PREFACE TO THE THIRD EDITION

As with the previous editions, the goal of this book is to describe the logic of genetic analysis as it applies in an era when genome sequences have become a standard research tool. The advances in genetic analysis over the three editions of this book are remarkable. The first edition appeared when sequencing genomes was becoming widespread; the second edition included much more information gained from the annotations of these genomes. With the third edition, our ability to make targeted changes—that is, to edit the genome—has emerged as the newest powerful tool in genetic analysis. But everything we learn from these new methods should be interpreted in light of what was known previously from work in classical genetics and molecular biology. As recounted in the book, the mantra of genetic analysis for decades has been: "Find a mutant!" In the current age, genome editing has modified this to "Make the mutant that you want!" But the same analytical principles apply no matter what methods have been used to connect mutant phenotypes with molecular changes. Geneticists worked successfully and intelligently for many years on many different biological questions before it became possible to find the DNA sequence of even a single gene, let alone an entire genome, and certainly before it was possible to make targeted edits to the genome. The new information and experimental methods do not replace this previous work, but rather add a rich dimension to it. That richness is what I hope to have captured in this book.

Course suitability

I have taught a course entitled "Advanced Genetic Analysis" for undergraduates at Haverford College for almost twenty-five years. These students have taken an introductory course in basic genetics and molecular biology and have a general familiarity with biochemistry and cell biology as well. The book is based on that course, so it is written with that level of preparation in mind. Although the structure is designed for one semester, this book covers far more topics than I include in my course. Even with that, I am keenly aware of the many topics that I have had to omit to keep the book to a manageable length and within my own areas of knowledge.

I have retained a focus on five model organisms, *Saccharomyces cerevisiae*, *Arabidopsis thaliana*, *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Mus musculus*, with occasional references or examples drawn from other well-studied model organisms or from humans; in this edition, Chapter 5, about identifying the DNA sequence affecting a variant phenotype, is now largely focused on human genetics. For those who work on a different model organism and feel slighted that I have not included, for example, fission yeast or zebrafish, I sincerely apologize for not including more about these organisms. I tend to be syncretic, so I would like to have the ability and the space to talk about many more model organisms than I do. In fact my mid-term exam for the past several years has consisted in provide students with

a recent paper about the genome of an organism, such as an octopus, a sea horse, a gar, a sponge, an acorn worm, or some other organism that has not been widely used for genetic analysis and that we have not discussed in class. I would then ask them to apply what they have learned from our analysis of model organisms to these completely different species. Since, in Charles Darwin's famous words, "[t]here is grandeur in this view of life," genome analysis is a type of art appreciation for biologists.

Organization and changes in the third edition

While the overall approach to the topics is similar to that of the previous editions, the organization has been changed substantially. Some topics that were included in the second edition, in particular about natural variation, are no longer included; many of these topics were moved, with revision, into the introductory genetics book that I have co-authored. At the suggestion of reviewers, some topics useful for thinking about mutant phenotypes were reintroduced; some of this was included in the first edition but not in the second, so these are now re-examined with a different focus, made possible in the age of genome editing. All of the chapters and every figure have been reviewed and revised, even if these revisions may not always be apparent. There are now twelve chapters in three units.

The first unit, "Genes, Genomes, and Organisms," retains a historical overview of genetic principles in Chapter 1. Much of this information will have been covered more thoroughly in an introductory genetics course, although probably with a different emphasis or synthesis. Chapter 2 is a substantially new chapter on chromosomes and epigenetics, a rapidly expanding topic in current genetic analysis. The concept, and even the examples, of epigenetic changes are not themselves new, but our knowledge of such examples and the connections to chromosome structure are completely new. Only some of this material was included in the second edition, as part of Chapter 3 on genome annotation. Genome annotation has now advanced to the point that we can focus on the underlying principles of epigenetic change rather than on the experimental methods used to study such effects. Chapter 3 again introduces the five model organisms that are very widely used in genetic analysis and that provide nearly all the examples used elsewhere in the book.

The second unit, "Mutants and Phenotypes," comprises roughly half of the book overall, some of the topics being brought forward and revised from the previous editions and others being new to this edition. Chapter 4, again, combines information on genetic screens and discusses the principles of mutant analysis. Chapter 5 describes how the variant or mutant phenotypes are connected to the underlying DNA sequence, both experimentally and conceptually, human genetic analysis being the most prominent here. For model organisms with sequenced genomes, "cloning a gene" now typically involves identifying the sequence among the annotated genome, so the emphasis has changed from previous editions. Chapter 6 is a discussion of how phenotypes and genotypes are connected to one another. This is

a completely new version of some topics that were included in the first edition, but not in the second edition. Geneticists working in the pre-molecular age and who probably never envisioned the genomic age thought carefully about the mutant phenotypes they observed and how such phenotypes could be studied and interpreted. This chapter attempts to make some of that so-called "classical genetics" accessible and applicable to the current student of genetics. Chapters 7 and 8 are about transgenic organisms and genome editing. The long-standing examples of genome editing in yeast and in mice are described in Chapter 7. These approaches set the stage for a new chapter on genome editing as a widespread tool for many organisms, that is, on CRISPR. The specific technology associated with genome editing will certainly change—Chapter 8 was updated multiple times as the book was being written and likely could be updated again—so this chapter attempts to put genome editing into the broader context of genetic analysis as it has been done for the past century. Chapter 9 is an updated chapter on genome-wide mutant screens, concluding this unit on the generation and analysis of phenotypes that arise from changes in single genes.

The third unit, "Interactions, Pathways, and Networks," focuses on gene interactions, that is, on the interpretation of the phenotypes of double and multiple mutants rather than on single mutant strains. Chapter 10, on suppressors and enhancers, and Chapter 11, on epistatic pathways, are revisions of the corresponding chapters from the previous editions. Chapter 12 is a much updated perspective on gene interactions networks studied on genome-wide scales. I regard this as one of the most intellectually provocative topics for modern geneticists, as we continue to attempt to connect molecular changes with phenotypes and to think about how the genotype of an individual, for all of its genes rather than for only a few well-defined genes, gives rise to the phenotypes we observe.

Pedagogical features

The book is designed to be accessible to different levels of expertise, on the basis of my experience of teaching these topics to undergraduates. For example, I have tried to maintain a tone that is conversational and familiar without being overly casual. For those who want more detail or want to find the source of some of the information, each chapter includes some references and sources I have relied on. Many of these references are embedded in literature links within the text, and additional readings are supplied at the end of each chapter.

To improve its use by students, the book also includes a glossary and an index. In the text, **glossary** terms are emboldened.

Nearly every chapter includes at least one "Tool Box," and a few chapters have two such boxes. These boxes discuss an underlying technique or an experimental strategy that is relevant to the chapter, for instance using zebrafish as a model organism to study seahorses (Chapter 2) or the role of balancer chromosomes (Chapter 4). Chapter 8, on genome editing, also includes a Human Angle Box (a device employed

in Meneely et al., *Genetics: Genes, Genomes, and Evolution*) to consider a few of the ethical issues that arise with genome editing in humans.

While experimental examples are used throughout the book, most chapters also have an associated "Case Study." Each of these looks at one particular example in detail, using the original papers and data as much as possible, to show how the strategies described in the chapter have been used in specific cases. These have been substantially revised from the previous editions, with an emphasis on their use as a pedagogical tool. Most significantly for pedagogical purposes, each case study now includes ten or more study questions in a section entitled "Thinking through the Experiment," which is designed to encourage the reader to engage more thoughtfully and analytically with the experiments being described. Some of these questions are relatively straightforward, while others ask about other interpretations, alternative ways in which the experiments might have been done, and so on. These are the types of questions that I usually ask the students in class as we work through the experiments. The case study examples were chosen not because they are familiar or groundbreaking (although some of them were) but because they illustrate how geneticists used the strategies the book describes to address a specific biological question. What better way to describe a strategy that to analyse an example in which it actually worked?

Genetics is a rapidly changing field, of course. The online resources will provide updates and corrections, as well as additional information and activities for each chapter to enhance student learning. As in the first two editions, the online resources include one or more guided journal clubs for each chapter. In these journal clubs, a student is guided through an original research paper, frequently one associated with the case study, via a series of questions with answers. I often use such journal clubs in my courses to help students learn to read the original papers and analyse the original data, so I encourage instructors to use these as well. Practice problems for each chapter are also included; these range from testing definitions and fundamental concepts to more advanced questions. These study questions focus primarily on the main narrative, so they are designed to be used together with the chapter to provide depth of coverage, while the case studies and journal clubs are designed to be used together to provide greater depth for interested or more advanced students.

Online resources

This book has been written with web usage in mind, so the reader is urged to consult the website associated with the book (www.oup.com/he/meneely3e) for updates and additional resources as they are developed. Key resources on this site include the following.

For registered adopters of the book

- figures from the book in electronic format, ready to download;
- journal club: suggested papers and discussion questions linked to topics covered in the book.

For students

- topical updates: key updates on topics or tools presented in the book, to keep you up to date with the latest developments in the field;
- additional case studies and text boxes that complement and add to those found in the book;
- practice problems designed to test your knowledge of the concepts presented and to help you master them.