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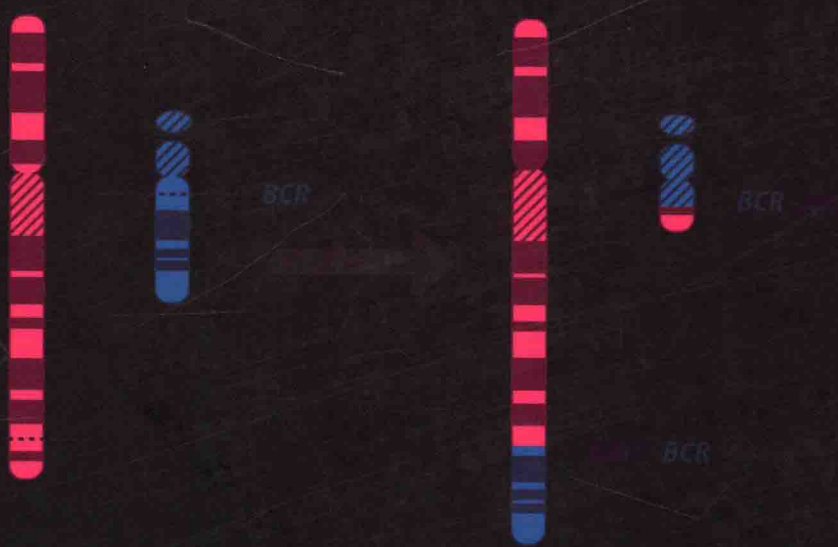
GENETICS OF COMPLEX DISEASE



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Preface

There is a scientific revolution happening in biomedical genetics. The new genetics does not just apply to the well-known and well-described Mendelian diseases with clear patterns of inheritance, nor is it limited to major chromosomal abnormalities. What makes the revolution so exciting is that it includes all human diseases and all aspects of human disease. Diseases that have been largely, but not entirely, ignored in the past are the main focus of this revolution. The potential arising from this work is astounding. It is already having an impact and the impact will only grow over time. There are many books on genetics, but few concentrate on complex diseases—those that do not fit the simple patterns of Mendelian disease and cannot be described as chromosomal abnormalities.

Over the past 15–20 years interest in these genetically complex diseases has taken full flight. Though earlier studies had identified some important genetic links and associations, many of the early studies had failed to be replicated and studies in this area of genetics had developed a poor reputation. There were some good studies and many bad studies. The difference between good and bad studies is quite well known. However, developments in the last 20 years have restored interest and confidence in studies of complex disease.

A number of important developments were the keys to opening up this area for high-quality research. The two most important developments have been the Human Genome Mapping Project and the development of supercomputers along with the necessary systems capable of handling the data that very-large-scale studies produce. These two developments go cap-in-hand, one is not possible without the other. In 2015, we have the human genome sequence, the SNP Map and the HapMap. Of course array platforms for genotyping and application of this knowledge as well as more sophisticated statistical analysis have also filled an essential gap. Indeed, the genetics of today is as much about statistics as it is about biology and there are Professors of Statistical Genetics in our academic institutions who dedicate their research to extracting important facts from the mountains of data that current studies can generate.

This book addresses the subject of genetics of complex disease and is designed in two parts. The first part (Chapters 1–5) provides a basic background to genetically complex diseases, and why and how we study them. The second part (Chapters 6–12) focuses on specific sub-branches of genetics of complex disease and specific examples to highlight the application of genetic data in complex disease and the extent to which this data is fulfilling the promises of the Human Genome Project.

Chapter 1 covers the necessary background to genetic variation in the human population, i.e. our evolutionary past and how genetic variation arises. Chapter 2 goes on to define complex diseases and compare them with Mendelian and chromosomal diseases. Chapter 3 looks at how we investigate complex diseases, including the different plans and strategies available to us. Do we chose a single gene or region to study, or do we throw the net wider and investigate the whole genome in a genome-wide association or linkage study? Chapter 4 considers why we are interested in complex diseases, focusing on the major

promises of the Human Genome Project in relation to complex disease. These suggested that genetic testing will be used in disease diagnosis, patient treatment and management, and in understanding disease pathology. Chapter 5 looks at how data from the studies described below is handled in a range of different statistical tests.

Sufficient information is given in each of Chapters 1–5 to enable students to understand the major points and, where appropriate, examples are used to illustrate the key concepts (e.g. in Chapter 2, where Crohn's disease and Hirschsprung's disease are discussed as two different models of genetically complex diseases). Chapter 4 uses quite a few disease examples to illustrate how the genetic information may be used to meet the promises of the Human Genome Project.

After Chapter 5, the book goes on to look at three specific areas: immunogenetics (Chapter 6), infectious disease (Chapter 7), and pharmacogenetics (Chapter 8).

Chapter 6 on immunogenetics deals with how common variation in genes that regulate the immune response can increase or reduce susceptibility to common diseases. The chapter concentrates on the major histocompatibility complex on chromosome 6p21.3. The chapter includes a considerable number of recently studied examples and discusses the different interpretations that can be applied to the data. In each case, the extent to which these examples do or do not fulfill the promises of the genome project is considered. There are positive examples of how genetics can be used as an aid to diagnosis (e.g. in ankylosing spondylitis), and also how associations and linkage with certain risk alleles may be helping us to understand disease pathogenesis (e.g. in autoimmune liver disease).

Chapter 7 on infectious disease looks at the past and the present considering how genetic variations may influence the likelihood of infection per se and the outcome following exposure to infectious agents. The discussion provides interesting links with mankind's early history. The chapter concentrates on a few selected examples to illustrate the concept and demonstrate how the studies discussed are helping to fulfill the promises of the Human Genome Project. Once again, there are clear examples of genetic investigations impacting on our understanding of disease pathology.

Chapter 8 on pharmacogenetics discusses past and present developments in a fast-expanding field that is at present providing some of the most promising results in complex disease genetics. Studies have shown that responses to commonly used pharmacological agents can be determined by common genetic variation. The impact of this variation ranges from failure to respond to a drug to life-threatening toxic reactions. The potential to use genetics to tailor therapy and also to develop new therapeutic agents is a real possibility in this sub-branch of complex disease genetics, and one that major pharmaceutical companies and academic institutions are aware of.

Chapters 9 and 10 focus on specific disease groups: cancer (Chapter 9) and diabetes (Chapter 10). These two chapters stand alone because one group of diseases (cancer) has a very significant impact in terms of morbidity and mortality in the developed and developing world and the other group (diabetes) is for the most part a perfect example of a complex disease. The potential medical impact of genetic studies in these diseases is vast. More rapid diagnosis, better patient care, personal life planning, and personal treatment planning are all possible. As we gain a greater knowledge of the genetics of these diseases we will start to have a better grasp on the underlying pathology of each disease, which will open up doors for diagnosis, treatment, and management. In some cases, this will mean simple things like changes to a person's diet; in others, selecting the appropriate chemotherapeutic agent to use for a patient. To some extent some of these aims have already been achieved, but as this book indicates, there is still much to be done.

In Chapter 9 (cancer), a selected number of examples are discussed. These include breast cancer, prostate cancer, and lung cancer. The selection is based on the most common cancers, which are also, to some extent, those about which we know the most. Links to useful websites are given for further information and updates. Diabetes (Chapter 10) is discussed in its various forms, especially type 1 and type 2 diabetes and is specifically used to illustrate the difference in the genetic portfolios in type 1 and type 2 diabetes. Here, the question is why are two diseases that have so much in common so different in terms of their genetic profiles?

The last two chapters deal with societal and ethical issues in the new genetic era and the future of genetics in complex disease. This is a fast-moving area of science. The facts being produced today will be marketed as diagnostic or prognostic indicators almost as quickly as they are identified. Genetic testing for risk alleles will soon be normal practice, but this will have ethical and social consequences. The potential for misuse of genetics is discussed in Chapter 11, highlighting the importance of understanding what a genetic test in complex disease is really telling you. You will need to know what a genetic profile is telling you before getting tested. There is considerable commercial interest in genetic profiling and this has ethical and societal impact. Other points discussed include who owns your genome and who can access your genetic data?

Chapter 12 closes the book by looking at the techniques and technologies that have been used and those that will be used in the future. The chapter reminds us that technologies used in the past will also be used in the future, but it also highlights some fascinating new possibilities. Most important will be direct sequencing either at the level of the exome (i.e. protein-coding genes only) or the whole genome.

The structure of the book is designed to provide a basic platform on which students can build their knowledge base. Each of the chapters (including the basic chapters) uses examples of disease to illustrate key specific points and provides a reasonable level of basic current data on each example used. In particular, the book focuses on the promises of the Human Genome Project that suggested genetics will be used to improve disease diagnosis, to develop individual treatment and management plans for patients, and to inform the debate on disease pathogenesis. At each stage and after each example, the text reflects on the extent to which these promises have been or will be met, looking at both the present and, if possible, the future. Links to the web are also provided for access to updates and further information throughout the book. There is an extensive Glossary at the end of the book.

These are very exciting times for genetics, especially in complex disease. They are also fast-moving times. The book is written as a starting point (a first block) and for the most part it is written in an historical style to ensure it remains in date whatever develops in the future.

This book provides a good starting point for anyone studying the genetics of so-called complex diseases. It is written for the undergraduate student and early postgraduate student alike. It is written for the medical and non-medically minded individual. This era is one of the most exciting eras in modern genetics, perhaps as exciting as when the structure of DNA was first revealed to the scientific community.

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