

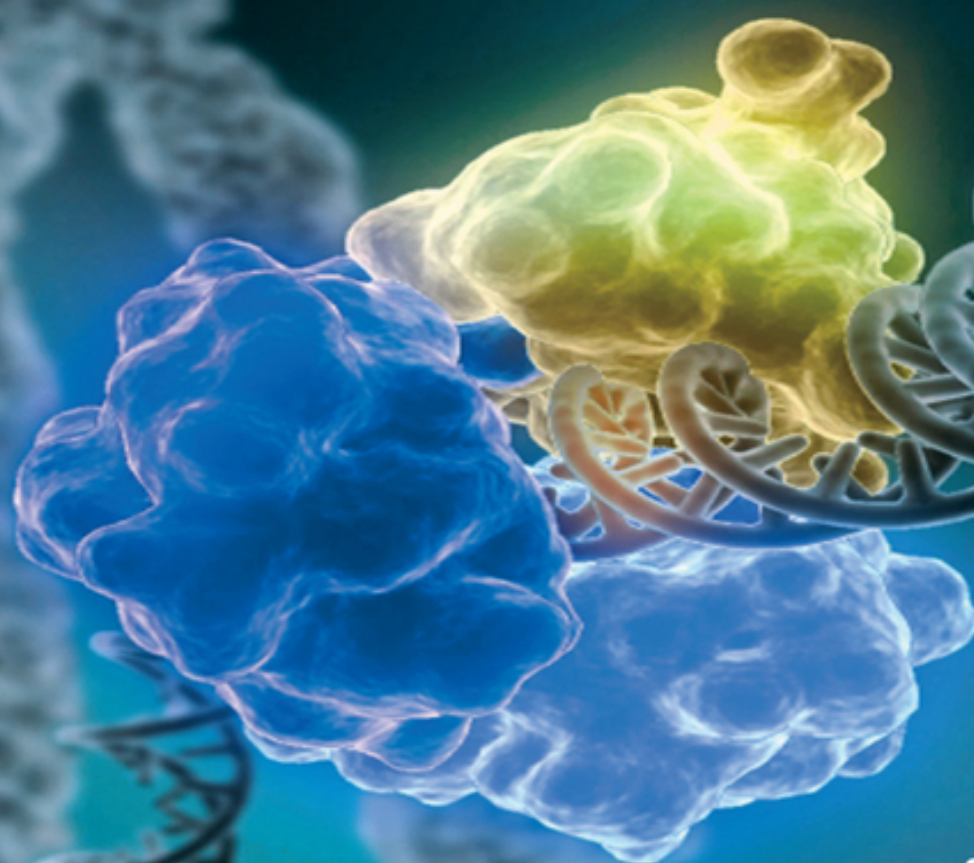
ESSENTIALS

ESSENTIAL MEDICAL GENETICS

EDWARD S. TOBIAS | MICHAEL CONNOR
MALCOLM FERGUSON-SMITH

6TH EDITION

with **Wiley** DESKTOP EDITION



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Essential Medical Genetics

Edward S. Tobias

BSc MBChB PhD FRCP

Senior Clinical Lecturer in Medical Genetics
University of Glasgow
and Honorary Consultant in Medical Genetics
West of Scotland Regional Genetics Service
Institute of Medical Genetics
Glasgow

Michael Connor

MD, DSc, FRCP

Professor of Medical Genetics
University of Glasgow
and Director of the West of Scotland
Regional Genetics Service
Institute of Medical Genetics
Glasgow

Malcolm Ferguson-Smith

MBChB, FRCPath, FRCP, FRSE, FRS

Emeritus Professor of Pathology
University of Cambridge
and formerly Director of the East Anglia Regional Genetics Service
Addenbrookes Hospital
Cambridge

Sixth edition

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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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Figure 7 Flow cytometry or ...

Figure 8 A dot plot of white cells ...

Table 1 B-cell surface antigens at ...

Figure 9 Conjunctival pallor.

Figure 59 Bilateral subconjunctival ...

244 figures

Case 7 A 35-year-old man with shortness of breath and anaemia

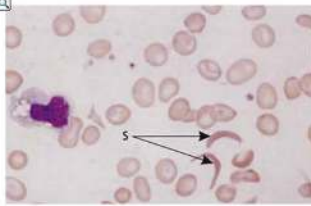
Ola Onyeabor, a 35-year-old computer analyst from Nigeria, presented to the accident and emergency department complaining of chest pain and shortness of breath for 48 hours. He was distressed. His pulse was 140/min (normal 75–90/min), his blood pressure was 140/90 mmHg. He was tachypnoeic (respiratory rate 35/min (normal 12–16/min)). His oxygen saturation was 82% (normal >96%). He was jaundiced and his temperature was 38°C. He was given oxygen, pain relief with morphine and hydrated intravenously.

When he was more comfortable Ola said that he had been diagnosed as having sickle cell anaemia when he was a child. He could not remember much about his childhood illness but he had many admissions to hospital for 'painful crises' and had become dependent on opioid analgesics (narcotic pain-relieving drugs).

What investigations should be carried out immediately?

A full blood count (Table 21), a blood film (Fig. 49), a biochemical screen (Table 22) and a chest radiograph (Fig. 50).

Figure 49 A blood film, showing 'sickle cells' (S).



A companion website ►

Your textbook is also accompanied by a FREE companion website that contains:

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- Updated information relating to the book's content
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Essential Medical Genetics

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Home

This website accompanies the textbook: [Essential Medical Genetics 6th edition \(2011\)](#)
Book authors: Edward Tobias, Michael Connor and Malcolm Ferguson-Smith

The website provides updated links, information regarding new developments and additional self-assessment questions.

Book Description:

Essential Medical Genetics provides students, clinicians, counsellors and scientists with the up-to-date information they need regarding the basic principles underlying medical genetics. It also provides guidance on how to apply current knowledge in clinical contexts, covering a wide variety of topics: from genome structure and function to mutations, screening and risk assessment for inherited disorders.

The sixth edition has been substantially updated to include, for instance, the latest information on the Human Genome Project as well as several new molecular genetic and chromosome analysis techniques. In full colour throughout, it includes a number of brand new features, including: a large number of self-assessment questions; 'Essentials' chapter summaries; further reading suggestions; and case study scenarios introducing clinical situations. An invaluable new section gives illustrated practical advice regarding how to choose the best available online genetic databases and also, importantly, how to most easily and most efficiently use them, for a wide range of purposes.

QUICK LINKS:

- [Updates](#)
- [Extra questions](#)
- [Clinical information](#)

Genome browsers

Primer design

Primer3Plus
pick primers from a DNA sequence

Basic | **Detections** | ☐ Select primer pairs to detect the given template sequence included/excluded regions can be specified

Main | General Settings | Advanced Settings | Internal Oligos

Sequence ID:

Paste source sequence below: Or upload sequence file:

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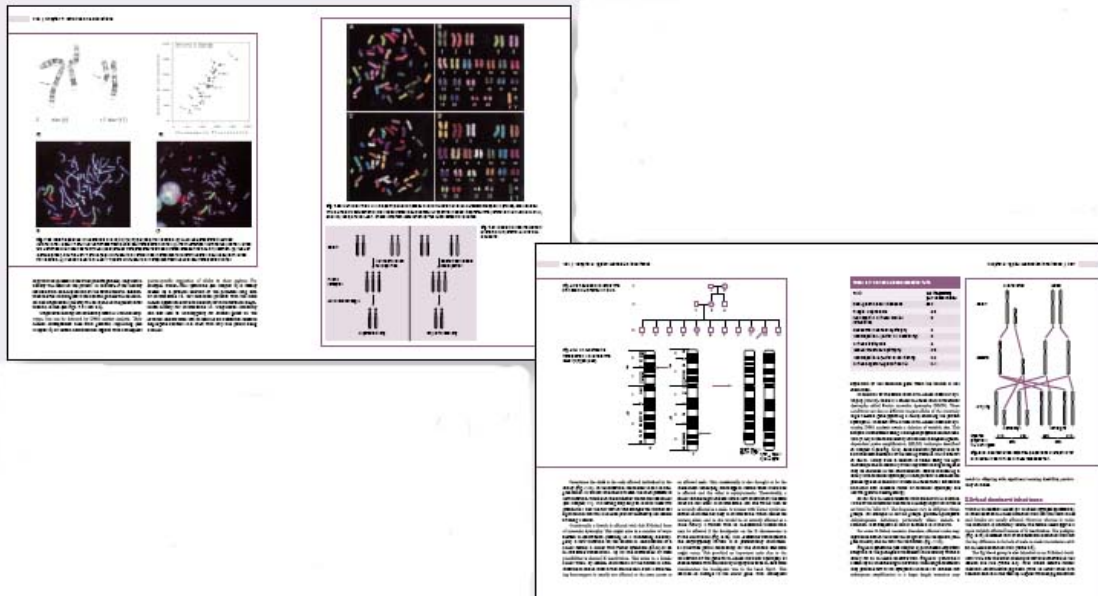
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SUMMARY

- Multifactorial inheritance implies a contribution of both genetic and environmental factors.
- Twin concordance and family correlation studies can provide support for the multifactorial inheritance of a trait. The observed frequencies in relatives provide the empiric risks upon which genetic counselling for multifactorial disorders is based.
- Multifactorial traits that are continuous (such as height) have a continuously graded distribution, while those that are discontinuous (i.e. with individuals being either affected or unaffected) are present only when a certain threshold of genetic factors is reached.
- For twins, placental membranes that are monochorionic indicate monozygosity, whereas dichorionic membranes represent either monozygous or dizygotic twins. Zygosity is determined most reliably by DNA fingerprinting.
- Monozygotic twins are identical genetically (i.e. at the DNA level), whereas dizygotic twins exhibit the same degree of genetic similarity as siblings.
- Genome-wide analyses of the genetic determinants of multifactorial traits may now be undertaken by association studies of the frequencies of each of hundreds of thousands of SNPs in cases and controls.

We hope you enjoy using your new textbook. Good luck with your studies!

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	<i>In vitro</i> 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 F₁ generation showed only the two dominant characteristics - in this case round/yellow. The F₂ 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