
Preface

Completion of the Human Genome Project (HGP) has provided us with a greatly enhanced understanding of human genetics, including a greater appreciation of how DNA shapes species development and evolution, biology, and disease susceptibility. The HGP has also affected the development and/or maturation of research disciplines such as genome annotation, knowledge of genome evolution and segmental duplication, and comparative genomics, among others. Yet, perhaps the greatest impact of the HGP has been on the manner in which researchers investigate the causes of complex human diseases. Completion of the HGP gave rise to the development of efforts to characterize genetic variation in the human genome, which has lead directly to the application of whole genome association studies to identify common alleles which contribute to complex disease risk.

Efforts to identify genetic mutations underlying highly penetrant diseases have been widely successful due to the facts that (1) a single mutation is enough to cause the disease (i.e., monogenic) and (2) the mutation is inherited in a simple manner between generations in affected families. To date, more than a thousand genes for such disorders have been identified. These monogenic diseases are rare compared to diseases such as type 2 diabetes mellitus, cardiovascular disease, and cancer, which have complex etiologies. Unlike monogenic diseases, which arise due to a single genetic aberration, complex diseases result from a complicated interaction of multiple genetic and environmental determinants, none of which are amenable to identification and characterization using the traditional approaches to monogenic disease gene discovery. Recent efforts to characterize genetic variation in the human genome, coupled with the rapidly developing field of genomics, have lead directly to the development of new and innovative approaches to the identification of genes contributing to complex human diseases. This volume is written to provide up-to-date molecular methodologies used in the process of identifying a disease gene, from the initial stage of study design to the next stage of preliminary locus identification, and ending with stages involved in target characterization and validation. The need for such a book derives from the intellectual revolution in biomedical science and the realization that the molecular determinants of human diseases are rapidly becoming identifiable through well-planned, technologically advanced approaches.

Although the research literature is replete with descriptions of technical procedures, there is typically a dearth of extensive practical detail in these publications, particularly in terms of modifications developed from personal experience, as well as discussions of potential problems that may be encountered throughout the protocol and ways to avoid them. The structure of this volume is unique in that it aims to address these deficiencies. The chapters contained within have been contributed by experts in their fields, who have kindly accepted the invitation to compile the protocols within this volume and share with us their expertise, experience, and results.

This text is written at a level accessible to graduate students, postdoctoral researchers, and bench scientists in the fields of molecular genetics and molecular biology. The primary aim of

this volume is to present detailed laboratory procedures in an easy-to-follow format that can be carried out with success by competent investigators lacking previous exposure to a specific research method. The book's main focus is on the application of molecular approaches to disease gene identification, but overviews and case studies are also presented.

The volume begins with three introductory chapters which provide an overview of disease gene identification strategies and a description of study sample selection and successful experimental design. The next section of the text contains chapters presenting methods for identifying potential susceptibility loci, including practical procedures for high-throughput SNP genotyping using whole genome arrays, medium-throughput SNP genotyping using mass spectrometry, and low-throughput, targeted SNP genotyping approaches commonly used in fine-mapping and candidate gene investigations. The section ends with a chapter on bar-coded, multiplexed sequencing of targeted DNA regions to pinpoint specific allelic variants which contribute to disease risk.

The volume follows with a section on current applications in human genomics, which provide tools for target validation and functional assessment. These protocols are typically associated with the steps of disease gene identification pursuant to initial locus discovery, such as those pertaining to functional characterization of susceptibility alleles and loci. Examples of such approaches include global mRNA expression profiling using mainstream platforms, the newly emerging field of microRNA profiling, and allelic expression profiling, as well as quantitative PCR and RNA mapping methods. Chapters on comparative genomic hybridization, which is a molecular-cytogenetic method to detect copy number changes, and high content analysis are also included.

Finally, we end with four discursive chapters, to provide examples of disease gene identification and application. The first chapter in this section is related to bioinformatics approaches to the elucidation of gene identity and function, with a particular focus on an integrative systems biology approach. The second chapter in this section illustrates the entire process of disease gene identification with a real-life case study, and the concluding chapter presents an RNA-interference approach to functional pharmacogenomics and an application of molecular diagnostics to the treatment of β -thalassemia.

Without the support and contributions of many individuals, completion of this volume would not have been possible. In particular, I thank Dr. John Walker, the editor of this series at Humana Press, who ensured the smooth and effortless completion of this project from the very start. I also express gratitude to the authors, all of whom contributed outstanding chapters, emanating from years of experience in the field. It was a pleasure working with this expert team of scientists, and I would gladly do so again at a moment's notice. It is my hope that this volume leads to the identification and characterization of many more disease-related genes, which may someday pave the way toward more accurate and improved methods for disease diagnosis, as well as novel and effective strategies for disease treatment and prevention.

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<http://www.springer.com/978-1-61737-953-6>

Disease Gene Identification

Methods and Protocols

DiStefano, J.K. (Ed.)

2011, XII, 312 p., Hardcover

ISBN: 978-1-61737-953-6

A product of Humana Press