ESSENTIALS

ESSENTIAL MEDICAL GENETICS

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6TH EDITION

with Wiley DESKTOP EDITION

with website

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Contents

Essential Medical Genetics

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Preface

This book has been written for those to whom an understanding of modern medical genetics is important in their current or future practice as clinicians, scientists, counsellors and teachers. It is based on the authors' personal experience in both clinical and laboratory aspects of busy regional genetics services over a period of many years. This period has seen the emergence of modern cytogenetics and molecular genetics alongside the development of medical genetics from a purely academic discipline into a clinical specialty of relevance to every branch of medicine. As in our undergraduate and postgraduate education programmes, we emphasize the central role of the chromosome and the human genome in understanding the molecular mechanisms involved in the pathogenesis of genetic disease. Within the term genetic disease, we include not only the classic Mendelian and chromosomal disorders but also the commoner disorders of adulthood with a genetic predisposition and somatic cell genetic disorders, such as cancer.

For this sixth edition, the text has been extensively updated throughout. The structure of the book has, where appropriate, been reorganised, in order to provide a clear description of the essential principles of the scientific basis and clinical application of modern medical genetics. Where appropriate, we have included descriptions of genetic conditions that have been carefully selected as examples of the important principles being described. Since the last edition of this book, several important and exciting new advances have been made in the field of medical genetics, and we have incorporated information about them into the book. Such advances include, for example, the completion of the sequencing of the human genome (with the generation of huge quantities of publicly accessible data), the identification of new classes of RNA molecules, the

development of a number of invaluable new molecular genetic and cytogenetic laboratory techniques, the further development of preimplantation genetic diagnosis, and improved methods for antenatal and neonatal screening.

A very significant additional advance has been the development and enormous expansion of many invaluable online clinical and molecular genetic databases. These databases have greatly facilitated the medical genetics work of most clinicians and scientists. The optimal use of several important databases is, however, in many cases far from straightforward. Consequently, retrieving specific information or data from them can take a great deal of time and effort for users who do not access them frequently. The final chapter of this book is therefore devoted to providing guidance on the most efficient use of these databases, together with clear illustrated advice explaining how to find different types of information via the internet as quickly as possible. It is hoped that this guidance, which to our knowledge is currently unavailable elsewhere, will make this process much more straightforward for the reader.

We have also provided an accompanying website (accessed via www.wiley.com/go/tobias) that we will regularly update in order to provide the reader with a way of easily accessing the very latest clinical and molecular genetic information relating to the thousands of genetic conditions, in addition to patient information and support organizations, the identified genes, and gene-testing laboratories worldwide. The links are grouped on the website in a very similar manner to the way in which they are categorised within the final chapter of this book, in order to make it as easy as possible for readers to find relevant information quickly.

Although we have made every effort to ensure that the information contained within this book is accurate at the time of going to press, we look to the continued generosity

of our readers in helping to correct any misconceptions or omissions. We would be happy to receive any comments, or recommendations for improvements, at essentialmedgen@gmail.com.

The role of genetic counselling, prenatal diagnosis, carrier detection and other forms of genetic screening in the prevention of genetic disease is now well established and this is reflected in the increasing provision of genetic services throughout the world. It is hoped that our book will be useful to those in training for this important task.

E.S.T, J.M.C. and M.A.F-S.

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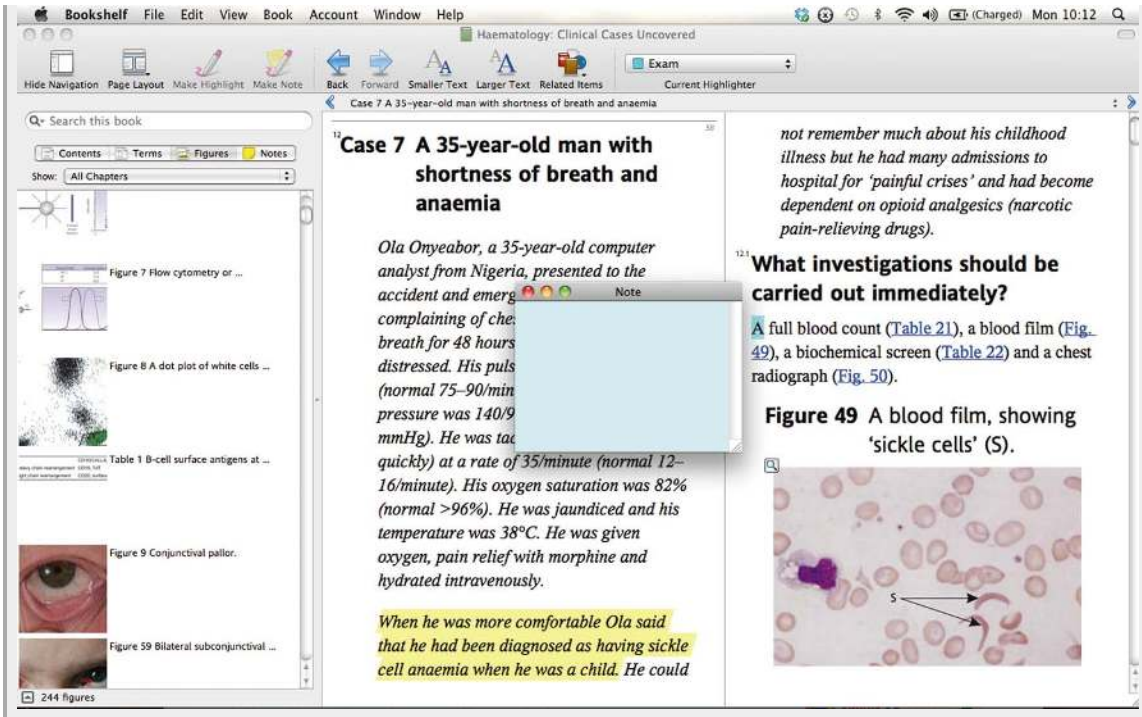

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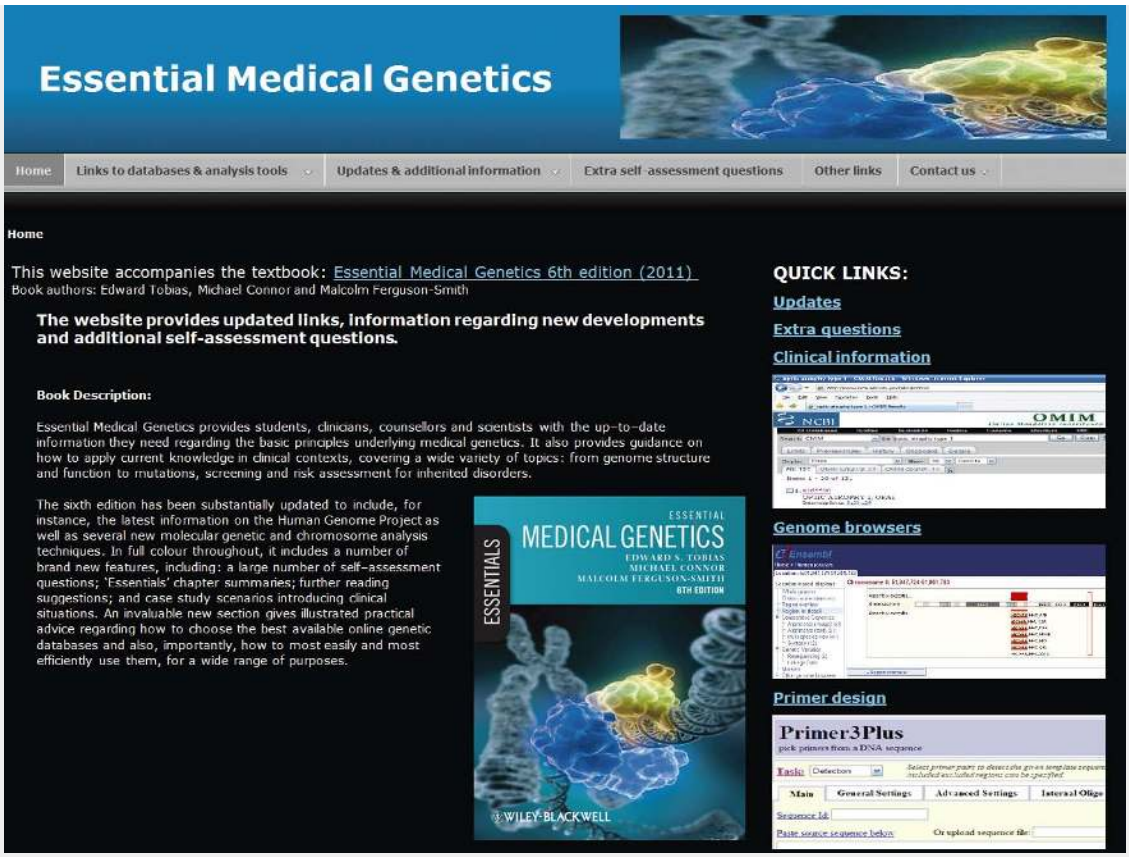

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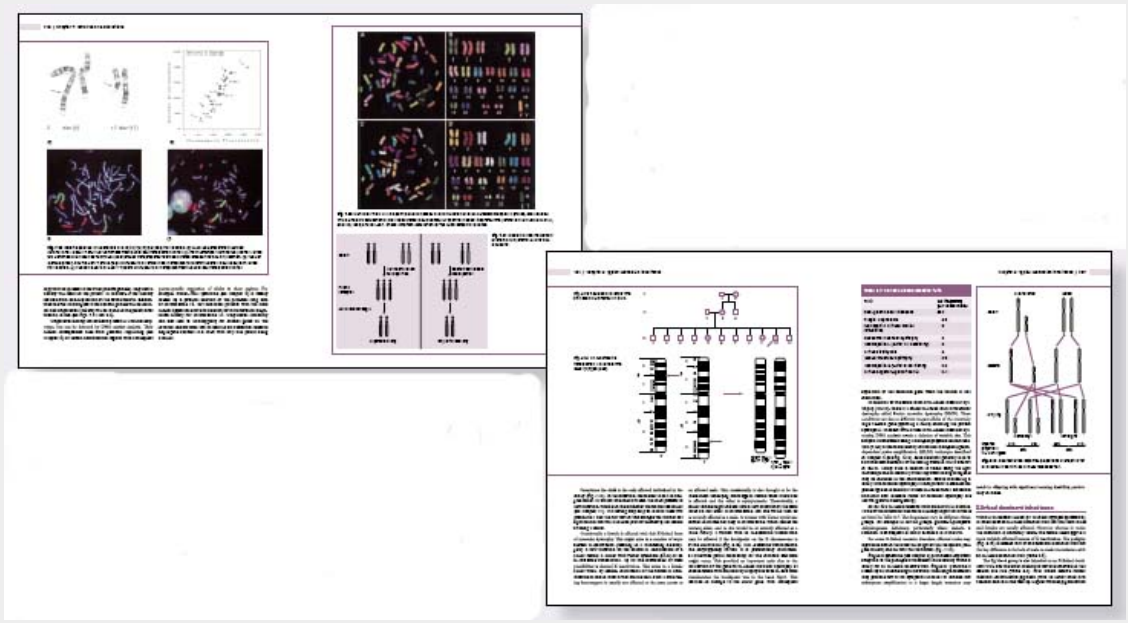

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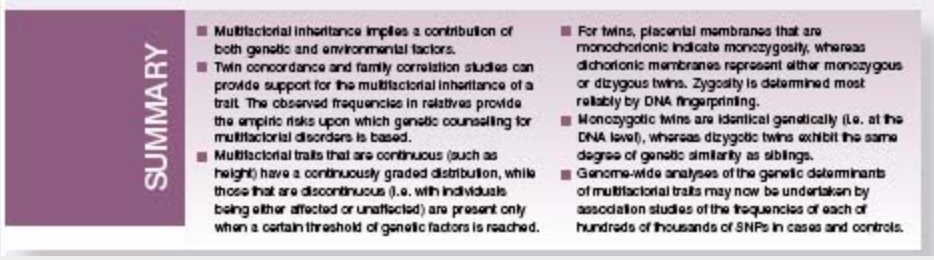

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Part 1

Basic Principles

Chapter 1

Medical genetics in perspective

Key Topics

- Scientific basis of medical genetics
- Clinical applications of medical genetics

Introduction

Medical genetics is the science of human biological variation as it relates to health and disease. Although people have long been aware that individuals differ, that children tend to resemble their parents and that certain diseases tend to run in families, the scientific basis for these observations was only discovered during the past 140 years. The clinical applications of this knowledge are even more recent, with most progress confined to the past 50 years (see Table 1.1). In particular, the rapid sequencing of the entire human genome, completed in 2003, has greatly accelerated the process of gene mapping for genetic conditions and a vast quantity of valuable and continuously updated information has become readily accessible via the internet (as described in detail in Part 3 and on this book's accompanying website at www.wiley.com/go/tobias).

Table 1.1 Some important landmarks in the development of medical genetics

Year	Landmark	Key figure(s)
1839	Cell theory	Schleiden and Schwann
1859	Theory of evolution	Darwin

Year	Landmark	Key figure(s)
1865	Particulate inheritance	Mendel
1882	Chromosomes observed	Flemming
1902	Biochemical variation	Garrod
1903	Chromosomes carry genes	Sutton, Boveri
1910	First US genetic clinic	Davenport
1911	First human gene assignment	Wilson
1944	Role of DNA	Avery
1953	DNA structure	Watson, Crick, Franklin and Wilkins
1956	Amino acid sequence of sickle haemoglobin (HbS)	Ingram
1956	46 chromosomes in humans	Tjio and Levan
1959	First human chromosomal abnormality	Lejeune
1960	Prenatal sexing	Riis and Fuchs
1960	Chromosome analysis on blood	Moorhead
1961	Biochemical screening	Guthrie
1961	X chromosome inactivation	Lyon
1961	Genetic code	Nirenberg
1964	Antenatal ultrasound	Donald
1966	First prenatal chromosomal analysis	Breg and Steel
1966	First print edition of Mendelian Inheritance in Man (MIM)	McKusick
1967	First autosomal assignment	Weiss and Green
1970	Prevention of Rhesus isoimmunisation	Clarke
1970	Chromosome banding	Caspersson and Zech
1975	DNA sequencing	Sanger, Maxam and Gilbert
1976	First DNA diagnosis	Kan
1977	First human gene cloned	Shine
1977	Somatostatin made by genetic engineering	Itakura
1979	*In vitro* fertilization	Edwards and Steptoe
1979	Insulin produced by genetic engineering	Goeddel

Year	Landmark	Key figure(s)
1982	First genetic engineering product marketed (Humulin)	Many contributors
1985	DNA fingerprinting	Jeffreys
1986	Polymerase chain reaction (PCR)	Mullis
1987	Linkage map of human chromosomes developed	Many contributors
1987	Online Mendelian Inheritance in Man (OMIM) first available	McKusick
1990	First treatment by supplementation gene therapy	Rosenberg, Anderson, Blaese
1990	First version of London Dysmorphology Database	Baraitser and Winter
1990	First clinical use of preimplantation genetic diagnosis (PGD)	Handyside, Winston and others
1991	First version of London Neurogenetics Database	Baraitser and Winter
1993	First physical map of the human genome	Many contributors
2000	First draft of the human genome sequence	Many contributors
2003	Completion of human genome sequencing (99.999%)	HGSC and Celera
2006	Preimplantation genetic haplotyping (PGH) announced	Renwick, Abbs and others
2007	Human genome SNP map (3.1 million SNPs) reported	International HapMap Consortium
2007	Completion of DNA sequencing of personal genomes	Watson and Venter
2008	Launch of project to sequence the genomes of over 1000 individuals from 20 different populations worldwide	International 1000 Genomes Project
2010	Publication of catalogue of human genetic variation (believed to be 95% complete)	International 1000 Genomes Project

HGSC: Human Genome Sequencing Consortium; OMIM: Online Mendelian Inheritance in Man; SNP: single nucleotide polymorphism.

Scientific basis of medical genetics

Mendel's contribution

Prior to Mendel, parental characteristics were believed to blend in the offspring. While this was acceptable for continuous traits such as height or skin pigmentation, it was clearly difficult to account for the family patterns of discontinuous traits such as haemophilia or albinism. Mendel studied clearly defined pairs of contrasting characters in the offspring of the garden pea (*Pisum sativum*). These peas were, for example, either round or wrinkled and were either yellow or green. Pure-bred strains for each of these characteristics were available but when cross-bred (the first filial or F_1 progeny) were all round or yellow. If F_1 progeny were bred then each characteristic was re-observed in a ratio of approximately 3 round to 1 wrinkled or 3 yellow to 1 green (in the second filial or F_2 progeny). Mendel concluded that inheritance of these characteristics must be particulate with pairs of hereditary elements (now called genes). In these two examples, one characteristic (or trait) was dominant to the other (i.e. all the F_1 showed it). The fact that both characteristics were observed in the F_2 progeny entailed *segregation of each pair of genes with one member to one gamete and one to another gamete* (Mendel's first law).

Figures 1.1 and 1.2 illustrate these experiments with uppercase letters used for the dominant characteristic and lower-case letters used for the masked (or recessive) characteristic. If both members of the pair of genes are identical, this is termed homozygous (for the dominant or recessive trait), whereas a heterozygote has one gene of each type.

In his next series of experiments Mendel crossed pure-bred strains with two characteristics, e.g. pure-bred round/yellow with pure-bred wrinkled/green. The F_1 generation showed only the two dominant characteristics – in this case round/yellow. The F_2 showed four combinations: the original two, namely round/yellow and wrinkled/green, in a ratio of approximately 9:1 and two new combinations – wrinkled/yellow and round/ green in a ratio of approximately 3:3 (Fig. 1.3).

In these experiments, there was thus no tendency for the genes arising from one parent to stay together in the offspring. In other words, *members of different gene pairs assort to gametes independently of one another* (Mendel's second law).

Although Mendel presented and published his work in 1865, after cultivating and studying around 28,000 pea plants, the significance of his discoveries was not realised until the early 1900s when three plant breeders, De Vries, Correns and Tschermak, confirmed his findings.

Chromosomal basis of inheritance

In 1839, Schleiden and Schwann established the concept of cells as the fundamental living units. Hereditary transmission through the sperm and egg was known by 1860, and in 1868, Haeckel, noting that the sperm was largely nuclear material, postulated that the nucleus was responsible for heredity. Flemming identified chromosomes within the nucleus in 1882, and in 1903 Sutton and Boveri independently realised that the behaviour of chromosomes during the production of gametes paralleled the behaviour of Mendel's hereditary elements. Thus, the chromosomes were discovered to carry the genes. However, at that time, although the chromosomes were known to consist of protein