, Steven Hyman (2007) offers a nuanced and qualified interpretation of the neurobiology of addiction. He proposes that addictive drugs tap into and, in vulnerable individuals, usurp the potent neurotransmitter dopamine system in the brain that regulates rewards. The neural circuits "over learn" from excessive and distorted dopamine signals. This usurpation of the dopamine system makes drugs salient to the addict at the expense of other, more adaptive, goals. The result is a brain in which drug cues powerfully activate drug seeking and create craving if use is delayed, thus undermining the addict's ability to avoid seeking and using. Nevertheless Hyman cautions that this model does not reduce afflicted individuals to "zombies" who are permanently controlled by external cues or devoid of other goals. He also suggests that despite likely multiple relapses, addicts can regain a good measure of control over their drug taking.

Recognition of the important contribution of neuroscience does not necessarily lead to a reductive neuro-essentialist conception of addiction. Many proponents of this perspective acknowledge the importance of social, environmental, and cultural factors as well. For example, an approach that includes a neuroscientific component, but also goes beyond it, termed a "biopsychosocial systems model," proposes that psychological and sociological factors complement and are in dynamic interplay with neurobiological and genetic factors (Buchman et al., 2010: 37).

Like the moral model, the medical model has implications for how society approaches and deals with addicted individuals. Many proponents hope it will decrease the stigma associated with addiction and will incline society to treat addicts more humanely. Other advocates believe that treating addiction more as a disease than a moral failing could encourage greater societal investment into medical research into addiction and the development of more effective medical interventions (Carter et al., 2009: 25–26). However, the very possibility that societies could move in this direction makes some analysts reluctant to replace the moral model with a neurobiological perspective – both for the benefit of the addict and the protection of society.

The acceptance of the view of addiction as a disease could also have unintended negative consequences. Some worry that if addiction is viewed as primarily a genetic or brain disease it will contribute to negative perceptions of substance-use problems, much as it has in the case of mental illness (Buchman et al., 2010: 37). An uncritical acceptance of the brain disease model of addiction could encourage an overemphasis on pharmacological strategies to try to cure addiction rather than social-policy measures to reduce use of alcohol and drugs, which are more likely to be effective. In some circumstances it might also be interpreted as a warrant for the coercive treatment of addicts (Carter and Hall, 2007: 16).

An issue underlying much of this debate on the nature of addiction is the extent to which an addicted individual is in control of his or her actions, and concomitantly, the extent to

which he or she should be held accountable by society. Specifically, how severely does addiction compromise the autonomous agency of the user and what are the implications? As Gideon Yaffe notes, there is both a legitimate moral and legal basis for distinguishing among: (1) those who pursue illegal or immoral courses of action freely; (2) those who do wrong out of compulsion – that is, unfreely; and (3) those who do wrong as a result of transitory powerful impulses (Yaffe, 2001: 179). The question is into which category addicts should be placed and whether the characterization applies to all addicts. This is a complex issue that has attracted much philosophical discussion too complex to recount adequately here.

To provide a simplified characterization, at one end of the spectrum there are those philosophers, psychologists, and medical doctors who believe that the autonomy or the capacity for self-determination of addicts is severely impaired. As noted, the two major medical classifications of dependence on psychoactive substances, one compiled by the WHO and the other by the American Psychiatric Association, cite a strong desire or sense of compulsion as one of the characteristics of addiction. Compulsion, which compromises the voluntary nature of choice, is one clinical defining feature of addiction that is usually taken to compromise decision-making capacity. Intoxication and withdrawal, which compromise the ability to comprehend choices, are two others (Charland, 2002: 40–41). Luis Charland argues that "the brain of a heroin addict has almost literally been hijacked by the drug" (Charland, 2002: 43). Although he acknowledges that the decisional impairments in heroin addiction fluctuate, he argues that their brain mechanisms and systems that govern evaluation have been disrupted and reoriented, thus entrenching the damage to their decision-making capacity (Charland, 2002: 43).

Charland's characterization, which comes in an article discussing whether heroin addicts are able to give consent to participating in clinical trials of heroin replacement therapy, is countered by other characterizations of addiction. Neil Levy argues that although addicts have impaired autonomy, the evidence available demonstrates that their actual behavior is sensitive to moderate incentives, both positive and negative in nature – for example, price increases in the drugs consumed – indicating they are not subject to irresistible desires. Levy argues that autonomy comes in degrees: it is not an all-or-nothing phenomenon. Addicts are subject to oscillations in preferences and suffer from diminished autonomy, but they are still capable of choice and are able to resist taking the substance to which they are addicted at least some of the time (Levy, 2011). Although Steven Hyman acknowledges that addiction impairs the capacity to make decisions about drug use, he, like Levy, maintains that this "loss of control is not complete or simple" (Hyman, 2007: 8). Similarly, Adrian Carter and Wayne Hall stress that "the fact that individuals with an addiction retain some control over their decisions about drug use and that the impulse to use drugs is resistible must be stated clearly" (Carter and Hall, 2007: 16).

Regardless of perspectives about the nature of addiction, most ethicists, even those who acknowledge at least a partial impairment of decision-making capacity, still argue that addicts should be held responsible. A (US) National Bioethics Advisory Commission Report concluded that the disease of addiction is not an excuse for behavior *per se*, because drug-dependent individuals are not always devoid of rational decision-making capacity (National Bioethics Advisory Commission, 1998: 8). Similarly, Stephen Morse points out that although an addict's rationality is often severely compromised at the time of drug seeking and using, it is not compromised at all times for most addicts. Therefore he or she is capable of and responsible for taking steps when not in a strongly driven state to prevent the maladaptive behavior that the addict knows will result when the craving returns (Morse, 2007: 13). Steven

Hyman cautions that some apparently voluntary behaviors of addicts may not be as freely planned and executed as they first appear (Hyman, 2007: 8), but he nonetheless still believes that it may be wise for societies to err on the side of holding addicted individuals responsible for their behavior – but "with a view to the rehabilitation of the addicted person and protection of society rather than moral opprobrium" (Hyman, 2007: 10). Likewise, Thomas Cochrane argues that fully replacing the moral model with a neurobiological perspective would be counterproductive because some demonstrations of moral judgment actually work to control addictive behavior. He goes on to say that "Even proof that addicts lack *all* control would not obviate the need for a moral stance on the part of others, as long as it can be shown that such a moral stance alters the addictive behavior" (Cochrane, 2007: 25).

Further complicating this whole issue, empirical studies of dependence symptoms indicate that the severity of dependence varies along a continuum from light to moderate and then severe. The cutoff point or threshold for addiction or dependence is somewhat arbitrary. Many people who use drugs and alcohol experience problems but do not meet criteria for dependence. To engage in genetic research it is important to have a good measure of the phenotype, but current diagnostic criteria for dependence and/or substance use are often highly correlated with a variety of other possible causes and consequences, including personality traits, demographic characteristics, and psychopathology. The complicated nature of addiction makes it unlikely that single causes and simple diagnostic criteria are likely to provide clear guidance on how best to define and diagnose the phenotype (T. Babor, personal communication, 2011).

Types of genetic research on addiction

The increasing evidence that addiction to alcohol and opioid substances has a genetic contribution has given rise to research to improve our understanding of addiction and thereby to be able to more effectively treat those afflicted and possibly improve our ability to prevent at least some addictive disorders. Genetic research on addiction seeks to identify the genes associated with a predisposition or vulnerability toward dependence and addiction. Qualitative family-based research designed to examine patterns of inheritance has been a cornerstone of this research. There are several types of family studies. Classical twin studies evaluate genetic inheritance by comparing data on a trait under study from identical/monozygotic and fraternal/dizygotic twin pairs. Additive genetic influences are shared 100% between members of monozygotic twin pairs, whereas dizygotic twin pairs on average share 50% of their genes, the same degree of genetic similarity as non-twin siblings. Adoption studies of biologically related people reared apart in presumably different environments help to separate genetic and environmental influences on variation in vulnerability to substance disorders. Some researchers have also pooled data from the various types of family studies to conduct a range of meta-analyses (Baker, 2004: 42–45).

Family, twin, and adoption studies provide robust evidence for a significant, but not exclusive, genetic contribution to the development of substance use and dependence. Environmental factors and individual experiences play an important role in shaping use patterns and dependence. Twin studies strongly indicate the existence of genetic risk factors for multiple aspects of smoking and AD, including initiation, continuation, amount consumed, and cessation (WHO, 2004: 151–152). Depending on the diagnostic criteria used, heritability estimates of AD range from 52 to 63% (WHO, 2004: 132). Heritability of opioid dependence is estimated to be even higher, at almost 70% (WHO, 2004: 136). However, the various

types of family designs, with the exception perhaps of adoption studies, cannot identify the relative contribution of genetic and environmental factors (Agrawal and Lynskey, 2008). Nor can they identify which genes or chromosomes are involved.

Technological advances spurred by the Human Genome Project have made molecular approaches more readily available to investigate regions of DNA that may be involved in the susceptibility to AD and other forms of addiction. Linkage analysis, which examines genetic samples to try to identify the correlation of a trait and genetic markers among related individuals who have the phenotype in question (e.g., AD), has been an important tool for identifying the approximate chromosomal region in which some of the major genes contributing to the trait are located. Another technique, association studies, focuses on a single gene that has already been isolated, referred to as the candidate gene, to identify whether variation in this gene's alleles (alternate forms of the gene) might be statistically associated with variations in its expression by comparing people with and without the phenotype. The development of microarray analysis has accelerated the process by enabling scientists to examine thousands of genes simultaneously (Baker, 2004: 45–49; WHO, 2004: 127–128).

It should be emphasized that we are still a long way from identifying the individual genetic differences that contribute to the development of any form of substance dependence. Despite good evidence that genes contribute to addiction susceptibility, the results of qualitative family studies and molecular approaches to addiction disorders have been fairly modest thus far. The lack of commonly occurring susceptibility alleles that strongly predict addiction risk has been a major challenge to this research. The complexity of unraveling the genetic contributions to AD and other addictions precludes any likelihood that genetic research can contribute to predictive genetic screening or pharmacogenetic testing to inform treatment selection of addictive disorders in the near future. After reviewing the scientific evidence, the next chapter in this volume, contributed by Rebecca Mathews, Adrian Carter, and Wayne Hall, concludes that genetic testing is not ready for use to predict AD liability, especially for population screening, but shows that the evidence linking genetic variants with differential responses to treatment appears to be more robust for some population groups.

The complexity of the task is a major challenge to the application of genetics in the field of addiction. Contrary to the popular view of human genetics, which assumes a simple or direct relationship between a mutation or a variant form of a single gene and the development of a specific disorder, single gene or Mendelian disorders, such as Huntington's chorea, are very rare. Predisposition toward alcohol and/or drug dependence is a complex disorder, and like other complex disorders it appears to be shaped by multiple alleles (variant forms of a gene), each contributing a small effect, that dynamically interact with each other and with environmental factors. Gene/environmental interactions are key to determining outcomes. As a recent WHO review of evidence on genetic vulnerability to substance dependence explains, "while individual genetic differences contribute to the development of substance dependence, genetic factors are but one contributor to the complex interplay of physiological, social, cultural and personal factors that are involved" (WHO, 2004: 125).

There are several implications of this understanding of genetic heterogeneity. Multiple risk alleles in different combinations can contribute to genetic risk in individual cases. It is unlikely, therefore, that everyone with a particular "risk gene" for substance use or dependence will become dependent. Conversely, some of those who become dependent may not carry a specific genetic risk factor being researched (WHO, 2004: 125). Or to put the matter another way, patients diagnosed with a clinical condition labeled as alcohol dependency or

another form of addiction presenting with similar symptoms can arrive at this phenotype through very different trajectories of genetic risk factors and exposure to environmental risk factors (Heilig et al., 2011: 671).

Ethical issues in conducting and translating genetic research on addiction

Like other areas of behavioral genetics, research on addiction touches on sensitive questions about the determinants of human behavior, the balance between freedom and determinism, and the extent and ways in which we share our genetic identity with other members of our family and our broader social community. The research raises ethical issues that fall under two broad categories: the ethical issues that arise in conducting the genetic research on addiction; and the broader social and ethical implications of interpreting the research and translating it into prevention and treatment programs and social policy. The decision of the directors of the Human Genome Project, funded by the National Institutes of Health, to devote 3–5% of their total research budget to ethical, legal, and social issues related to the science attests to the significance of these issues. It is hoped that this volume will contribute to the sensitization of genetics researchers to the ethical requirements of this research and will help to inform policymakers to be cautious in interpreting and applying the research findings.

Ethical issues in human genetic research on addiction

There is an international consensus that biomedical research should conform to a series of foundational ethical principles. Informed consent to protect a subject's right to make an autonomous choice is arguably the most important of these. The informed consent process requires that potential subjects be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; that they understand this information and be able to apply it to their own situation; and also that they make a voluntary and uncoerced decision as to whether to participate in the research (Emanuel et al., 2000). Genetic research on addiction pushes the limits of the protection typically accorded by informed consent when it seeks to obtain consent from addicted individuals, who may have reduced decision-making capacity or competence. Given this concern and the complexity of understanding the implications of genetic research, it is important that genetic research on addiction take special precautions to assess whether the requirements for informed consent can be met.

Concern with vulnerability, understood in terms of the ability to give or withhold informed consent or otherwise be taken advantage of in research, has been central to the development of the Common Rule, the portion of the Code of Federal Regulations that governs much of the human research conducted in the United States. The Common Rule restricts the research that may be conducted on a number of groups – which do not include persons suffering from addiction *per se*, but also notes that others may also be vulnerable. It also requires that research protocols include protections for those who might be vulnerable but does not specify what those should be. In recent years the association of vulnerability with membership in a specific group, such as children or prisoners, has been supplemented or in some cases reconceptualized to apply to the characteristics of individual persons or the factors or conditions that may render individuals vulnerable in a specific research setting (Iltis, 2009). The potential vulnerability of subjects in research on the genetics of addiction suggests the need for appropriate protections to be designed.

Obligations to protect the privacy and confidentiality of the research data collected constitute another ethical challenge for genetic research on addiction. The right to privacy and confidentiality has special salience for genetic research for several reasons. Genetic information may be seen by individuals as central to their personal identities in ways that other medical information is not. This reflects the genetic essentialism conveyed by images and narratives found in popular culture and the media that equates human beings with their genes. Some analysts even suggest that DNA functions in many respects as a secular equivalent of the medieval Christian conception of the immortal soul (Nelkin and Lindee, 1995: 2). In addition, genetic information carries implications not just for individuals but for their families as well. Therefore the release of that information can adversely affect relationships among family members. Also the predictive nature of genetic information has the potential to adversely affect people's lives. For example, it may foster a sense of determinism that causes depression or reduces the inclination to take precautionary measures. Yet another factor is that genetic information has the potential to be used for discriminatory purposes by employers and insurance companies. Like some other areas of behavioral genetics research, a known predisposition to addiction is also likely to be a stigmatizing health condition. Protection of the confidentiality of genetic data is more complex than for other forms of medical information, because genetic data are intrinsically identifiable – that is, traceable back to the individual – and cannot be easily de-identified. The development of genomic databases and biobanks that store large amounts of genetic data and make them available to researchers, although central to the advancement of biomedical research, complicates protection of the confidentiality of research participants.

Ethical issues in translating and applying genetic research

The need to guard against genetic research being misunderstood or misused is underscored by the early history of genetic research. In the first half of the twentieth century human genetics as a program of research was intertwined with the early eugenics movement, which sought to improve the physical, mental, and behavioral qualities of the human race through selective breeding. As a result, belief in the heritability of addiction translated into negative eugenic programs to prevent the reproduction of those persons considered to be genetically defective. This latter category often had more to do with cultural beliefs and prejudices at the time than with scientific findings.

Charles Davenport, the founding director in 1909 of Cold Spring Harbor Laboratory, a facility that played an important role in early genetics research, was also a leading figure in the American eugenics movement. Davenport argued that patterns of human heritability acting through physiological and anatomical mechanisms were evident in a wide range of mental deficiencies. The mental deficiencies he identified and sought to eliminate included alcoholism as well as insanity, epilepsy, pauperism, criminality, and feeblemindedness – a catchall used for a wide range of mental problems (Kevles, 1995: 46). Davenport's interest in fostering the development of good human stock led him to advocate for a selective immigration policy that would deny entry to individuals and families with what he viewed as a poor hereditary history. He also supported the introduction of state-enforced sterilization to prevent the reproduction of the genetically defective (Kevles, 1995: 47).

Several states enacted components of the eugenics movement's program into public policies. In 1907, Indiana became the first state to adopt a law mandating compulsory sterilization of the mentally deficient. Eventually 30 US states passed such laws. Until the

repeal of these laws in the 1960s and 1970s, more than 60 000 sterilizations were performed. Alcoholism was a ground for compulsory sterilization in many of these states (Stern, 2005: 84, 144).

The much reviled Nazi eugenics program was modeled in part on American policies, especially the draconian California law. Going far beyond the American statutes, the Nazi Eugenic Sterilization Law was compulsory with respect to all people, institutionalized or not, who suffered from allegedly hereditary disabilities, including severe drug or alcohol addiction (Kevles, 1995: 116).

Although contemporary state-supported eugenic applications of genetic research on addiction seem unlikely, there are other concerns that should be noted. In a population that is inclined toward assumptions about genetic determinism, there is a need for careful and precise interpretation of the research findings to prevent them from being misunderstood as providing evidence for a direct causal relationship between genes and addiction. It is also important to guard against genetic research on addiction influencing public policy in the direction of supporting simple-minded policies that attempt to identify the minority of the community who are genetically vulnerable to addiction in order to treat them, while neglecting broader and more effective social policy options directed at the whole community to discourage substance and alcohol use and make these substances less available. A related concern expressed in Jonathan Kaplan's chapter (Chapter 14) in this volume is that genetic research into addiction susceptibility might result in an increased focus on the individual as the proper locus of research and less attention to the contribution of the social environment in explaining individual variations in addiction and in developing interventions. Some researchers have also expressed the concern that the development of more effective pharmacological and immunological treatments for addiction might lead to the coerced treatment of addicts, particularly for drug-dependent people who commit criminal offences (Hall et al., 2002: 1486–1467).

Another issue is the appropriate role of investments in genetic research in setting priorities for scarce public resources devoted to addiction disorders. The challenges of applying genetic research to complex disorders, such as addictions, and the limited progress in doing so have led some scientists to question substantial investment in high-cost molecular genomic profiling for this purpose. Arpana Agrawal and Michael Lynskey (2008) recommend focusing addiction research on less-expensive twin studies, especially designs with the power to examine genetic–environmental interaction. Kathleen Merikangas and Neil Risch (2003) propose according priority to a select number of complex diseases that appear to have the strongest genetic contribution, limited ability to modify exposure or risk factors, and high public health impact. They conclude that public health approaches may ultimately lead to far more effective prevention and intervention initiatives than genomics tools. Many public health specialists and policymakers would concur.

Overview of volume

This volume has four sections. The first of these, the introductory section, contains three chapters. The current "Introduction" chapter is followed by the chapter on "The implications of genetic research on alcohol dependence for prevention and treatment" written by Rebecca Mathews, Adrian Carter, and Wayne Hall, which assesses the current status of the evidence on the genetics of AD and its application to treatment programs. The chapter considers the research about susceptibility alleles for AD and its implications for the feasibility of undertaking population-level predictive genetic screening for AD. The chapter also reviews the

potential application of research on pharmacogenetics to improve AD treatment efficacy. Prospective participants in genetic studies of risk for alcohol, drug, or nicotine disorders must decide if the benefits of participation outweigh the risks. Whereas the risks are largely (although not entirely) personal, the benefits are largely not personal, but rather societal in nature, and involve future scientific developments that build on genetics studies as one step in the process toward better prevention and treatment. The third chapter, coauthored by Carl Erik Fisher, Deborah Hasin, and Paul Appelbaum with the title "Promises and risks for participants in studies of genetic risk for alcohol or drug dependence," identifies the trade-offs between these risks and benefits.

Section 2 of the volume, on research ethics, contains seven chapters dealing with human subject protection issues in conducting genetic research on AD and addiction research more generally. Despite the centrality of informed consent to the protection of research participants and the poor levels of consent comprehension and retention reported in the literature, few have empirically examined studies for improving understanding of consent information or reducing perceptions of coercion to inter-research studies, particularly among vulnerable populations, such as substance abusers. David S. Festinger's and Karen L. Dugosh's chapter "Improving the informed consent process in research with substance-abusing participants" addresses these issues. They also examine a number of novel and effective consent strategies that have been developed over the past two decades and evaluate the potential of applying these methods to research with addicted subjects. Using ethical principles, empirical data, and practice guidelines, Thomas McMahon's chapter, "Ethical considerations in genetic research with children affected by parental substance abuse," explores challenges associated with the enrolment of minor asymptomatic children living in high-risk family systems in developmental research designed to clarify genetic risk for chronic addictive disorders that do not typically emerge until sometime during late adolescence or early adulthood. Researchers in many areas of addiction research collect sensitive information about the behavior, health status, and associations of human subjects. Because disclosure of that information could expose research subjects to a variety of harms, maintaining the confidentiality of this sensitive research data is critical to the relationship of trust between research subjects and researchers as well as protecting the subjects. Zita Lazzarini's chapter, "Certificates of Confidentiality: Uses and limitations as protection for genetic research on addiction," describes the scope of protections provided by federal Certificates of Confidentiality, their limitations, and their uses in research on addiction.

One of the most significant recent trends in biomedical research with human subjects is the development of large databases and biobanks to study associations between genetic or genomic variation and diseases. The chapter "Protecting privacy in genetic research on alcohol dependence and other addictions" by Mark A. Rothstein covers two main issues: first, privacy issues raised by large-scale research studies and sources including biobanks, electronic health records, and intervention research with human subjects; and second, the efficacy of different strategies to protect subjects' privacy, particularly when dealing with research on vulnerable populations, such as de-identification, sequestration of sensitive health information, and certificates of confidentiality. This section also contains David B. Resnik's chapter, "Ethical issues in genomic databases in addiction research," which considers additional ethical issues related to genomic databases and biobanks, such as informed consent for the future use of biological samples and data, safeguarding the privacy and confidentiality of human subjects, sharing samples and data, returning study results and incidental findings to individuals, protecting communities and third parties from harm, and intellectual property and benefit sharing.

The rest of this section has two chapters that address the ethical issues in seeking or accepting support for addiction research from industry. Some of the sizable profits generated from the sale of tobacco, alcohol, and gambling are made available in various ways to support research into addiction. Public interest and academic researchers are in a sensitive position relative to such profits, as their research efforts often set out to reduce the harm associated with consumption of these products. Peter J. Adams' chapter "Should addiction researchers accept funding derived from the profits of addictive consumptions?" identifies five of the main risks researchers need to consider and provides indicators of risk to estimate the moral jeopardy faced by addiction researchers in three quite different contexts. Thomas Babor and Katherine Robaina's chapter "Ethical issues related to receiving research funding from the alcohol industry and other commercial interests" evaluates the ethical challenges that have emerged from industry involvement in alcohol science research, including: industry involvement in sponsorship of research funding organizations; direct financing of university-based scientists and centers; efforts to influence public perceptions of research, research findings, and alcohol policies; publication of scientific documents and support of scientific journals; and sponsorship of scientific conferences and presentations at conferences.

Section 3 of the volume has four chapters addressing ethical and policy issues in translating addiction research. The first of these chapters, written by Rebecca Mathews, Wayne Hall, and Adrian Carter, "The public health implications of genetic research on addiction" focuses on the public health policy implications of genetic research on AD. The chapter outlines both the potential benefits of the research in improving public health and the risks that the research may be misused and misinterpreted in ways that harm individual and population health. It also provides an overview of the implications of the research for population-level policies that aim to reduce alcohol consumption, stigmatization, and discrimination against alcohol-dependent persons and individuals at increased genetic risk of developing these disorders, and priorities for research on alcohol as a public policy issue. In the next chapter, "Genetics, addiction, and stigma," Jo C. Phelan and Bruce G. Link explore the implications of genetic research for stigma related to addictions. They first discuss concepts related to stigma and then apply those concepts to the particular case of genetics, addiction, and stigma.

Using data from a 2006 survey of 193 Americans residing in the Midwest, the chapter "Lay beliefs about genetic influences on the development of alcoholism: Implications for prevention," written by Toby Jayaratne, Alicia Giordimaina, and Amy Gaviglio, examines the association between the lay public's genetic explanations for alcoholism and the belief that alcoholism cannot be prevented or controlled. It also discusses the implications of these findings for prevention and treatment of alcoholism. The fourth chapter in this section, by Jonathan M. Kaplan, "Personalizing risk: How behavior genetics research into addiction makes the political personal" addresses the problem that research into the genetic correlates of differences in individual susceptibility to addiction and/or addictive behaviors may tend to shift the focus of both research and policy discussions away from the social determinants of addiction/addictive behavior rates and toward treating addiction as primarily a problem of individual risk, susceptibility, and decisions. It raises the warning that these individual approaches fail to deal with the serious social consequences of addiction and addictive behavior and avoid the difficult but likely far more effective social interventions that are known to have real impacts on addictive behaviors and the harms caused by addiction.

In the concluding chapter, which constitutes Section 4, Jonathan Kaplan, Adrian Carter, and I draw conclusions from the essays in the volume and propose a set of research and policy guidelines.

References

Agrawal, A. and Lynskey, M. T. (2008). Are there genetic influences on addiction: Evidence from family, adoption and twin studies. *Addiction*, 103, 1069–1081.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV). Washington, DC: American Psychiatric Association.

Baker, C. (2004). *Behavioral Genetics*. Washington, DC: American Association for the Advancement of Science.

Buchman, D. Z., Skinner, W., and Illes, J. (2010). Negotiating the relationship between addiction, ethics, and brain science. *AJOB Neuroscience*, 1, 36–45.

Carter, A. and Hall, W. (2007). The social implications of neurobiological explanations of resistible compulsions. *American Journal of Bioethics*, 7, 15–17.

Carter, A., Hall, W., and Copps, B. (2009). What is addiction? In A. Carter, B. Copps, and W. Hall (eds), *Addiction Neurobiology: Ethical and Social Implications*. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction.

Charland, L. C. (2002). Cynthia's dilemma: Consenting to heroin prescription. *American Journal of Bioethics*, 2, 37–41.

Cochrane, T. J. (2007). Brain disease or moral condition? Wrong question. *American Journal of Bioethics*, 7, 24–25.

Emanuel, E. J., Wendler, D., and Grady, C. (2000). What makes clinical research ethical? *JAMA*, 283, 2701–2711.

Foddy, B. and Savulescu, J. (2007). Addiction is not an affliction: Addictive desires are merely pleasure-oriented desires. *American Journal of Bioethics*, 7, 29–32.

Foddy, B. and Savalescu, J. (2010). A liberal account of addiction. *Philosophy, Psychiatry, & Psychology*, 17, 1–22.

Hall, W., Carter, L., and Morley, K. I. (2002). *Ethical Implications of Advances in Neuroscience Research on the Addictions.* NDARC Technical Report No. 143. Sydney, Australia: Office of Public Policy and Ethics, Institute for Molecular Bioscience, University of Queensland and National Drug and Alcohol Research Centre, University of New South Wales.

Heilig, M., Goldman, D., Berrettini, W., and O'Brien, C. P. (2011). Pharmacogenetic approaches to the treatment of alcohol addiction. *Nature Reviews Neuroscience*, 12, 670–684, available at www.nature.com/reviews/neuro [accessed April 10, 2012].

Hyman, S. E. (2007). The neurobiology of addiction: Implications for voluntary control of behavior. *American Journal of Bioethics*, 7, 8–11.

Iltis, A. S. (2009). Introduction: Vulnerability in biomedical research. *Journal of Law, Medicine & Ethics*, 37, 6–11.

Kevles, D. J. (1995). *In the Name of Eugenics: Genetics and the Uses of Human Heredity*. Cambridge, MA: Harvard University Press.

Leshner, A. (1997). Addiction is a brain disease, and it matters. *Science*, 278, 46–47.

Levy, N. (2011). Autonomy, responsibility and the oscillation of preference. In A. Carter, W. Hall, and J. Illes (eds), *Addiction Neuroethics: The Ethics of Addiction Neuroscience Research and Treatment*, London: Elsevier, pp. 139–152.

Merikangas, K. R. and Risch, N. (2003). Genomic priorities and public health. *Science*, 302, 599–601.

Merriam-Webster Dictionary (n.d.) Available online at: www.merriam-webster.com/dictionary/addiction [accessed March 14, 2012].

Morse, S. J. (2007). Voluntary control of behavior and responsibility. *American Journal of Bioethics*, 7, 12–13.

National Bioethics Advisory Commission (1998). *Research Involving Subjects with Mental Disorders that May Affect Decision-making Capacity: Report and Recommendations of the National Bioethics Advisory Commission*. Rockville, MD: National Bioethics Advisory Commission.

Nelkin, D. and Lindee, M. S. (1995). *The DNA Mystique: The Gene as a Cultural Icon*. New York: W.H. Freeman.

Peele, S. (1990). Cures depend on attitude, not programs. *Los Angeles Times*, quoted on The Stanton Peele Addiction Website.

Available online at: www.peele.net/philosophy/ [accessed February 29, 2012].

Peele, S. (2004). The suprising truth about addiction. *Psychology Today* (May–June): 43–46. Available online at: www.psychologytoday.com/articles/200405/the-surprising-truth-about-addiction [accessed February 29, 2012].

Sellman, D. (2009). The 10 most important things known about addiction. *Addiction*, 105, 6–13.

Stern, A. (2005). *Eugenic Nation: Faults and Frontiers of Better Breeding in Modern America*. Berkeley and Los Angeles: University of California Press.

World Health Organization (2004). *Neuroscience of Psychoactive Substance Use and Dependence*. Geneva: World Health Organization.

World Health Organization (2011). *Global Status Report on Alcohol and Health*. Geneva: World Health Organization.

Yaffe, G. (2001). Recent work on addiction and responsible agency. *Philosophy & Public Affairs*, 30, 178–221.

Chapter 2

The implications of genetic research on alcohol dependence for prevention and treatment

Rebecca Mathews, Adrian Carter, and Wayne Hall

Introduction

Alcohol dependence is a disorder that causes significant harm, not only to the health of affected individuals, but also through the significant social and economic costs borne by society. About 4% of the global burden of disease (measured by disability-adjusted life years; DALY) has been attributed to alcohol consumption and 1.6% to alcohol-use disorders specifically (WHO, 2008). In high-income countries such as the United States, alcohol-use disorders cause 3.4% of total disease burden (WHO, 2008).

Alcohol dependence (AD) may manifest in tolerance, withdrawal symptoms, or the use of alcohol to avoid or relieve withdrawal, drinking more than intended, unsuccessful attempts to cut down use, excessive time related to alcohol consumption (including alcohol seeking), impaired social or work activities, and continued use despite physical or psychological consequences. AD may increase a person's risk of other forms of substance abuse, psychiatric disorders, and physical illnesses, such as heart disease and cancers, and lead to unemployment, relationship breakdowns, accidents, and imprisonment due to crimes committed as a result of alcohol abuse.

The existence of a genetic component of AD has long been suggested by the observation that the disorder runs in families. The substantial genetic contribution has subsequently been confirmed by twin and adoption studies that estimate the heritability of AD to range from 50 to 60% (Agrawal and Lynskey, 2008). Approximately 56% of the variance in AD is caused by genetic factors, whereas 44% is as a result of specific environmental factors not shared by family members, including peer influences and experiences after leaving the home environment (Kendler and Prescott, 2006). Shared environmental factors such as social class, parental rearing styles, familial attitudes to drinking, parental drinking practices, and – in the case of twins – intrauterine environment, make little contribution to AD itself (Kendler and Prescott, 2006) but explain about 15% of the variance in initiation of alcohol use (Sartor et al., 2009).

Recent genetic research has identified a number of genetic variants thought to be involved in the development and persistence of AD. Researchers and clinicians hope that these discoveries will lead to reductions in the harms caused by alcohol, including in the numbers of people developing dependence, as well as more effective treatments of AD.

Advancements in genetic technology arising from the mapping of the human genome have reduced the costs of genome-wide scans and heralded optimistic predictions about the potential use of genetic information to personalize medicine and improve health (Collins

Genetic Research on Addiction, ed. Audrey R. Chapman. Published by Cambridge University Press.

et al., 2003). Proponents of this personalized genomic medicine have proposed that genetic research could be used preventively in the form of predictive genetic screening to identify healthy persons at a greater risk of developing AD and prevent them from doing so. It could also be used therapeutically through pharmacogenetic approaches to allow clinicians to better match alcohol-dependent individuals to more effective treatments. Given the significant challenges in effectively intervening to help persons with AD and in reducing harmful alcohol consumption, such proposals have great appeal.

Despite over a decade of research on the genetic basis of complex disorders, these optimistic predictions have yet to be realized (Williams, 2010). Although genetic research for some pseudo-Mendelian disorders has yielded clinically relevant genetic tests (e.g., for the neurodegenerative Canavan disease), for complex diseases such as diabetes, obesity, AD, and other mental illnesses that are shaped by multiple biological, social, and cultural factors, such reasearch has been less fruitful.

This chapter reviews the current evidence regarding the genetics of AD. It then assesses the feasibility of clinical applications arising from this research, such as predictive genetic screening for AD and pharmacogenetics for AD treatment.

Candidate genes for alcohol dependence: A summary

Candidate genes for AD have been identified primarily via linkage studies and genome-wide association studies (GWAS). Linkage studies examine the inheritance of a disorder through family members or pedigrees to try to identify coinheritance between a genetic marker and the disorder of interest. Typically, when linkage is found, it implicates a gene in a broader chromosomal region around the genetic marker in the development of the disorder. Linkage mapping projects, in particular the Collaborative Study on the Genetics of Alcoholism (COGA), have identified promising chromosomal regions for AD susceptibility loci, some of which have led to the identification of disease-influencing loci (Edenberg, 2002; Edenberg and Foroud, 2006). Linkage studies are best suited to conditions for which genes have a major effect on disease risk and typically identify large chromosomal regions that may be implicated in the development of a disorder (Ball, 2008). As we shall illustrate later in this chapter, the genes contributing to alcoholism do not appear to meet these criteria.

GWAS typically examine the differences in the distribution of a genetic variant in a sample of unrelated persons affected with a disorder compared to matched controls. These studies examine variants across the entire human genome and are designed to analyze whether certain alleles (alternative forms) of a gene are associated with a disease, trait, or symptom. Unlike linkage studies, association studies have the potential to identify genes of smaller effect sizes. However, false positives are common in association studies (Ball, 2008). See Buckland (2001) for an analysis of the impact of false positives on association studies investigating the genetics of AD.

Candidate gene association studies examine genetic markers in genes whose functions are related to the pathophysiology of the disease or genes that lie in a chromosomal region linked to disease through linkage studies. Candidate gene studies have identified multiple susceptibility alleles for AD that are only weakly predictive of disease liability. This suggests that AD is a polygenic disorder in which multiple genes of weak individual effect size predict disease risk, rather than a quasi-Mendelian disorder in which a small number of genes predict risk. Two broad groups of susceptibility alleles have been identified: (1) those that impact on alcohol metabolism; and (2) those that impact on the rewarding, reinforcing, and

other cognitive effects of alcohol (e.g., impact on learning and memory) by regulating the activity of various neurotransmitter systems of the brain.

In the next section we highlight the genetic variants that have been most reliably associated with AD to illustrate the challenges in understanding and applying genetic research on dependence on alcohol. We do not provide an exhaustive review of all potential genetic variants associated with AD, as this is beyond the scope of this chapter, and comprehensive reviews of this already exist (see Kohnke, 2008; Gelernter and Kranzler, 2009; Kalsi et al., 2009).

Genes that impact on alcohol metabolism

Genes that regulate alcohol metabolism are the most significantly and reliably associated with alcohol dependence (Ball, 2008; Kohnke, 2008; Gelernter and Kranzler, 2009). These include genes that influence the enzymatic activity of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). ADH converts ethanol to the toxin acetaldehyde, which is further broken down into acetate by ALDH. Seven genes encoding ADH isoforms have been identified (*ADH1–7*) and two encoding ALDH (*ALDH1A1* and *ALDH2*) (Edenberg, 2007).

Alleles that increase ADH or decrease ALDH activity cause an accumulation of acetaldehyde in the body. Acetaldehyde produces unpleasant facial flushing, sweating, and mild headaches. In more severe cases, it can result in cardiovascular collapse, arrhythmias, unconsciousness, and convulsions. These aversive symptoms reduce alcohol consumption and protect against developing AD.

Three alleles that encode high-activity ADH enzymes, *ADH1B*2*, *ADH1B*3*, and *ADH1C*1*, are thought to protect against AD: individuals carrying these alleles are likely to have higher levels of acetaldehyde (Chen et al., 1999; Osier et al., 1999; Choi et al., 2005). *ADH1B*2* and *ADH1B*3* are thought to alter the enzymatic activity of ADH by more than 30-fold (Bosron et al., 1983), and both have been shown to protect against alcohol-related birth defects and fetal alcohol syndrome (McCarver et al., 1997; Viljoen et al., 2001; Warren and Li, 2005). A meta-analysis found that one copy of *ADH1B*2* reduced AD risk fourfold, whereas two copies reduced risk fivefold (Luczak et al., 2006; Eng et al., 2007). Because *ADH1C*1* is in linkage disequilibrium with *ADH1B*2* and thus is usually coinherited with it, it remains unclear whether it exerts a protective effect independently of *ADH1B*2* (Chen et al., 1999; Osier et al., 1999; Choi et al., 2005).

The prevalence of these alleles varies by ethnicity. *ADH1B*2* is common in East Asian populations (around 60% prevalence) (Crabb et al., 2004), shows moderate frequency in Jewish populations (Neumark et al., 1998), and is associated with a lower risk of alcoholism in both (Hasin et al., 2002; Luczak et al., 2002; Luczak et al., 2006). *ADH1B*3* is common in African Americans (over 15% prevalence), in whom it has been shown to have protective effects against alcoholism (Edenberg and Foroud, 2006). Protective effects of *ADH1B*3* have also been reported in Native American populations (Wall et al., 2003). Both *ADH1B*2* and *ADH1B*3* are rare in Caucasians and have lower protective effects in them than in Asian and African populations, respectively (Whitfield, 2002). *ADH1C*1* is very common in Han Chinese populations (about 90% prevalence) and is prevalent in about 55 to 60% of Caucasians (Osier et al., 1999).

Variants in the *ALDH1A1* and *ALDH2* genes (*ALDH1A1*2*, *ALDH1A1*3*, and *ALDH2*2*), have also been shown to protect against alcoholism (Thomasson et al., 1991; Chen et al., 1999; Ehlers et al., 2004b; Luczak et al., 2006). However, the protective effects of *ALDH2*2* are the strongest and most well replicated. Low ALDH2 activity prevents the conversion of toxic acetaldehyde to acetate. Persons with two copies of *ALDH2*2* (homozygotes) produce

an inactive ALDH enzyme and are thought to have a ten times lower risk of AD, although such homozygotes are rare (Luczak et al., 2006). Persons with only one copy (heterozygotes) retain between 30 and 50% enzyme activity, which confers a fivefold reduction in risk of AD (Luczak et al., 2006). *ALDH2*2* is common in East Asians (as high as 30% prevalence) (Oota et al., 2004) but virtually non-existent in Caucasian and African populations. It is particularly protective against AD in Han Chinese, who also possess the *ADH1B*2* allele (Chen et al., 1999). Both *ALDH1A1*2* and *ALDH1A1*3* have been shown to protect against AD in African Americans (Spence et al., 2003). *ALDH1A1*2* also has protective effects in Native Americans (Ehlers et al., 2004a).

Genes that code for lower activity variants of ADH (e.g., *ADH4*, *ADH5*, *ADH6*, and *ADH7*) increase the risk of AD because they result in lower levels of the aversive acetaldehyde. Twelve single nucleotide polymorphisms (SNP) associated with the *ADH4* gene have been correlated with a greater risk for AD in European Americans (Edenberg and Foroud, 2006). Variants in *ADH4* have also been shown to be associated with AD in Brazilian populations (Guindalini et al., 2005), and in case–control studies of European American and African American families (Luo et al., 2005), as well as in European American families only (Luo et al., 2006).

Genes that influence neurotransmission

Several neurotransmitter systems have been implicated in AD including the dopaminergic, opioidergic, GABAergic, serotonergic, cholinergic, and glutamatergic systems (Heinz et al., 2009). These neurotransmitter signaling systems are central to neural circuits for a range of cognitions and behaviors involved in AD, such as reward and reinforcement, learning and memory, emotion and affect regulation, stress, impulse inhibition, and executive control (Koob and Le Moal, 2006). The neural circuits responsible for these cognitive behaviors are referred to as the mesolimbic reward pathway. A full discussion about the neuropsychology of AD is beyond the scope of this report. See Heilig et al. (2010) for a more detailed review.

A number of candidate genes have been identified that are thought to increase AD liability through their influence on these neurotransmitter systems. However, our understanding of the actual physiological mechanisms through which genetic variants in neurotransmission increase liability is much more limited than our understanding of genetic impacts on alcohol metabolism. Also, little is known about how these different neurotransmitter systems interact in causing dependence on alcohol (Heinz et al., 2009).

The gamma-aminobutyric acid system: GABRA2

Gamma-aminobutyric acid (GABA) is the brain's main inhibitory neurotransmitter whose activity is mediated by a family of two receptors (GABA-A and GABA-B). Alcohol is believed to activate the GABAergic system, inhibiting the activity of related neural circuits. Recent reviews (Gelernter and Kranzler, 2009) have confirmed *GABRA2* as a risk locus for AD. *GABRA2* is a gene that encodes for the alpha-2 subunit of the GABA-A receptor (the GABA-A receptor consists of five subunits in total). GABA-A mediates several important effects of alcohol, including sedation, anxiolysis, impairment of motor coordination, and withdrawal symptoms (Soyka and Rosner, 2008). The association between AD and *GABRA2* has been replicated with three different populations (Covault et al., 2008; Enoch et al., 2009; Gelernter and Kranzler, 2009). *GABRA2* has also been associated with subjective response to alcohol in healthy controls (Pierucci-Lagha et al., 2005). No specific causal (i.e., functional) variant in *GABRA2* has been identified, nor is a precise mechanism of action known (Gelernter

and Kranzler, 2009). Given this, it is difficult to know how prevalent the association between *GABRA2* and AD is. It is also possible that associations between *GABRA2* and AD are in part driven by variants in *GABRG1*, an adjacent location on the gene that codes for the GABA-A gamma subunit receptor that has also been repeatedly associated with AD, and has been shown to be in linkage disequilibrium with *GABRA2* (Gelernter and Kranzler, 2009).

The dopaminergic system: The Taq1A polymorphism of DRD2

It is well known that consumption of alcohol activates dopamine receptors in the brain, stimulating the release of dopamine. This causes rewarding effects, leading to craving for alcohol and alcohol-seeking behavior (Heinz et al., 2009). Consequently, changes in the activity of dopamine receptors, particularly dopamine 1 and dopamine 2 receptors, are thought to increase the reward caused by alcohol and its resultant desirability (Kohnke, 2008), and have therefore been implicated in AD.

Variants in *DRD2*, the gene encoding the dopamine 2 receptor, have been the most extensively studied in AD (Le Foll et al., 2009). However, their role in AD is still controversial because of conflicting findings and nonreplication of associations. The Taq1A polymorphism of *DRD2* has been most consistently linked to AD, with meta-analyses showing that persons with the allele are 1.3 times more likely to have AD than those without (Munafò et al., 2007b; Smith et al., 2008). Recent evidence suggests Taq1A may not directly map onto *DRD2* but rather an adjacent gene (*ANKK1*) (Gelernter and Kranzler, 2009), leading researchers to question whether Taq1A directly impacts on AD risk or is a marker of a region of multiple co-located alleles involved in AD risk. Meta-analyses of the association between the A1 allele of Taq1A and AD revealed publication bias may have influenced initial optimism about the links (Munafò et al., 2007b). It also showed that the significance of the association varied for different population groups.

The opioid system: OPRM1

Intake of alcohol also stimulates the endogenous opioid system in the brain through activating various opioid receptors, including the mu opioid receptor. This is thought to release endorphins, which indirectly activate the dopaminergic reward system (Kohnke, 2008) leading to feelings of euphoria, analgesia, and withdrawal associated with alcohol use (Bond et al., 1998; Gianoulakis, 2001). Consequently, individual differences in the activity of the mu opioid receptor have been associated with the rewarding effects and desirability of alcohol and therefore AD liability.

Evidence suggests that differences in the activity of the mu opioid receptor may be genetically mediated. Specifically, genetic variants in *OPRM1* (the gene that encodes the mu opioid receptor) have been linked to AD, but their role is unclear because some studies have shown variants to be more prevalent in alcoholics (Kohnke, 2008), whereas others have shown the opposite (Szeto et al., 2001; Kim et al., 2004) or no association at all (van der Zwaluw et al., 2007).

More robust evidence exists for the association between variants in *OPRM1* and differential responses to opioid antagonist treatments (namely naltrexone) for AD (e.g., Anton et al., 2008). However, cases of nonreplication of this association have been reported (Gelernter et al., 2007). We discuss its impacts on treatment response in more detail in the section on clinical applications of genetic research.

Many other genes linked with AD risk include, but are not limited to, *CHRM2* (the gene that encodes the muscarinic acetylcholine receptor in the brain), variants of the *NMDAR*

(glutamatergic N-methyl-D-aspartate receptor) gene, variants in the promoter region of the serotonin transporter gene (*SLC6A4*), as well as genes encoding dopamine-metabolizing enzymes [dopamine beta hydroxylase (DBH); catechol-*O*-methyltransferase (COMT) and monoamine oxidase A (MAOA)] and variants in genes encoding the dopamine transporter (DAT). However, the evidence regarding these associations is unclear because of conflicting results and nonreplications.

The serotonergic system: 5-HTTLPR

The serotonin, or 5-HT, transporter (5-HTT) regulates the reuptake of serotonin following synaptic release. The presence of long versus short alleles in the promoter region (*5-HTTLPR*) of the gene *SLC6A4*, which encodes 5-HTT, has been linked with compulsive craving (e.g., Heinz et al., 2004; Huang, 2010) and relapse (e.g., Pinto et al., 2008) in AD. However, some attempts to replicate these associations have failed (e.g., Kohnke et al., 2006) and gene–environment interactions have also been implicated in association with the *5-HTTLPR* genetic variation in alcohol use (e.g., Nilsson et al., 2005). To try to resolve these inconsistencies, McHugh et al. (2010) recently conducted a meta-analysis of the association between having a clinical diagnosis of AD and variants in the *5-HTTLPR* allele. They found that of the 22 case–control studies examined, 15 showed a significant association between the presence of a short allele in the *5-HTTLPR* gene and having a clinical diagnosis of AD. The results were consistent across age and cultural groups. However, analyses indicated that the results were moderated by sample size and publication bias, suggesting that they must be interpreted with caution (Feinn et al., 2005; McHugh et al., 2010).

Endophenotypes

In attempting to tie together these explanations of genetic mechanisms of alcohol metabolism and neurotransmission, researchers have argued that the alleles that influence susceptibility to alcoholism do so through individuals' subjective responses to the pharmacological and neurobiological effects of alcohol (Ray et al., 2010). These subjective responses are one example of an intermediate behavioral manifestation of alcoholism that is genetically mediated, commonly referred to as an "endophenotype." Subjective response to alcohol has been shown to be heritable (e.g., 60% heritability in twin studies; Viken et al., 2003) and affected by family history of alcoholism (Conrod et al., 1997). This supports its classification as an endophenotype. Genetic variations in an individual's stress response system caused by exposure to different substances (e.g., alcohol, opioids, nicotine, etc.) is another example of an endophenotype that is thought to be linked to an individual's susceptibility to various addictive behaviors (Zhou et al., 2010).

Examining endophenotypes can help to increase the power to detect genes implicated in risk of AD (e.g., Ray et al., 2010). They can also be useful in the prevention and treatment of alcoholism. In secondary prevention, they can be used as a marker of alcoholism risk and improve detection and subsequent prevention efforts. In treatment, they can be used as targets of pharmacological and psychological interventions such that measurable changes in the endophenotype indicate a positive treatment response.

Challenges in establishing a genetic basis for AD

The susceptibility alleles for AD identified to date account for only a fraction of the heritability estimated from twin and adoption studies. Identifying alleles that reliably predict AD

liability is challenging for a number of reasons. First, with the exception of genetic variants related to ADH and ALDH activity, the AD-associated alleles identified to date only weakly predict risk of AD, have not been well replicated, and, for some markers, are of low prevalence in the population. ADH and ALDH variants that protect against AD are highly prevalent, particularly in Asian populations, but those that increase risk of AD are less prevalent in other racial groups, with estimates of their frequency in the COGA sample of Caucasians ranging from 8 to 30% (Edenberg, 2007).

Second, for non-Mendelian disorders such as AD, many alleles will only result in disease when combined with certain environmental factors or other genes, irrespective of the effect size and population prevalence of these alleles. For instance, polymorphisms in the promoter region of the serotonin transporter gene, i.e., *5-HTTLPR*, have been associated with increased alcohol use in the presence of maltreatment (Rose and Dick, 2005), poor family relations (Nilsson et al., 2005), and multiple negative life events (Covault et al., 2007). Similarly, the promoter region of the *MAOA* gene has also been shown to interact with maltreatment, quality of family relations, and child sexual abuse in predicting alcoholism (Nilsson et al., 2007; Ducci et al., 2008). Both the A1 allele of the Taq1A polymorphism and variants in the CRF (corticotropin releasing factor 1) gene have also been linked to AD when combined with stressful life events (Clarke and Schumann, 2009; van der Zwaluw and Engels, 2009).

Because gene–environment interaction studies vary significantly in the measures, methods, and sample sizes used, it is difficult to draw clear conclusions or to replicate them. Indeed, most of the gene–environment interactions mentioned above have not been replicated. Also, because most gene–environment studies use small samples, some have questioned whether their findings are anything more than false positives (Flint and Munafò, 2008). Consequently, a degree of caution is needed in interpreting evidence from gene–environment interaction studies, including those pertaining to AD.

Third, genetic research on AD is revealing that multiple alleles, either from the same group or different groups of genes, predict disease risk via their interactions with other alleles. Associations between a low-activity variant of *ADH1C*1* and reduced AD risk have been attributed to its interactions with *ADH1B*1* (Kohnke, 2008). More recently, interactions between serotonin-related genes and *ADH* genes (Huang, 2010), and *MAOA* and *ALDH2*, have also been implicated in liability for AD (Lee et al., 2010). The number and complexity of gene–gene and gene–environment interactions involved in AD would be a major obstacle to the reliability and validity of predictive screening for susceptibility genes.

Fourth, advances in epigenetics may potentially complicate our understanding of the genetics of AD and the relative predictive strength of any genetic variations. Epigenetic mechanisms are cellular processes that integrate diverse environmental stimuli to modulate gene expression through the regulation of the chromatin structure (Renthal and Nestler, 2008). In more simple terms, they cause changes to gene expression without changing the underlying sequence of nucleotides that comprises DNA. Epigenetic modifications may mean that carrying a particular allele that confers disease risk does not necessarily translate to expression of that allele exemplified in manifestation of disease symptoms.

Alcohol is one environmental stimulus that could cause epigenetic modifications that modulate or even silence the expression of certain genes. Epigenetic modifications may be transferred from the carrier to their offspring, such as in cases of exposure to alcohol *in utero* (Kaminen-Ahola et al., 2010). A recent study found chromatin remodeling could be a plausible mechanism for AD itself (Pandey et al., 2008). To date such epigenetic research has