Advances in Behavior Genetics
Series Editor: Yong-Kyu Kim

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Animal Models of Behavior Genetics

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This book is dedicated to the memory of Irving Gottesman, who epitomized the endophenotypes of kindness and wisdom.

Preface

When the editors of this book were in graduate school in the early 1990s studying the biological basis of behavior in rats (JCG) and *Drosophila* (YKK), the availability of new approaches in molecular biology and genetics brought about a near-exponential growth in our capacity to explore the nervous system of invertebrate and vertebrate species. And it was around that time that a new form of an old word entered the lexicon of behavioral neuroscience: the noun, "phenotype," had transformed itself into a verb. Whereas "genotyping" means to identify the sequence of nucleotides in DNA, "phenotyping" came to refer to the task of identifying the structural, physiological, and behavioral consequences of genotypic variations. To these ends, new facilities were built with the express purpose of characterizing the behavior of genetically altered mice. These developments reflected recognition among geneticists and neurobiologists that behavior was an important endpoint of genotypic variation and even among some scientists that characterizing behavioral differences was a *sine qua non* for establishing the functional significance of a given genotype.

The expectation of many in the field was that this part of the scientific enterprise would be relatively straightforward. "Give the animal to the behavioral experts to run through their behavioral battery," ran the thinking, "and we will have our phenotype." In reality, however, discovery of the behavioral corollaries of genotypic variations frequently trailed the rapid pace of discovery of intracellular or morphological intermediaries within the CNS.

At least two problems stood in the way of the success of this enterprise. The first was that the process of discovery was all too often unidirectional, with genetics as the driver and behavior as a destination. An approach in which genetic, molecular, physiological, anatomical, and behavioral analyses are all mutually informative leads us in directions that are more interesting and better suited to the ultimate goal of understanding the bidirectional chains of causality between genes and behavior.

A second, not unrelated, obstacle was the way in which behavioral assays were seen as little more than diagnostic devices. "Phenotyping" was frequently reduced to a pattern of gains or losses of function among a set of standardized tests. The limitations of a "checklist" approach are obvious to anyone who has dedicated

much time to understanding a single behavioral domain, such as those covered in this book. There is, for a start, a tendency to label behavioral profiles derived from these checklists with terminology taken straight from the realm of clinical psychopathology. This is despite the fact that the nosology of psychiatric disorders is plagued by issues, such as comorbidity among, and heterogeneity within, diagnostic categories (Helzer et al., 2009). If there can be so little agreement among clinicians as to how to diagnose psychiatric illnesses, what hope is there for the success of a similar approach in animal models?

The checklist approach also encourages the tendency to overdiagnose. The writer Jerome K. Jerome (1889) concluded after running through each letter of a medical encyclopedia that he suffered from every ailment listed except housemaid's knee. Now enter the behavioral experimenter, who runs each animal through an array of tests, each bearing an embarrassment of potential outcome measures. It is all too tempting under such circumstances for one to become a hypochondriac by proxy, taking a significant aberration in a single test as confirming a hypothesis that an animal of a given genotype suffers from an "anxiety-like" or some-other-psychiatric-disorder-like phenotype.

How can such pitfalls be avoided and the field be advanced? The purpose of this volume is to aid in answering these two questions. In common to all the chapters in this book is a focus on establishing reliable behavioral measures in animal models for identifying the functional consequences of genotypic variations. Some of the chapters highlight issues that are pertinent to the development of animal models in behavioral genetics in general. These include consideration of possible pleiotropic effects of genes on multiple behavioral domains, the sometimes-insidious influence of genetic background on mouse behavior, and the significance of the environment in which the animals are routinely housed while they await behavioral testing. Other chapters evaluate specific behavioral tests and how their results should be interpreted in light of differences observed in animals with different genetic characteristics. Finally, a number of the chapters apply this knowledge to summarize our best, current understanding of the genetics of specific domains of mentation and mental illness.

A compelling case has been made by our colleagues in human behavioral genetics that core variables undergirding mental illnesses should be viewed as falling on continua from normal and adaptive to abnormal and maladaptive. Of course, much of the usefulness of this approach depends on adequately characterizing the most important continua along which these diagnoses fall (see, e.g., Chap. 8 on the "endophenotype" concept). With this in mind, it may seem contradictory that we have divided the book into sections focusing on animal models of adaptive or "normal" behavior and maladaptive or "abnormal" behavior. This division reflects the fact that, in determining genetic influences on behavior, some models are relatively more focused on understanding normative behavior. One example of this approach is to study variations in naturally occurring behaviors across the genotypic spectrum of healthy, outbred rats (see Chap. 3). Other models are focused on phenomena at the dysfunctional ends of the behavioral spectrum, such as compulsive drug-taking behavior. Since the overarching goal of all of us is to understand the effects of genes

on a given psychological or behavioral construct along the entire continuum, this division is recognized to be somewhat arbitrary. Nevertheless, we think it is a helpful organizational principle when setting out to describe, analyze, and summarize the field of animal behavioral genetics.

Part I of this volume covers animal models of behavioral genetics across a range of domains. Chapters 1 and 2 review our understanding of the genetics of the two closely associated domains of mating and aggressive behavior in *Drosophila*. It is appropriate that the book should begin with a look at fly behavior since this has been a formative and—for want of a better word—fruitful model species in the field of behavioral genetics for several decades. Above all, these chapters demonstrate the advantage of invertebrate models in being able to locate causal mechanisms—whereby genes affect neural substrates that affect behavior—with an extraordinary degree of specificity. Chapter 3 reviews the literature on the behavioral genetics of the trait of "impulsivity." It highlights translational research on genetic determinants of this trait in rodents and humans. In Chap. 4, the authors review the extensive literature on genetic influences on attachment and pair bonding, primarily from a developmental perspective. Much of the work reviewed utilizes the prairie vole, a microtine rodent that is especially suitable for study owing to its unusually monogamous lifestyle. Overall, therefore, the chapters of this section exemplify how, for modeling purposes, finding the most suitable animal model critically depends on matching the questions one is asking with the particular neurobiological and behavioral attributes of a given species.

Part II of this volume is concerned with animal models of cognition and cognitive decline. Chapter 5 assesses the relative merits of a broad array of approaches for modeling the genetics of intellectual disability. These range from studying behavior in different species of mammals to comparing morphological and molecular changes within homologous brain structures across more phylogenetically distant species. The usefulness of a given model for understanding clinical cases of intellectual disability is evaluated by the extent to which it fulfills a given set of criteria—criteria, indeed, that could be applied equally well to other domains of mental processes and mental illness. The following two chapters address animal models of highly genetically penetrant neurodegenerative diseases and Alzheimer's disease in particular. Chapter 6 provides an overview of the range of genes involved in producing different biomarkers of Alzheimer's disease and the relationship of these to cognitive deficits. Chapter 7 focuses on mouse models that have harbored mutations in ApoE genes, the family of genes perhaps most strongly implicated in the cognitive deficits associated with the later stages of this disease.

Part III dips into the genetics of neurodevelopmental and psychopathological conditions, as they have been characterized using animal models. The first two chapters in this section both address animal models of social interaction and how these can inform as to the genetics of autism spectrum disorders. Chapter 8 applies the "endophenotype" concept, which has been increasingly influential in the field of human behavioral genetics, to animal models of social interaction. Chapter 9 assesses how genetic variations affect key indicators of sociability in rodents, such as communication, imitation, and empathy. Importantly, this chapter highlights how

genetic effects on expression of these behaviors can be moderated by the qualities of the environment in which the animals are housed.

Chapter 10 reviews the extensive and informative use of inbred and selective bred lines of rats to ascertain the nature of individual differences in vulnerability to compulsive drug taking. Chapter 11 establishes appropriate parameters for studying the phenomenon of "fear-potentiated startle" in mice as a means toward the clearer characterization of the genetics of fear and anxiety. As researchers in the fields of both drug addiction and affective disorders are aware, translating behavioral paradigms successfully from rats to mice is challenging. But overcoming the challenges can clearly be beneficial, given the greater accessibility of the mouse genome to experimental manipulation.

The final chapter considers future directions for animal models of behavioral genetics. Much of how the field is going to progress over the next 10 years will be consequent to advances in the technologies available for manipulating genes. As described in Chap. 12, these techniques are rapidly improving in terms of their spatial, temporal, and molecular specificity. If there is not one already, there ought to be an axiom in behavioral genetics much like Moore's law in the field of computing, which predicts the phenomenal rate of advancement of molecular genetic technologies. Chapter 12 concludes by reiterating our theme that instead of focusing on clinical syndromes, these new technologies should be harnessed to establish the genetic determinants of core factors that underlie different manifestations of normal and abnormal behavior.

The study of behavioral genetics in animal models has come a long way since the concept of "behavioral phenotyping" first emerged. It is to be hoped that the guiding principles embedded throughout this book, together with the burgeoning of new technologies, will help accelerate our accumulation of knowledge as to how specific nucleotide sequences influence adaptive and maladaptive behavior.

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Part I
Animal Models of Normative Behavior

Chapter 1
Male Fruit Fly's Courtship and Its Double Control by the *Fruitless* and *Doublesex* Genes

Daisuke Yamamoto

Introduction

Since Morgan (1910), *Drosophila melanogaster* has been one of the most favored animal models in genetics, a field that has experienced, by now, several rounds of renovations and revolutions in techniques and conceptual frameworks. Its small genome size (compiled in large chromosomes, 1–3, and a very small chromosome 4) with a minimum redundancy in functional genes (total *ca*. 15,000 genes) makes genetic analysis easier and simpler (Adams et al. 2000), offering opportunities to explore the molecular and cellular bases of complex higher biological functions, including the behavior and underlying neural mechanisms. The existence of numerous mutants and other genetic rearrangements together with balancer chromosomes that suppress recombination between the homologous chromosomes is the firm basis for the classic genetic approach in *Drosophila*. The germ line transformation achieved by introducing an engineered DNA construct into the fly genome is now a routine task, and several companies currently perform this service on a commercial basis. New analytical technologies specialized for *Drosophila* genetics come up every year, making this organism even more attractive for a wide range of biological research.

Drosophila displays a vast spectrum of behaviors, some of which are instinctive and others of which are learned. One of the most successful genetic analyses of the instinctive behavior in *Drosophila* stems from isolation of the circadian rhythm mutants *period*^{S} (*per*^{S}), *per*^{l} and *per*^{0} (Konopka and Benzer 1971), which stimulated an impressive expansion of circadian clock research and led to the

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discovery of the conserved molecular mechanism for biological timing. The genetic studies on learning in *Drosophila* were initiated by the isolation of a mutant in a cAMP phosphodiesterase-coding locus, *dunce* (*dnc*; Dudai et al. 1976), which demonstrated the involvement of the cAMP-CREB pathway in learning and memory, and reinforced the hypothesis that cAMP-mediated synaptic enhancement is the key for classical conditioning, a notion derived from physiological studies in *Aplysia* (Kandel 1976). These two divergent streams of the genetic basis of behavior in *Drosophila* have further enhanced the status of this organism as a model for the study of complex functions relevant to those in higher organisms, including humans, and prompted us to apply this neurogenetic approach in deciphering the neural basis for other behaviors.

The progress in studies on mating behavior is particularly intriguing; the principle of decision-making, the prime integral function of the brain, is now emerging from the neurogenetic study of mating behavior in *Drosophila* (Yamamoto and Koganezawa 2013). In this chapter, such cutting edge research results will be reviewed, together with a historical overview of critical experiments that led to the recent explosion of neurogenetic researches on *Drosophila* mating behavior.

Current Research

The Field of Mating Research Began with Fruitless

In 1963, Gill reported in a scientific meeting a male-sterile mutant he named *fruity* (*fru*; later, the name was changed to *fruitless* by Hall and the original allele isolated by Gill was designated fru^1), the males of which vigorously courted both males and females but copulated with neither (Gill 1963). Gill wanted to isolate mutants with defects in gametogenesis, so for him, fru^1 was just a side product and consequently this mutant was not further characterized for an additional 15 years, when Hall finally published the first paper on fru^1 (Hall 1978). Hall (1978) quantified the male preference of fru^1 mutant males in courtship and observed that, when placed together, these males court each other by forming a suitors' chain, now known as the "courtship chain" (Fig. 1.1). He also noted that even wild-type males court fru^1 mutant males although they usually do not court other males (Hall 1978). This indicates that fru^1 males have two distinct phenotypes: courting other males (the courting male phenotype) and being courted by other males (the courted-by-male phenotype). Gailey and Hall (1989) mapped cytologically the courted-by-male phenotype to 90C and the courting male phenotype to 91B, at which two break points of an inversion associated with the *fru* mutation are located, respectively. Therefore, the courted-by-male phenotype and the courting male phenotype are induced by mutations at two independent loci. The courting male phenotype mapped at 91B corresponds to the *fru* locus in