Preface

Much has changed since the fourth edition of *Human Molecular Genetics* (HMG4) appeared in 2011, so this fifth edition has seen a comprehensive rewrite and reorganization. Few of the chapters retain their identity from HMG4, but our aims throughout the book remain the same: to provide a framework of principles rather than to list facts (which are better found in online resources), to provide a bridge between basic textbooks and the research literature, and to communicate our excitement and enthusiasm for this very fast-moving area of science.

The biggest single development since HMG4 has been the massive expansion of DNA sequencing in every area of human genetics. In response, we have provided a much-extended and updated coverage of massively-parallel sequencing technology, including the exciting new field of single-cell genomics. In some respects, the sequencing revolution has made things simpler. Many specific techniques covered in HMG4 have been largely or completely superseded by sequencing. The reader will note, however, that we still illustrate karyotypes. We make no apology for showing these where appropriate because they have educational value—it is often easier to understand what is going on by looking at a karyotype rather than sequence data, even though nowadays most laboratories would use sequencing rather than microscopy for these purposes.

In the preface to HMG4 we wrote, "we can confidently expect that the genomes of huge numbers of organisms and individuals will have been completed before the next edition of this book," and that expectation has been amply realized. Human genetics is now firmly in the world of Big Data and big international collaborations—and our coverage reflects this.

Among new or rearranged chapters we were particularly gratified when Mark Jobling and the team who produced the excellent *Human Evolutionary Genetics* (2nd edn, Garland Science, 2013) agreed to contribute a chapter on human evolution. Analysis of contemporary and ancient DNA has progressed enormously in the past few years and is revealing fascinating insights into our origins and history—but neither of us felt qualified to write with sufficient authority on this important topic.

Other developments include:

- A radical revision of coverage of early mammalian development and stem cells, with a detailed explanation of the origins of cellular differentiation and an in-depth survey of pluripotent stem cells as well as tissue stem cells and cell reprogramming.
- A specific chapter on genetic manipulation of mammalian cells, bringing together material from different HMG4 chapters and tracing the evolution of genome editing from a focus on simply using homologous recombination to the modern emphasis on using programmable nucleases.
- A chapter that deals with both the architecture of the human genome and also the ENCODE Project and other new initiatives to understand how our genome functions.
- A chapter giving unified coverage of gene regulation and epigenetics.
- A chapter giving an overview of human genetic variation that includes the origins of DNA sequence variation, DNA repair mechanisms, variant classes, population genomics, and functional genetic variation.

- A new chapter on human population genetics—a topic that we felt received inadequate coverage in previous editions.
- A specific chapter on molecular pathology, bringing together and expanding material from HMG4.
- Greatly expanded discussion of the achievements and limitations of genome-wide association studies (GWAS) in identifying susceptibility factors for common complex conditions. As the GWAS era is giving way to large-scale sequencing approaches, this seems a particularly apposite time for a critical analysis.
- New coverage of DNA diagnostics reflecting the major changes that have come with the routine use of whole exome and whole genome sequencing.
- Revised discussion of cancer genetics and genomics reflecting developments in multiplatform analyses, liquid biopsies, and targeted treatments.
- A new chapter that brings together model organisms and disease modeling, including the fast-moving new field of cellular disease modeling, especially organoid models that arose from basic developmental studies.

Apart from these specific topics, every page of the text has been revised and updated to provide an overview of human molecular genetics in 2018.

This book has only been possible because of the work of the team under Joanna Koster at Taylor & Francis who have converted our drafts and sketches into the finished product—Paul Bennett, Jordan Wearing, Matt McClements, Ruth Maxwell, Becky Hainz-Baxter, and probably others who have worked from time to time on the project. As ever, we are deeply grateful to our wives, Meryl and Gilly, for their forbearance and support during the long gestation of this book.

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