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Textbook of Medical Genetics

医学遗传学

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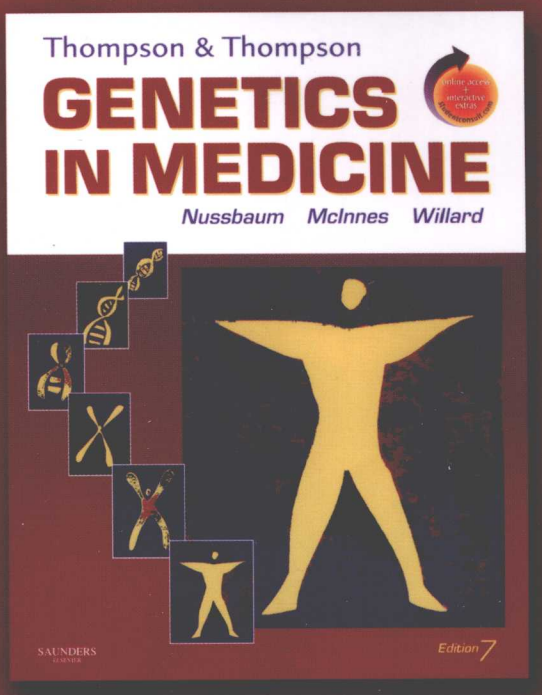
McInnes
Willard

《Thompson & Thompson 医学遗传学》第7版中英文改编版



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原　著： **Robert L. Nussbaum**
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双语版前言

尽管对目前盛行的我国高等医学教育实行双语、英语教学的做法存在许多不同的争论和意见，但似乎前进的脚步并没有停止。因为这毕竟是我国的医学教育尽快接轨国际一流以培养高级医学人才的需要。然而，绝大多数的医学课程仍然没有合适的双语教材。就我们所从事的《医学遗传学》或《遗传医学》课程教学来说，几乎所有已开展双语教学的高等院校，都是采用不匹配的一套英文教材和一套中文教材的做法，给广大师生的教和学带来显而易见的不便，严重影响了教学效果。因此，出版合适的双语教材，应该是实施正确的双语教学的第一步。本书出版的目的正在于此。

由 Nussbaum、McInnes 和 Willard 三位教授主编的《Thompson & Thompson Genetics in Medicine（第 7 版）》(2007) 为美国绝大多数医科院校的通用教材，当然应该是医学遗传学双语教材的首选。为了克服英、中双语带来的页数增多、成本上涨问题，我们采取了以下主要措施，以利于广大师生的使用：

1. 所有的对应中文翻译内容全部置于本书所附的 CD 中，仅将每章的重点或难点段落印刷出来。

2. 全书采用黑白印刷而非英文版的彩色印刷（所有英文版彩图、插图和照片均包括在 CD 中），并压缩有关插图的尺寸，适当缩小全书的字号。

3. 将英文版中央部分列举的疾病病案“Clinical Case Studies Illustrating Genetic Principles”，以及每章后的参考文献置于 CD 中。

4. 书末的“Index”部分尽量只保留英文版的一级索引。

通过上述方法，我们力争在英文版全书 585 页的基础上，使双语版控制在最少的页码以内，却不影响英文版的全貌和正常使用。

另外，对于英文版的一些不当之处，我们仍照原样翻译。如第 16 章等讨论的慢性髓细胞性白血病（CML）标记染色体，一般应写为 Ph，而非英文版的 Ph^1。原因是当时发现费城染色体后，学者们预测今后将会有更多的肿瘤标记染色体：Ph^2、Ph^3 等被发现，但至今却未有报道。故学者们习惯上将费城染色体统称为 Ph。还有，所有的专业名词尽量采用全国科学技术名词审定委员会所公布的统一命名和释义（包括书末的词汇部分），如 haplotype 为“单体型”而非“单倍型”等。对个别专业名词，我们采取了自认为合适的译法，如 homoplasmy 和 heteroplasmy 分别译为“纯质性”和“杂质性”。本书的这些情况，请在教、学中予以注意。

翻译（尤其是专业外语书籍的翻译）从来都是不轻松的一项工作。从民国的“milk way”（银河系）被误译为“牛奶路”，到今天的“genetic disorder”（遗传病）被译为“遗传紊乱”，从侧面说明知识永无止境，“愈学习，愈发现自己无知。”因此，虽然参与双语版编译的各位教师都是各自单位里长期从事医学遗传学教学和科研的骨干，历来兢兢业业，但因工作和事务日日繁忙缠身，时间仓促，加上水平有限，本书肯定会存在这样或那样的谬误和笔误。在此恳请广大师生批评斧正，谅解为盼。我们随时欢迎大家指出译文的不当之处，请发送 E-mail 至以下地址：zhangxianning@zju.edu.cn；jzuo@shmu.edu.cn；qiming_14618@yahoo.com。以便再版时臻于完善。

我们十分感谢各译者单位的领导、同事、学生以及北京大学医学出版社陆银道社长和王凤廷副社长等给予本书的大力支持和帮助。

译者谨识

2009 年 1 月

Preface

In their preface to the first edition of *Genetics in Medicine*, published over 40 years ago, James and Margaret Thompson wrote:

Genetics is fundamental to the basic sciences of preclinical medical education and has important applications to clinical medicine, public health and medical research. With recognition of the role of genetics in medicine has come the problem of providing a place for it in the undergraduate curriculum, a problem which is as yet only partly solved in most medical schools. This book has been written to introduce the medical student to the principles of genetics as they apply to medicine, and to give him (her) a background for his own reading of the extensive and rapidly growing literature in the field. If his (her) senior colleagues also find it useful, we shall be doubly satisfied.

What was true then is even more so now as our knowledge of genetics and of the human genome is rapidly becoming an integral part of public health and the practice of medicine. This new edition of *Genetics in Medicine*, the seventh, seeks to fulfill the goals of the previous six by providing an accurate exposition of the fundamental principles of human and medical genetics. Using illustrative examples drawn from medicine, we continue to emphasize the genes and molecular mechanisms operating in human diseases.

Much has changed, however, since the last edition of this book. Completion of the Human Genome Project provides us with a catalogue of all human genes, their sequence, and an extensive, and still growing, database of human variation. Genomic information has stimulated the creation of powerful new tools that are changing human genetics research and medical genetics practice. We therefore have expanded the scope of the book to incorporate the concepts of "Personalized Medicine" into *Genetics in Medicine* by providing more examples of how genomics is being used to identify the contributions made by genetic variation to disease susceptibility and treatment outcomes.

The book is not intended to be a compendium of genetic diseases nor is it an encyclopedic treatise on human genetics and genomics in general. Rather, the authors hope that the seventh edition of *Genetics in Medicine* will provide students with a framework for understanding the field of medical genetics while giving them a basis on which to establish a program of continuing education in this area. The clinical cases, first introduced in the last edition to demonstrate and reinforce general principles of disease inheritance, pathogenesis, diagnosis, management, and counseling, continue to be an important feature of the book. We have expanded the set of cases to add more common complex disorders to the original set of cases, which comprised mostly highly informative and important disorders with mendelian inheritance. To enhance further the teaching value of the Clinical Cases, we have added an additional feature to the seventh edition: at specific points throughout the text, we provide a case number (highlighted in blue) to direct readers to the case in the Clinical Case Studies section that is relevant to the concepts being discussed at that point in the text.

Any medical or genetic counseling student, advanced undergraduate, graduate student in genetics, resident in any field of clinical medicine, practicing physician, or allied medical professional in nursing or physical therapy should find this book to be a thorough but not exhaustive (or exhausting!) presentation of the fundamentals of human genetics and genomics as applied to health and disease.

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The authors wish to express their appreciation and gratitude to their many colleagues who, through their ideas, suggestions, and criticisms, improved the seventh edition of *Genetics in Medicine*. In particular, we are grateful to Leslie Biesecker for sharing his knowledge and experience in molecular dysmorphology and genetics in the writing of Chapter 14, "Developmental Genetics and Birth Defects." We also thank Win Arias of the National Institutes of Health; Peter Byers and George Stamatoyannopoulos of the University of Washington; Diane Cox of the University of Alberta; Gary Cutting and David Valle of the Johns Hopkins School of Medicine; Robert Desnick of the Mount Sinai School of Medicine; Curt Harris of the National Cancer Institute; Douglas R. Higgs of the Weatherall Institute of Molecular Medicine; Katherine High of the Children's Hospital of Philadelphia; Jennifer Jennings of the Institute of Genetics of the Canadian Institutes of Health Research; Mark Kay of Stanford University; Muin Khoury of the Centers for Disease Control; Joe Clarke, Don Mahuran, Chris Pearson, Peter Ray, and Steve Scherer of the Hospital for Sick Children, Toronto; Joseph Nevins and Hutton Kearney of Duke University; John Phillips III of the Vanderbilt University School of Medicine; Jennifer Puck and Mel Grumbach of the University of California, San Francisco; Eric Shoubridge of McGill University; Richard Spielman of the University of Pennsylvania; Peter St. George-Hyslop of the University of Toronto; Lyuba Varticovski of the National Cancer Institute; Paula Waters of the University of British Columbia; Huda Zoghbi and Arthur Beaudet of the Baylor College of Medicine; and David Ledbetter and Christa Lees Martin of Emory University. We also thank the many students in the Johns Hopkins/NIH Genetic Counseling Training Program for their constructive criticisms of the previous edition during the gestation of this new edition.

We once again express our deepest gratitude to Dr. Margaret Thompson for providing us the opportunity to carry on the legacy of the textbook she created 40 years ago with her late husband, James S. Thompson. Finally, we again thank our families for their patience and understanding for the many hours we spent creating this, the seventh edition of *Genetics in Medicine*.

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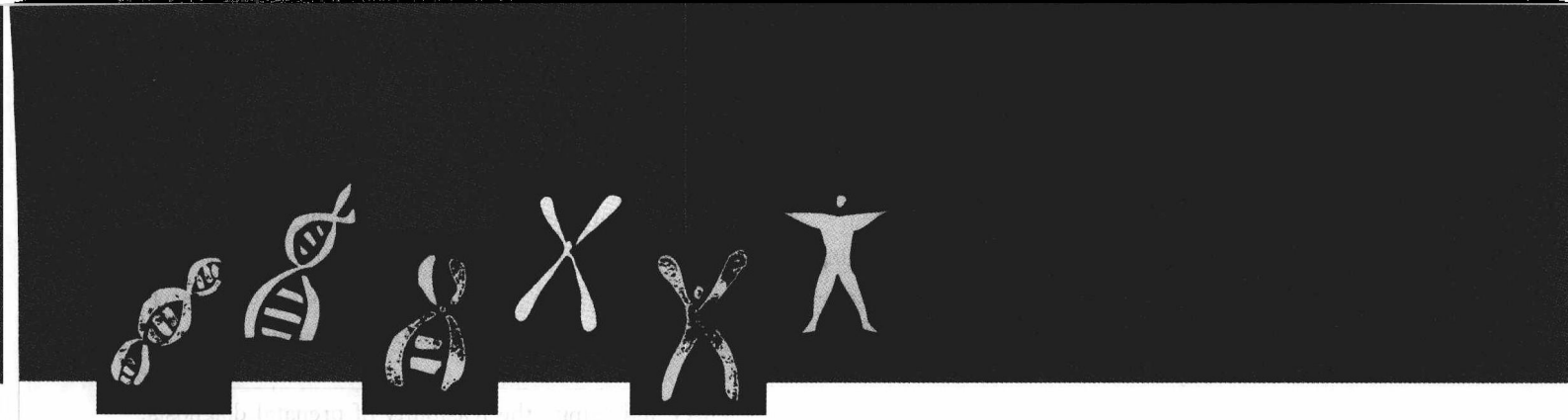


Chapter 1 Introduction

第 1 章 引 言

GENETICS AND GENOMICS IN MEDICINE (遗传医学和基因组医学)

[1]Genetics in medicine had its start at the beginning of the 20th century, with the recognition by Garrod and others that Mendel's laws of inheritance could explain the recurrence of certain disorders in families. During the ensuing 100 years, medical genetics grew from a small subspecialty concerned with a few rare hereditary disorders to a recognized medical specialty whose concepts and approaches are important components of the diagnosis and management of many disorders, both common and rare. This is even more the case now at the beginning of the 21st century, with the completion of the **Human Genome Project**, an international effort to determine the complete content of the human genome, defined as the sum total of the genetic information of our species (the suffix-ome is from the Greek for "all" or "complete"). We can now study the human genome as an entity, rather than one gene at a time. Medical genetics has become part of the broader field of genomic medicine, which seeks to apply a large-scale analysis of the human genome, including the control of gene expression, human gene variation, and interactions between genes and the environment, to improve medical care.

[1]早在 20 世纪初期，Garrod 等发现，孟德尔遗传定律可以解释某些家族性疾病的遗传现象，就此诞生了医学遗传学。更具里程碑意义的是，21 世纪初叶，经多国科学家们的通力合作，对人类基因组 DNA 的测序即**人类基因组计划 (Human Genome Project, HGP)**终于完成。人类基因组 (genome)的定义是：人类全部遗传信息的总和。

[2]Medical genetics focuses not only on the patient but also on the entire family. A comprehensive family history is an important first step in the analysis of any disorder, whether or not the disorder is known to be genetic. As pointed out by Childs, "to fail to take a good family history is bad medicine." A family history is important because it can be critical in diagnosis, may show that a disorder is hereditary, can provide information about the natural history of a disease and variation in its expression, and can clarify the pattern of inheritance. Furthermore, recognizing a familial component to a medical disorder allows the risk in other family members to be estimated so that proper management, prevention, and counseling can be offered to the patient *and* the family.

[2]医学遗传学不仅着眼于患者，而且关注整个家系。无论是否发现遗传病，分析某一种疾病的首要步骤就是进行全面的家系调查。正如 Childs 所言，"不仔细了解家族史的大夫是个庸医"。

[3]In the past few years, the Human Genome Project has made available the complete sequence of all human DNA; knowledge of the complete sequence allows the identification of all human genes, a determination of the extent of variation in these genes in different populations, and, ultimately, the delineation of how variation in these genes contributes to health and disease. In partnership with all the other disciplines of modern biology, the Human Genome Project has revolutionized human and medical genetics by providing fundamental insights into many diseases and promoting the development of far better diagnostic tools, preventive measures, and therapeutic methods based on a comprehensive view of the genome.

[3]利用 HGP 已经获得了人类基因组 DNA 的全序列。通过序列分析可鉴定所有的人类基因，识别不同种族或

民族中人类基因的变异信息，阐明基因突变和疾病的关联性。

[4]Genetics is rapidly becoming a central organizing principle in medical practice. Here are just a few examples of the vast array of applications of genetics and genomics to medicine today:

- A child who has multiple congenital malformations and a normal routine chromosome analysis undergoes a high-resolution genomic test for submicroscopic chromosomal deletions or duplications.
- A young woman with a family history of breast cancer receives education, test interpretation, and support from a counselor specializing in hereditary breast cancer.
- An obstetrician sends a chorionic villus sample taken from a 38-year-old pregnant woman to a cytogenetics laboratory for examination for abnormalities in the number or structure of the fetal chromosomes.
- A hematologist combines family and medical history with gene testing of a young adult with deep venous thrombosis to assess the benefits and risks of initiating and maintaining anticoagulant therapy.
- Gene expression array analysis of a tumor sample is used to determine prognosis and to guide therapeutic decision-making.
- An oncologist tests her patients for genetic variations that can predict a good response or an adverse reaction to a chemotherapeutic agent.
- A forensic pathologist uses databases of genetic polymorphisms in his analysis of DNA samples obtained from victims' personal items and surviving relatives to identify remains from the September 11, 2001 World Trade Center attack.
- Discovery of an oncogenic signaling pathway inappropriately reactivated by a somatic mutation in a form of cancer leads to the development of a specific and powerful inhibitor of that pathway that successfully treats the cancer.

[4]在临床上，遗传学正迅速地成为“核心要素”的角色。

[5]Genetic principles and approaches are not restricted to any one medical specialty or subspecialty but are permeating many areas of medicine. To give patients and their families the full benefit of expanding genetic knowledge, all physicians and their colleagues in the health professions need to understand the underlying principles of human genetics. These principles include the existence of alternative forms of a gene (**alleles**) in the population; the occurrence of similar **phenotypes** developing from mutation and variation at different loci; the recognition that familial disorders may arise from gene variants that cause susceptibility to diseases in the setting of gene-gene and gene-environmental interactions; the role of somatic mutation in cancer and aging; the feasibility of prenatal diagnosis, presymptomatic testing, and population screening; and the promise of powerful gene-based therapies. These concepts now influence all medical practice and will only become more important in the future.

[5]内容包括：**群体的等位基因**（基因的不同存在形式）；位于不同基因座的基因变异（突变）可导致相同的**表型**；家族性疾病可能源于基因变异体，疾病的易感性是由基因-基因或基因-环境的相互作用决定的；恶性肿瘤和衰老由体细胞基因突变所致；产前诊断、症状前诊断和群体筛查的可行性；基因治疗的可观前景等。

Classification of Genetic Disorders(遗传病的分类)

[6]In clinical practice, the chief significance of genetics is in elucidating the role of genetic variation and mutation in predisposing to disease, modifying the course of disease, or causing the disease itself. Virtually any disease is the result of the combined action of genes and environment, but the relative role of the genetic component may be large or small. Among disorders caused wholly or partly by genetic factors, three main types are recognized: chromosome disorders, single-gene disorders, and multifactorial disorders.

[6]完全或部分受遗传因素决定的疾病主要包括3类：染色体病、单基因病和多因子病。

[7]In **chromosome disorders**, the defect is due not to a single mistake in the genetic blueprint but to an excess or a deficiency of the genes contained in whole chromosomes or chromosome segments. For example, the presence of an extra copy of one chromosome, chromosome 21, produces a specific disorder, Down syndrome, even though no individual gene on the chromosome is abnormal. As a group, chromosome disorders are common, affecting about 7 per 1000 liveborn infants and accounting for about half of all spontaneous first-trimester abortions. These disorders are discussed in Chapter 6.

[7]**染色体病**并非遗传组成中单个基因的突变，而是涉及包含于整条染色体或染色体节段上的一组基因的重复或缺陷。染色体病较为常见，在活婴中的发病率约为7‰，在早期妊娠自然流产胎儿中约占50%。

[8]**Single-gene defects** are caused by individual mutant

genes. The mutation may be present on only one chromosome of a pair (matched with a normal allele on the homologous chromosome) or on both chromosomes of the pair. In a few cases, the mutation is in the mitochondrial rather than in the nuclear genome. In any case, the cause is a critical error in the genetic information carried by a single gene. Single-gene disorders such as cystic fibrosis, sickle cell anemia, and Marfan syndrome usually exhibit obvious and characteristic pedigree patterns. Most such defects are rare, with a frequency that may be as high as 1 in 500 to 1000 individuals but is usually much less. Although individually rare, single-gene disorders as a group are responsible for a significant proportion of disease and death. Taking the population as a whole, single-gene disorders affect 2% of the population sometime during an entire life span. In a population study of more than 1 million live births, the incidence of serious single-gene disorders in the pediatric population was estimated to be 0.36%; among hospitalized children, 6% to 8% probably have single-gene disorders. These disorders are discussed in Chapter 7.

[8]**单基因病**由单个基因突变所引起。突变等位基因可位于一对同源染色体的一条或两条上。囊性纤维化、镰状细胞贫血和 Marfan 综合征等都属于单基因病，具有明显的系谱特征。以总人口数为基数，某些单基因病的终身发病风险可达 2%。

[9]**Multifactorial inheritance** is responsible for the majority of diseases, all of which have a genetic contribution, as evidenced by increased risk for recurrence in relatives of affected individuals or by increased frequency in identical twins, and yet show inheritance patterns in families that do not fit the characteristic patterns seen in single-gene defects. Multifactorial diseases include prenatal developmental disorders, resulting in congenital malformations such as Hirschsprung disease, cleft lip and palate, or congenital heart defects, as well as many common disorders of adult life, such as Alzheimer disease, diabetes, and hypertension. There appears to be no single error in the genetic information in many of these conditions. Rather, the disease is the result of one, two, or more different genes that together can produce or predispose to a serious defect, often in concert with environmental factors. Estimates of the impact of multifactorial disease range from 5% in the pediatric population to more than 60% in the entire population. These disorders are the subject of Chapter 8.

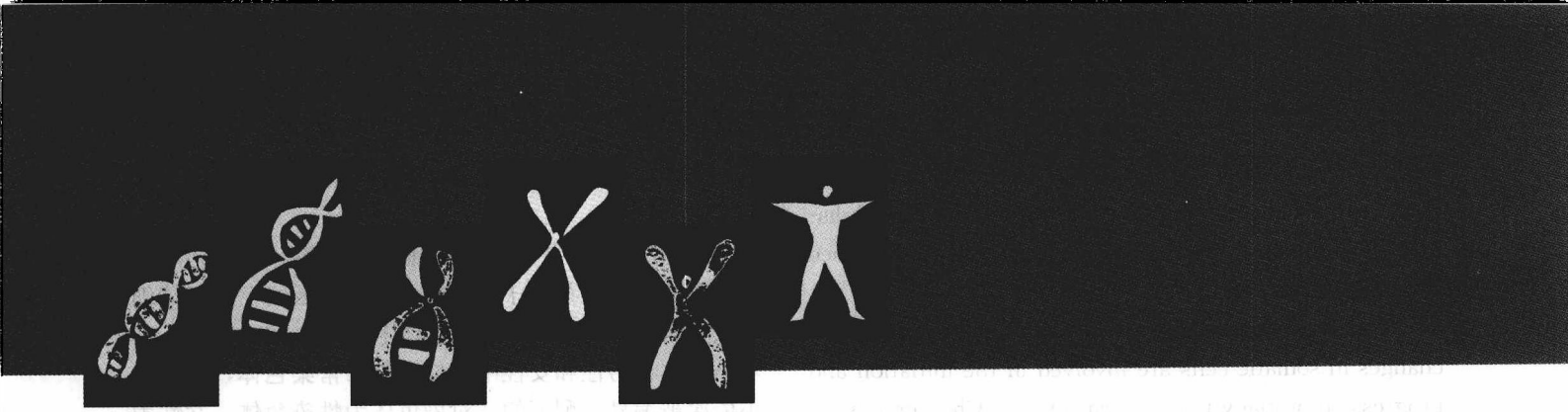
[9]**多因子遗传**与绝大多数疾病有关。常见病都有其遗传基础。多因子病由 2 个或多个不同基因的协同作用造成，这些基因也可能增加发病的易感性，并且往往有环境因素的参与。

ONWARD（展望）

[10]During the 50-year professional life of today's professional and graduate students, extensive changes are likely to take place in the discovery, development, and use of genetic and genomic knowledge and tools in medicine. It is difficult to imagine that any period could encompass changes greater than those seen in the past 50 years, during which the field has gone from first recognizing the identity of DNA as the active agent of inheritance, to uncovering the molecular structure of DNA and chromosomes and determining the complete code of the human genome. And yet, judging from the quickening pace of discovery within only the past decade, it is virtually certain that we are just at the beginning of a revolution in integrating knowledge of genetics and the genome into public health and the practice of medicine. An introduction to the language and concepts of human and medical genetics and an appreciation of the genetic and genomic perspective on health and disease will form a framework for lifelong learning that is part of every health professional's career.

[10]对每一位医务人员来说，了解人类和医学遗传学的术语、概念，并从遗传学与基因组学的视角探讨健康和疾病，应该是其毕生学习的一个框架。

（ZUO Ji 左 伋）



Chapter 2 The Human Genome and the Chromosomal Basis of Heredity

第 2 章 人类基因组和遗传的染色体基础

[1]Appreciation of the importance of genetics to medicine requires an understanding of the nature of the hereditary material, how it is packaged into the human **genome**, and how it is transmitted from cell to cell during cell division and from generation to generation during reproduction. The human genome consists of large amounts of the chemical deoxyribonucleic acid(**DNA**) that contains within its structure the genetic information needed to specify all aspects of embryogenesis, development, growth, metabolism, and reproduction-essentially all aspects of what makes a human being a functional organism. Every nucleated cell in the body carries its own copy of the human genome, which contains, by current estimates, about 25,000 **genes**. Genes, which at this point we define simply as units of genetic information, are encoded in the DNA of the genome, organized into a number of rod-shaped organelles called **chromosomes** in the nucleus of each cell. The influence of genes and genetics on states of health and disease is profound, and its roots are found in the information encoded in the DNA that makes up the human genome. Our knowledge of the nature and identity of genes and the composition of the human genome has increased exponentially during the past several decades, culminating in the determination of the DNA sequence of virtually the entire human genome in 2003.

[1]每个有核细胞都存在一套完整的人类基因组，估计约含 25000 个**基因**。在过去的几十年里，有关基因鉴定和人类基因组组成的知识指数式地增长。至 2003 年，已完成了人类基因组的测序工作。

[2]Each species has a characteristic chromosome complement(**karyotype**) in terms of the number and the morphology of the chromosomes that make up its genome. The genes are in linear order along the chromosomes, each gene having a precise position or **locus**. A **gene map** is the map of the chromosomal location of the genes and is characteristic of each species and the individuals within a species.

[2]每一个基因都有其特定的位置，即**基因座**。**基因图**则是基因在染色体上的定位图谱。

[3]The study of chromosomes, their structure, and their inheritance is called **cytogenetics**. The science of modern human cytogenetics dates from 1956, when it was first established that the normal human chromosome number is 46. Since that time, much has been learned about human chromosomes, their normal structure, their molecular composition, the locations of the genes that they contain, and their numerous and varied abnormalities.

[3]现代人类细胞遗传学始于 1956 年，当时首次确定了人类染色体的数目为 46 条。

[4]Chromosome and genome analysis has become an important diagnostic procedure in clinical medicine. As described more fully in subsequent chapters, some of these applications include the following:

Clinical Diagnosis Numerous medical disorders, including some that are common, such as Down syndrome, are associated with microscopically visible changes in chromosome number or structure and require chromosome or genome analysis for diagnosis and genetic counseling (see Chapters 5 and 6).

Gene Mapping and Identification A major goal of