Flexibook

Color Atlas of Genetics

Eberhard Passarge

Fifth Edition

basic sciences

Thieme

At a Glance

Bernhard Horsthemke
(“Benno”)

in appreciation of thirty years
of successful work together

Color Atlas of Genetics

Eberhard Passarge, MD
Professor of Human Genetics
Emeritus Director
Institute of Human Genetics
University Hospital Essen
Essen, Germany

Fifth edition, revised and updated
With 186 color plates prepared
by Jürgen Wirth

Thieme
Stuttgart · New York

Library of Congress Cataloging-in-Publication Data is available from the publisher.

Previous and foreign editions of this book:
1st German edition 1994
1st English edition 1995
1st French edition 1995
1st Japanese edition 1996
1st Chinese edition 1998
1st Italian edition 1999
1st Turkish edition 2000
2nd English edition 2001
2nd French edition 2003
1st Portuguese edition 2004
1st Spanish edition 2004
2nd German edition 2004
1st Polish edition 2004
1st Greek edition 2005
1st Arabic edition 2006
3rd English edition 2007
4th English edition 2013
3rd German edition 2008
3rd French edition 2008
2nd Turkish edition 2009
2nd Japanese edition 2009
2nd Spanish edition 2010
2nd Portuguese edition 2010
3rd Turkish edition 2017

Note: The English and the German editions are written by the author and are not translations.

Rüdigerstrasse 14, 70469 Stuttgart, Germany
http://www.thieme.de
Thieme Medical Publishers, Inc., 333 Seventh Avenue,
New York, NY 10001, USA
http://www.thieme.com

Color plates prepared by Jürgen Wirth, Professor of Visual Communication, Dreieich, Germany

Cover design: Thieme Publishing Group
Typesetting by Thomson Digital, India
Printed in China by Everbest Printing Ltd., Hong Kong

ISBN 978-3-13-241440-2
eISBN 978-3-13-241441-9

Important note: Medicine is an ever-changing science undergoing continual development. Research and clinical experience are continually expanding our knowledge, in particular our knowledge of proper treatment and drug therapy. Insofar as this book mentions any dosage or application, readers may rest assured that the authors, editors, and publishers have made every effort to ensure that such references are in accordance with **the state of knowledge at the time of production of the book.**

Nevertheless, this does not involve, imply, or express any guarantee or responsibility on the part of the publishers in respect to any dosage instructions and forms of applications stated in the book. **Every user is requested to examine carefully** the manufacturers' leaflets accompanying each drug and to check, if necessary in consultation with a physician or specialist, whether the dosage schedules mentioned therein or the contraindications stated by the manufacturers differ from the statements made in the present book. Such examination is particularly important with drugs that are either rarely used or have been newly released on the market. Every dosage schedule or every form of application used is entirely at the user's own risk and responsibility. The authors and publishers request every user to report to the publishers any discrepancies or inaccuracies noticed. If errors in this work are found after publication, errata will be posted at www.thieme.com on the product description page.

Some of the product names, patents, and registered designs referred to in this book are in fact registered trademarks or proprietary names even though specific reference to this fact is not always made in the text. Therefore, the appearance of a name without designation as proprietary is not to be construed as a representation by the publisher that it is in the public domain.

Preface

As its preceding editions of 1995, 2001, 2007, and 2013, this small book provides an overview of the field of genetics, including selected aspects of genomics. It is based on a visual approach using 186 color plates designed by the author and graphically prepared for print by Jürgen Wirth, a professor of Visual Communication. Each plate corresponds to a small chapter illustrating a concept and related facts. An explanatory text accompanies each plate on its opposite page.

The subjects of the plates have been chosen based on their importance as fundamentals and their role in the understanding the genetic bases of inherited diseases. Owing to the limited space, individual diseases are not described in detail, but references are provided for further information. In addition, the corresponding Online Mendelian Inheritance of Man (OMIM) number is provided for each disease mentioned. The OMIM is a catalog of human genes and phenotypes introduced by Victor A. McKusick in 1966. It is freely available online as Online Mendelian Inheritance of Man (OMIM: www.ncbi.nlm.nih.gov/omim). It provides all genetically relevant information about the known genetic diseases (see p. 392).

This book maintains the general structure of the previous editions: Part I addresses Fundamentals; Part II, Genomics; and Part III, Genetics in Medicine. Part III illustrates the role of genetic and genomic principles underlying the causes of human diseases. From a genetic point of view a disease can be classified on the basis of its genetic causes (genotype) rather than its manifestations (phenotype), as is otherwise customary in medicine.

The book presents ancillary information in the Introduction. Genetics and genomics as viewed today are defined and some key developments of the past are traced. The Chronology specifically lists important discoveries in the history of genetics and genomics. The historical perspectives are a reminder that the platform of knowledge today rests on previous advances.

The Appendix provides tables with supplementary genetic data. The extensive Glossary defines genetic terms. For young readers naturally interested in the future, whenever possible and appropriate, I have included a historical perspective by referring to the first description of a discovery.

This fifth edition has been extensively rewritten, reorganized, and updated. Nineteen plates are entirely new or have new parts. New topics, represented by new plates, include overviews of human evolution, aging, the CRISPR-Cas principle, genetic signaling pathways, genomic disorders and genome-wide association studies, cancer genomes, laminopathies, chromatin disorders, cohesinoptathies, and other emerging topics. About the same number of plates have also been deleted because they are no longer needed. The fifth edition is slightly smaller than the fourth edition of 2013.

This book is written for two kinds of readers: for students of biology or medicine, as an introductory overview, and for their mentors, as a visual teaching aid. It will also help other interested individuals obtain selected information about current developments and achievements in this rapidly evolving field. The reader should keep in mind that each plate and its text represent an abstract rather than a treatise, with many related details necessarily omitted. Therefore, this book is meant to be a supplement to classic textbooks rather than a substitute.

The term *Atlas* for a book was introduced in 1594 by Gerard de Kremer (1512-1594), a Flemish mathematician and cartographer also known as Mercator. His book, with a collection of 107 double page geographic maps with the title *Atlas sive Cosmographicae Meditationes de Fabrica Mundi et Fabrica Figura,* was published in 1595, a year after his death. With Africa, Asia, the "New World", and the northern polar region represented by only one map each, it was the first world atlas. Mercator explains in his introduction that he derived the term from the mythic king, Atlas of Mauretania

because of his outstanding knowledge of astronomy. Earlier it was assumed that the term atlas referred to the titan, Atlas, of Greek mythology. When Mercator's atlas appeared, many geographic regions were not yet known and had remained unmapped in his collection. Establishing genetic maps is an activity not unlike mapping new, unknown territories 500 years ago. Genetic maps are a leitmotif in genetics and a recurrent theme in this book.

Throughout the book I have emphasized the role of the evolution of genes, genomes, and organisms in understanding genetics. As noted by the great geneticist Theodosius Dobzhansky, "Nothing in biology makes sense except in the light of evolution." Indeed, genetics and the science of evolution are closely related. Today one could say, "Nothing in evolution makes sense except in the light of genetics." As a single-author book, this book represents a personal view that has developed over a period of more than fifty years of active participation in the field.

I am deeply indebted to Professor Jürgen Wirth, Professor of Visual Communication at the Universities of Applied Sciences, Darmstadt and Schwäbisch Gmünd, Germany (during the period 1978 to 2005) for his most skillful work, which is a fundamental part of this book. I thank my wife, Mary Fetter Passarge, M.D., for her helpful suggestions. At Thieme Publishers, Stuttgart, I was guided and supported by Stephan Konnry, Andreas Schabert, Nidhi Chopra, Apoorva Goel, and others.

Eberhard Passarge

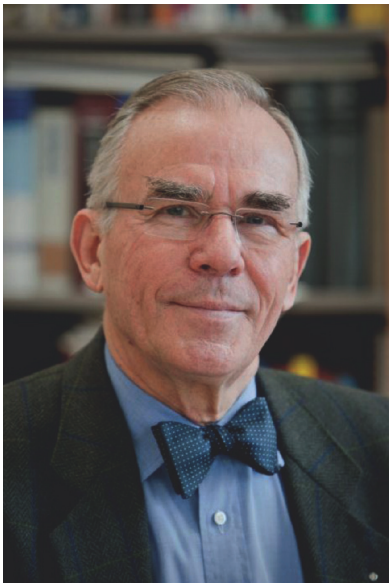
Acknowledgments

In preparing this fifth edition, I was supported by several colleagues who provided photographs and/or advice with information and text review. I am highly indebted to Gabriele Gillessen-Kaesbach and Frank Kaiser, Lübeck; Bernhard Horsthemke, Essen; Wolfram Kress, Würzburg; Stefan Mundlos, Berlin; Gesa Schwanitz, Bonn; Anne-Christin Teichmann, Sieglinde Siegert, and Andreas Scheduikat, Leipzig; and DagmarWieczorek, Düsseldorf.

For the previous editions, I would sincerely like to thank Mohammad Reza Ahmadian (Institute of Biochemistry and Molecular Biology II, University Hospital Düsseldorf, Germany); Beate Albrecht, Tea Berulava, and Bernhard Horsthemke (Institute for Human Genetics, Essen, Germany); Thomas Langmann (Pro Retina Professorship, Institute of Human Genetics, University of Regensburg, Germany); Maximilian Muenke (Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States); Heike Olbrich and Heymut Omran (Department of Pediatrics, University of Münster, Germany); and Martin Zenker (Institute of Human Genetics, University of Magdeburg, Germany). Their contributions are also acknowledged in the text accompanying the relevant plates.

Last but not least, the following colleagues deserve a mention for their generous contribution of valuable advice and additional information: Karin Buiting, Stephanie Gkalympoudis, Deniz Kanber, Dietmar Lohmann, Hermann-Josef Lüdecke, and Nicholas Wagner (Essen, Germany); Nicholas Katsanis (Duke University, Durham, North Carolina, United States); James R. Lupski (Houston, United States); Maximilian Muenke (Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States); Arne Pfeuffer (Helmholtz-Zentrum, Munich, Germany); and Friedrich Stock (Leipzig, Germany). A token of appreciation goes to the following colleagues for providing photographs or drafts for illustrations received previously for earlier editions, which are also used in the fourth edition: Alireza Baradaran (Mashhad, Iran, now Vancouver, Canada); Dirk Bootsma (Rotterdam, Netherlands); Laura Carrel (Hershey, Pennsylvania, United States); Aravinda Chakravarti and Richard I. Kelley (Baltimore, United States); Thomas Cremer (Munich, Germany); Robin Edison (National Institutes of Health, Bethesda, Maryland, United States); Evan E. Eichler (Seattle, United States); Wolfgang Engel (Göttingen, Germany); Reiner Johannisson (Lübeck, Germany); Nikolaus Konjetzko, Alma Küchler, Dietmar Lohmann, Axel Schneider, and Dagmar Wieczorek (Essen, Germany); Nicole McNeil and Thomas Ried (National Institutes of Health, Bethesda, Maryland, United States); Clemens Müller-Reible (Würzburg, Germany); Stefan Mundlos (Berlin, Germany); Helga Rehder (Marburg, Germany/Vienna, Austria); David L. Rimoin (Los Angeles, United States); Evelin Schröck (Dresden, Germany); Peter Steinbach (Ulm, Germany); Hans Hilger Ropers (Berlin, Germany); Sabine Uhrig and Michael Speicher (Graz, Austria); Michael Weis (Cleveland, Ohio, United States); and Eberhard Zrenner (Tübingen, Germany).

About the Author



Eberhard Passarge, MD, is a German human geneticist at the University Institute of Human Genetics at Essen, Germany. He graduated from the University of Freiburg, Germany in 1960 with an MD degree and received general medical training at the General Hospital Hamburg-Harburg, Germany (1961–1962) and at the Worcester Memorial Hospital, Worcester, Massachusetts, United States (1962–1963) with a stipend from the Ventnor Foundation. His postgraduate education was in pediatrics from the Cincinnati Children's Hospital Medical Center, Ohio, United States (1963–1966) with Josef Warkany and in human genetics from the Cornell Medical Center, New York, United States (1966–1968) with James German. After completing his training, he established a new division of Cytogenetics and Clinical Genetics at the Department of Human Genetics, University of Hamburg, Germany in 1968 and directed it until 1976, when he became the Professor of Human Genetics and the Founding Chairman of the Institute of Human Genetics, University of Essen, Germany, where he served until his retirement in 2001. He has remained active in the field of human genetics. From 2010 to 2014, he was the Interim Chairman at the Institute of Human Genetics at the University of Leipzig, Germany. Among his main scientific interests are the investigation of hereditary and congenital diseases and their application in genetic diagnosis and counseling. He is the author or coauthor of more than 250 scientific articles in international, peer-reviewed journals; the author of chapters in several international textbooks; and the author of three books on human and medical genetics. His experience in teaching human genetics is reflected in the *Color Atlas of Genetics*. He has served on the editorial board of several international human genetic journals. He has been the Secretary-General of the European Society of Human Genetics (1989–1991) and the President of the German Society of Human Genetics (1990–1996), of which he became an honorary member in March 2011. He is a member of the American Society of Human Genetics, a corresponding member of the American College of Medical Genetics, a founding member of the European Society of Human Genetics and the Teratology Society, and several other scientific societies.

Table of Contents

Introduction

Genetics and Genomics

Scientific advances in genetics and genomics during the past 15 years have increased our knowledge about the structure and function of the processes carrying life at the molecular and cellular levels. These have yielded insights into a better understanding of the development and differentiation of cells and tissues, functional networks, distinguishing hereditary and nonhereditary influences on the causes of diseases and the differences between normal and cancer cells.

British biologist, William Bateson (1861–1926), proposed the term *genetics* for a new biological field devoted to the scientific investigation of heredity and variations in 1906. The new science of genetics provided a theoretical framework that could also be applied to the practice of plant and animal breeding. In the opening sentence of the *Mendel's Principles of Heredity*, published in 1909, Bateson stated, "Among the biological sciences the study of genetics occupies a central position." This was subsequently borne out by the long series of discoveries and technical advances that ensued and culminated in the completion of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence (IHGSC, 2001 and 2004). These unprecedented milestones provided information about the underlying biological structures and functions in genetics not available previously (see Part I, Fundamentals).

William Bateson
(1861–1926)

The term *genome* was introduced in 1920 by Hans Winkler (1877–1945) in Hamburg, from which the term *genomics* was derived. In addition, it was used for naming a new biomedical journal, *Genomics*, founded in 1987 by V. A. McKusick (1921–2010) and F. H. Ruddle (1929–2013). Genomics defines a novel field devoted to analyzing entire genomes rather than selected genes reflecting dramatic progress during the past two decades. The genome of animals, plants, and microorganism comprises the entirety of information required for life (see Part II, Genomics). Genomics integrates genetics, molecular biology, and cell biology and is concerned with all genes and their structure and function. According to the different scientific goals and methods employed in genomics, derivative terms are used, e.g., *transcriptome* for the analysis of all molecules involved in transcription and translation and their regulation; *proteome* for the analysis of all proteins that a cell or an organism produces; and *epigenome* for the analysis of nonhereditary (epigenetic) processes. Other areas are *functional genomics* (functional analysis), *comparative genomics* (establishing genomic maps with regard to the evolution of genomes), and *bioinformatics* (assembly, storage, and management of data).

Currently, genetics and genomics constitute a scientific area relevant to all fields of medical and biological disciplines, including anthropology, evolution, biochemistry, physiology, psychology, ecology, and their related fields of science. As both are theoretical and experimental science, genetics and genomics provide an understanding of the biology of the living world and genetic diseases (see Part III, Genetics in Medicine).

Genetic Basis of Life

Each of the approximately 80 trillion (10^{12}) cells of an adult human contains a program with life-sustaining information in its nucleus (except for red blood cells, which are devoid of nucleus). This information is contained in a longitudinal molecule, DNA (deoxyribonucleic acid, see later). The instructions are encoded in discrete units, the *genes*. Around 200 different types of cells perform the complex molecular transactions under the control of various genes. Genetic information enables the cells to convert atmospheric oxygen and ingested food into energy, regulate the synthesis and transport of biologically important molecules, protect themselves from harmful invaders, such as bacteria, fungi, and viruses by means of immune defense systems, and maintain the shape and mobility of bones, muscles, and skin. Genetically determined functions of the sensory organs enable us to see, hear, taste, and perceive heat, cold, and pain. Genetic information supports brain function with the ability to learn from experience, develop speech, and integrate the environmental input into cognate behavior. Reproduction and the detoxification of exogenous molecules are also under genetic control. In addition, structural modifications in the cell nucleus, not involving DNA directly contribute important regulatory functions (see epgenetics).

The living world consists of two basic types of cells, the smallest membrane-bound units capable of independent reproduction known as *prokaryotic* cells without a nucleus (represented by bacteria and archaea) and *eukaryotic* cells with a nucleus and complex internal structures in multicellular higher organisms. Genetic information is transferred from one cell to both the daughter cells formed at each cell division and from one generation to the next through specialized cells, the *germ cells, oocytes,* and *spermatozoa*.

Biological processes are mediated by biochemical reactions involving biomolecules called *proteins*. Genes contain encoded information for the intracellular synthesis of proteins. Each protein is made up of dozens to several hundreds of amino acids arranged in a linear sequence. This primary sequence of amino acids is called a *polypeptide,* which is subsequently folded into a specific three-dimensional structure, often in combination with other polypeptides, allowing biological function. All proteins that can be synthesized constitute the *proteome*. However, most cells do not produce all possible proteins, but rather a selection, depending on the type of cell. In addition to protein-coding genes, other genes encode information for the synthesis of small molecules made up of ribonucleic acid (RNA) required for regulatory functions.

Genetic information is stored in a linear fashion like a text of individual letters and words in a defined sequence that alone makes biological sense. This text consists of the nucleotide bases of DNA that is a read-only memory device of a genetic information system called the *genetic code*. In contrast to the binary system of strings of ones and zeros used in computers ("bits," which are then combined into eight binary digits, "bytes"), the genetic code in the living world uses a quaternary system of four nucleotide bases whose chemical names have the initial letters A, C, G, and T (see Part I, Fundamentals). The quaternary code used in living cells uses three building blocks, called a *triplet codon*. Each amino acid of a protein is encoded by a specific triplet. This genetic code is universal and is used by all living cells, including plants and viruses.

Genes

A gene is a unit of genetic information contained in a DNA segment. It is equivalent to a single sentence in a meaningful text. Thus, genetic information is highly analogous to a linear text and is amenable to being stored in computers. Depending on the organizational complexity of an organism, the number and size of genes vary considerably. Their number ranges from about 500 to 5,000 in most prokaryotes and about 6,000 to 40,000 in most eukaryotes. The minimal number of genes required to sustain independent cellular life is surprisingly small: around 250 for certain bacteria. Since many proteins are involved in related functions of the same pathway, they and their corresponding genes can be grouped into families of related function. It is estimated that approximately 21,000 protein-coding genes can be assigned to around 1,000 gene families (Demuth et al, 2006).

Genes are located on chromosomes in the nucleus of each cell. Chromosomes are individual, complex structures consisting of DNA and special

DNA-related proteins (histone proteins or simply histones). Chromosomes in eukaryotes come in homologous pairs, one of each pair derived from the mother and the other from the father. Humans have 23 pairs of chromosomes, consisting of chromosomes 1–22 and an X and a Y chromosome in males or two X chromosomes in females. The number and size of chromosomes vary in different organisms, but the total number of chromosomes is characteristic for each species. Genes are arranged linearly along each chromosome with each gene having a defined position, called a *gene locus*. In higher organisms, genes are structured into contiguous sections of coding and noncoding DNA sequences, called *exons* (coding) and *introns* (noncoding), respectively. Genes in multicellular organisms vary with respect to size (ranging from a few thousand to over a million nucleotide base pairs) and the number and size of exons. Each gene has regulatory DNA sequences, some of which act from a distance. The latter determine the state of activity of a gene called *gene expression*. Most genes in differentiated, specialized cells are permanently turned off. More than 90% of the 3 billion (3×10^9) base pairs of DNA in higher organisms do not carry known coding information but contain information with regulatory functions (see Part II, Genomics).

The linear text of information contained in the coding sequences of DNA in a gene cannot be read directly. Rather, its total sequence is first converted into a structurally related molecule with a corresponding sequence of codons. This process is called *transcription*. The entire set of molecules involved is called the *transcriptome*. The molecule resulting from transcription is known as ribonucleic acid (RNA) that serves as a template to arrange the amino acids into a polypeptide in the sequence specified by the genetic code. This process is called *translation*. Each of the 21 amino acids used by living organisms is encoded by a specific sequence of three RNA molecules.

Early Genetics between 1900 and 1910

Genetic information is transmitted from one generation to another according to defined rules known as Mendelian rules, named after the Augustinian monk, Gregor Mendel (1822–1884). When Mendel conducted crossbreeding experiments with garden peas in his monastery garden in Brünn (Brno, Czech Republic), he recognized that heredity was based on individual factors that were independent of each other (Mendel, 1866). These factors are transmitted from one plant generation to the next in a predictable pattern, each factor responsible for an observable trait. The trait one can observe is the *phenotype*. The underlying genetic information is the *genotype*.

Gregor Mendel
(1822–1884)

Gregor Mendel is credited with the discovery of basic principles of genetics and is regarded as the father of genetics. However, the fundamental importance of Mendel's conclusion was only recognized in 1900 independently by Correns, Tschermak, and De Vries. The term, *gene* for the type of heritable factors observed by Mendel was introduced in 1909 by the Danish biologist, Wilhelm Johannsen (1857–1927). Beginning in 1901, Mendelian inheritance was systematically analyzed in animals, plants, and humans. Some human diseases were recognized as having a hereditary cause. A

Thomas H. Morgan
(1866–1945)

form of brachydactyly (type A1, McKusick number OMIM 112500) observed in a large Pennsylvania sibship by W. C. Farabee (PhD thesis, Harvard University, 1903) was the first condition in humans to be described as being transmitted by autosomal dominant inheritance (Haws and McKusick, 1963).

Chromosomes were first observed in dividing cells in mitosis by Flemming in 1879 and in meiosis by Strasburger in 1888. Waldeyer coined the term, *chromosome* in 1888.

Theodor Boveri (1862–1915) recognized the genetic individuality of chromosomes in 1902. He wrote that not a particular number but a certain combination of chromosomes was necessary for normal development indicating that each individual chromosome possessed different genetic qualities.

Genetics became an independent scientific field in 1910 when Thomas H. Morgan introduced the fruit fly (*Drosophila melanogaster*) for systematic genetic studies at the Columbia University in New York. Among several other fundamental discoveries, Morgan and his coworkers demonstrated that genes were arranged on chromosomes in a sequential order. Morgan summarized this in 1915 as the *chromosome theory of inheritance* (Morgan, 1926). Although genetics was well established as a biological field by the end of the second decade of the last century, knowledge of the physical and chemical nature of genes was sorely lacking. However, their structure and function remained unknown.

Changes in Genes: Mutations

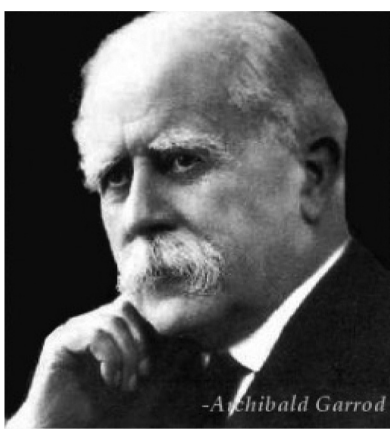
The integrity of the genetic program must be maintained without compromise; yet, it must be adaptable to respond to long-term changes in the environment during evolution. In 1901, H. de Vries recognized that genetic information was susceptible to changes. He introduced the term, *mutation* to describe the new observation. The systematic analysis of mutations contributed greatly to the further development of genetics. In 1927, H. J. Muller determined the spontaneous mutation rate in *Drosophila* and demonstrated that mutations could be induced by Rontgen rays. C. Auerbach and J. M. Robson in 1941 and F. Oehlkers independently in 1943 observed that certain chemical substances could also induce mutations. However, it remained unclear what a mutation actually was, since the physical basis for the transfer of genetic information was not known. Errors in maintaining and transmitting genetic information occur in all living systems.

Genes of fundamental importance do not tolerate changes (mutations) that compromise function. As a result, deleterious mutations do not accumulate in any substantial number. Elaborate cellular systems can recognize and eliminate faults in the integrity of DNA and genes (*DNA repair*).

Genetic Individuality

The sequence of DNA differs among unrelated individuals. This is referred to as *DNA polymorphism*. Usually, this involves just one nucleotide (*single nucleotide polymorphism*, SNP). Other forms of DNA polymorphism involve small or large blocks of repeated nucleotide sequences (*copy number variation*, CNV). Such individual genetic differences form the basis of genetic individuality. In 1908, the English mathematician, G. H. Hardy and the German physician, W. Weinberg independently recognized that Mendelian inheritance accounted for regularities in the distribution of genetic variants in different populations.

In 1902, Archibald Garrod (1857–1936), who served as Regius Professor of Medicine at the Oxford University, demonstrated that four congenital metabolic diseases (albinism, alkaptonuria, cystinuria, and pentosuria) were transmitted by autosomal recessive inheritance. He called these *inborn errors of metabolism*. In addition, Garrod was the first to recognize that subtle biochemical differences among individuals resulted from individual genetic differences. In 1931, he published a prescient monograph entitled *The Inborn Factors in Disease* (Garrod, 1931). He suggested that small genetic differences might contribute to the causes of diseases. Garrod, together with W. Bateson, introduced genetic concepts into medicine in the early years of genetics between 1902 and 1909. In late 1901, Garrod and Bateson began an extensive correspondence about the genetics of alkaptonuria and the significance of consanguinity, which Garrod had observed among the parents of affected individuals. In a letter to Bateson on January 11, 1902, Garrod wrote, "I have for some time been collecting information as to specific and individual differences of metabolism, which seems to me a little explored but promising field in relation to natural selection, and I believe that no two individuals are exactly alike chemically any more than structurally"



Archibald Garrod
(1857–1936)

(Bearn, 1993). However, Garrod's concept of genetic individuality of man was not recognized at the time. One reason might have been that the lack of knowledge on the structure and function of genes despite early fundamental discoveries. At present, we recognize individual susceptibility to a disease as an important factor in its causes (see Part III, Genetics in Medicine). Today, genetic individuality has been defined by structural DNA variants in 26 human populations (Sudmant et al, 2015).

Rise of Modern Genetics between 1940 and 1953

With the demonstration in the fungus, *Neurospora crassa* that one gene was responsible for the formation of one enzyme ("one gene, one enzyme" as formulated by Beadle and Tatum in 1941), the relationship between genetics and biochemistry became apparent. Systematic studies in microorganisms led to other important advances in the 1940s. Bacterial genetics began in 1943 when Salvador E. Luria and Max Delbrück discovered mutations in bacteria. Other important advances were the demonstration of genetic recombination demonstrated in bacteria by Lederberg and Tatum in 1946 and in viruses by Delbrück and Bailey in 1947 as well as the observation of spontaneous mutations in bacteriophages by Hershey in 1947. The study of genetic phenomena in microorganisms turned out to be as significant for the further development of genetics as the analysis of *Drosophila* had been 35 years earlier (Cairns et al, 1978). A very influential, small book entitled *What is Life?* by the physicist, E. Schrödinger (1944) postulated a molecular basis for genes. Henceforth, the elucidation of the molecular biology of the gene became a central theme in genetics.

Genetics and DNA

A major discovery by Avery, MacLeod, and McCarty, at the Rockefeller Institute in New York in 1944, indicated that DNA carried genetic information in bacteria. DNA was recognized as a chemically relatively simple, long-chained molecule by Friedrich Miescher in 1869 but considered too simple for genetic information. In 1928, F. Griffith observed that permanent (genetic) changes could be induced in pneumococcal bacteria by a cell-free extract derived from other strains of pneumococci,

called the *transforming principle*. Avery and his coworkers demonstrated DNA to be the transforming principle. In 1952, Hershey and Chase proved that DNA alone carried genetic information and excluded other molecules. With this discovery, the question of the structure of DNA took center stage in biology as described by McCarty (1985) and Dubos (1976).

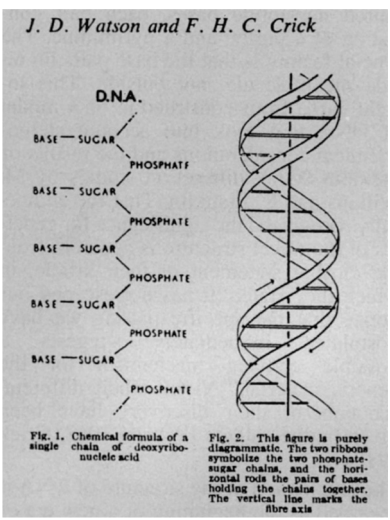
This question regarding the structure of DNA was resolved in a short, one-page article in the journal, *Nature* on April 25, 1953 (Watson and Crick, 1953). The authors proposed the structure of DNA as a double helix, which consisted of two complementary chains of alternating sugar (deoxyribose) and monophosphate molecules, oriented in opposite directions. Inside the helical molecule are the paired nucleotide bases. Each pair consists of a pyrimidine and a purine, either of a cytosine (C) and a guanine (G) or of a thymine (T) and adenine (A). The crucial feature is that the base pairs (C-G and A-T) are located inside the molecule, not outside. The DNA structure as a double helix was derived from model building using the. This idea was largely supported by an X-ray diffraction photograph of crystalline DNA obtained by Rosalind E. Franklin (Franklin and Gosling, 1953), indicating DNA to be a helix (Maddox, 2002).

The structure of DNA as a double helix with the nucleotide bases inside explains two fundamental genetic mechanisms: the storage of genetic information in a linear, readable pattern and the replication of genetic information to ensure its accurate transmission from one generation to another.

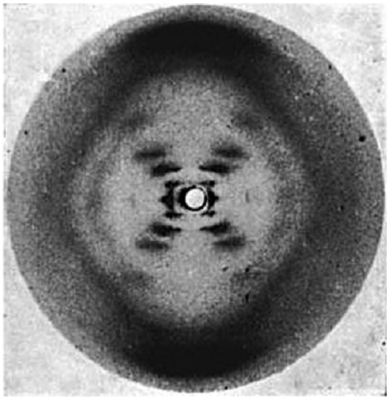
Two publications accompanied the article by Watson and Crick (1953) describing additional aspects of the DNA structure (Wilkins et al, 1953; Franklin and Gosling, 1953). An earlier basis for recognizing the structure of DNA was the discovery by E. Chargaff in 1950 who demonstrated that cytosine and guanine as well as adenine and thymine were present in the same quantity in DNA. However, this was not recognized as a result of pairing (Wilkins, 2003). Vivid, albeit different, accounts of the discovery of the structure of DNA have been provided by the scientists involved (Watson, 1968; Crick, 1988; Wilkins, 2003; Maddox, 2002 about Rosalind Franklin).

The elucidation of the structure of DNA is regarded as the beginning of a new era of

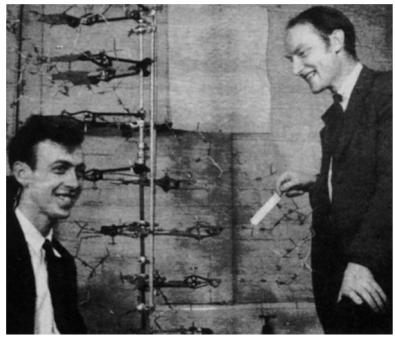
Oswald T. Avery in 1937
(1877–1955)



DNA structure 1953



Franklin's photograph 51 indicating DNA to be a helix.



Watson and Crick in 1953
(Photograph by Anthony Barrington Brown, Nature 421: 417, 2003)

molecular biology and genetics. The description of DNA as a double-helix structure led directly to an understanding of the possible structure of genetic information. When F. Sanger determined the sequence of amino acids of insulin in 1955, he provided the first proof of the primary structure of a protein. This showed that the sequence of amino acids in proteins corresponded to the sequential character of DNA. The genetic code required for the synthesis of proteins from DNA and mRNA was determined in the years from

Maurice Wilkins (1916–2004)

Rosalind Franklin (1920–1958)

1963 to 1966 by Nirenberg, Mathaei, Ochoa, Benzer, Khorana, and others. Several authors have presented detailed accounts of these developments (Watson, 1968, 2000; Chargaff, 1978; Stent, 1981; Watson and Tooze, 1981; Crick, 1988; Judson, 1996; Wilkins, 2003).
With the structure of DNA known, the nature of the gene could be redefined in molecular terms. In 1955, Seymour Benzer (1921–2007) established the first genetic fine structure. He

established a genetic map of contiguous deletions of a region (rII) of the bacteriophage T4. He found that mutations could be divided into two functional groups: A and B. Mutants belonging to different groups could complement each other by eliminating the effects of the deletion; those belonging to the same group could not. This work defined the gene in terms of molecular function.

New Methods in the Development of Genetics after 1953

From the beginning, genetics has been a field in which new concepts are based on the development of new experimental methods. In the 1950s and 1960s, the groundwork was laid for *biochemical genetics* and *immunogenetics*. Relatively simple but reliable procedures for separating complex molecules by different forms of electrophoresis, methods of synthesizing DNA in vitro by Kornberg in 1956, and other approaches were applied to genetics. The introduction of cell culture methods was of particular importance for the genetic analysis of humans. G. Pontecorvo introduced the genetic analysis of cultured eukaryotic cells (*somatic cell genetics*) in 1958. The study of mammalian genetics, with increasing significance for studying human genes, was facilitated by methods for fusing cells in culture (*cell hybridization*) introduced by T. Puck, G. Barski, and B. Ephrussi in 1961 and the development of a cell culture medium for selecting certain mutants in cultured cells (hypoxanthine–aminopterin–thymidine [HAT] *medium*) by J. Littlefield in 1964. The genetic approach that had been successful in bacteria and viruses could now be applied to higher organisms, thus avoiding the obstacles of a long generation time and breeding experiments. A hereditary metabolic defect in humans (galactosemia) was demonstrated for the first time in cultured human cells in 1961 by R. S. Krooth. The correct number of chromosomes in humans was determined independently in 1956 by Tjio and Levan and by Ford and Hamerton. Lymphocyte cultures were introduced for chromosomal analysis by Hungerford, and Nowell and coworkers in 1960. The first chromosomal aberrations in humans were described in 1959. The replication pattern of human chromosomes was described by German in 1962. These and other developments paved the way for a new field, *human genetics*.

Molecular Genetics

From around 1970 onward, genetics developed a new molecular dimension based on new techniques, which allowed the analysis of DNA directly. It became possible to determine the sequence of the DNA nucleotide bases by methods developed in 1977 by F. Sanger and Maxam and Gilbert (DNA sequencing). Even small amounts of DNA could be multiplied by a polymerase chain reaction (PCR) introduced in 1985. Today, molecular DNA analysis has been replaced by automated procedures allowing a high throughput analysis in a few days of what used to take weeks and longer, and at lower costs.

The discovery of reverse transcriptase, independently by H. Temin and D. Baltimore in 1970, upset the central dogma in genetics that the flow of genetic information was in one direction only, from DNA to RNA and from RNA to a protein as the gene product. *Reverse transcriptase* is an enzyme complex in RNA viruses (*retroviruses*) that transcribes RNA into DNA. Apart from being an important biological finding, such an enzyme can be utilized to obtain *complementary DNA* (cDNA) that corresponds to the coding regions of an active gene. Thus, a gene can be analyzed directly without knowledge of its gene product. Enzymes that cleave DNA at specific sites, *restriction endonucleases* or simply *restriction enzymes*, were discovered in bacteria by W. Arber in 1969 and by D. Nathans and H. O. Smith in 1971 (restriction analysis). Using these enzymes, DNA fragments of reproducible and defined sizes can be obtained and selected regions of a DNA molecule analyzed. DNA fragments of different origins could be joined and their properties analyzed. All these methods are collectively referred to as *recombinant DNA technology* (see Part I, Fundamentals).

In 1977, recombinant DNA analysis led to the unexpected finding that genes in higher organisms are not continuous segments of coding DNA but are interrupted by noncoding segments. The size and pattern of coding DNA segments, called *exons* and of the noncoding segments, called *introns* (two new terms

introduced by W. Gilbert in 1978) are characteristic for each gene, known as the *exon/intron* structure.

Genes and Evolution

The evolutionary biologist, Theodosius Dobzhansky at the Rockefeller University had stated, "Nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973) at a time when a relationship between genetics and evolution was not yet generally accepted. Today, one could say, "Nothing in evolution makes sense except in the light of genetics." Genes with comparable functions in different organisms share structural features. Occasionally, these are nearly identical, which is attributed to the process of evolution. Living organisms are related to each other by their origin from a common ancestor. Genes evolve within the context of the genome of which they constitute a part. An important evolutionary mechanism is the duplication of a gene or other DNA sequences (Ohno, 1970). During the course of evolution, existing genes or parts of genes are duplicated and reshuffled and brought together in new combinations. The human genome contains multiple sites that were duplicated during evolution (see Part II, Genomics). Most genes arise during evolution from preexisting ones or parts of genes existing before.

Transposable DNA

Certain DNA sequences can change their location by moving to a new site. Several mechanisms exist, collectively called *transposition*. This was first described between 1950 and 1953 by Barbara McClintock at the Cold Spring Harbor Laboratory, New York. She described genetic changes in Indian corn plants (maize) and their effect on the phenotype induced by a mutation in a gene that was not located at the site of the mutation. Surprisingly, such a gene could exert a type of remote control. In subsequent work, McClintock described the special properties of this group of genes, which she called *controlling genetic elements*. Different controlling elements could be distinguished according to their effects on other genes and the mutations caused. Originally, her work was received with skepticism (Fox Keller, 1983; Fedoroff and Botstein, 1992). In 1983, she received the Nobel Prize (McClintock, 1984). Today, we know that different types of transposons with different mechanisms form families of transposons. Transposition lends the genome flexibility during the course of evolution. Occasionally, a transposon inserts itself into a gene and causes a disease (Reilly et al, 2913; see Part II, Genomics).

Epigenetics

The term, epigenetics refers to a branch of biology aimed at studying the causal interactions between genes and gene products (proteins and small RNA molecules involved in the regulatory processes), which result in a phenotype. Epigenetics has attracted considerable interest in recent years. In 1942, C. H. Waddington derived the term from the words, genetics and epigenesis. It brings genetics and developmental biology together by focusing on heritable changes in gene expression without concomitant changes in the DNA sequence. Epigenetic changes are important mechanisms for control of genetic activity of many genes or groups of genes.

DNA-associated proteins (histone proteins or for short, histones) in the chromatin (the packaged DNA in the cell nucleus) are modified by different molecular mechanisms. Special enzymes add or remove methyl groups, acetyl groups, or phosphate groups at specific sites. This alters the functional state in chromatin (see p. 180 and 238). Certain states are associated with genetic activity, whereas others represent a repressed genetic state (inactivity). More than 250 differentially methylated regions (DMRs) in the genomes of human and mouse depict a specific pattern of DNA methylation.

Methylated DNA is associated with a genetically inactive state, whereas unmethylated DNA is found in genetically active regions. With certain genes, only one allele is expressed, either the one of maternal (mat) or the one of paternal (pat) origin.

Here, only one allele of a given gene or region is unmethylated and active, whereas the other allele is methylated and inactive. The methylation pattern is determined by the parental origin of the allele. Thus, either the allele of paternal origin (pat) or the allele of maternal origin (mat) is methylated. This pattern, called *genomic imprinting*, is transmitted to daughter cells and maintained. DNA methylation is an important control mechanism in gene expression such that errors in establishing or maintaining the correct methylation pattern result

in imprinting disorders (pp.194 and 368 in CAG4e).

Genetic Classification of Diseases

Modern genetic and genomic analysis immensely contributes to the diagnosis and management of human diseases (human genetics). Arguably, human genetics was inaugurated when The American Society of Human Genetics and the first journal of human genetics, *The American Journal of Human Genetics* were established in 1949. In addition, the first textbook of human genetics appeared in 1949, Curt Stern's *Principles of Human Genetics* (Stern, 1973).

As outlined in detail by Barton Childs (1999 and 2016; Childs and Pyeritz, 2013), two different views of the concept of disease can be distinguished. One, first introduced by William Osler in his fundamental textbook, *Principles and Practice in Medicine* in 1892, views a disease as a "broken machine" that needs to be recognized and repaired. In this system, diseases are mainly classified according to their phenotype, i.e., the manifestation according to organ systems, age, and gender. It does not ask why a particular disease affects one individual and not another. In contrast, Garrod's concept of genetic individuality poses the question of why a particular disease occurs. The Garrodian view of disease considers disease as a consequence of an imbalance within a patient's genetic individuality and with environmental living conditions. In human genetics, diseases are classified according to the genotype rather than the phenotype (clinical manifestation). Here, causal changes at gene loci and in genes primarily define a disease rather than the phenotype. The types of mutations represent a *molecular pathology*. Many genetic diseases have a similar phenotype, although they result from pathological changes in different genes. This is referred to as *etiological* (genetic) *heterogeneity*. Furthermore, rearrangements at different sites in one and the same gene may result in different phenotypes. Genetic heterogeneity is an important principle that always needs to be considered in the diagnosis of human genetic disorders.

A disease is genetically determined if it is mainly or exclusively caused by a functional failure in genes or their regulation. Genetic disorders can be assigned to six broad categories: (1) monogenic, (2) chromosomal, (3) complex (multigenic with interaction with environmental influences), (4) genomic disorders resulting from certain structural features of the human genome that predispose to disease-causing rearrangements of DNA segments, (5) somatic mutations (different forms of cancer), and (6) imprinting disorders resulting from aberrant patterns of imprinted genes (see epigenetics).

Several disorders can be grouped according to a signal pathway that is interrupted by a mutation or a rearrangement (see Part III, Genetics in Medicine). The estimated overall frequency of genetically determined diseases of different categories in the general population is about 3 to 5% (see Table).

Table Categories and frequency of genetically determined diseases

Category of disease	Estimated frequency per 1,000 individuals[a]
Monogenic diseases total	5–17
Autosomal recessive	2–7
Autosomal dominant	2–8
X-chromosomal	1–2
Chromosome aberrations (light microscopy)	5–7
Complex disorders (multigenic)	70–90
Genomic disorders	5–10
Somatic mutations (cancer)	200–250
Mitochondrial disorders	2–5
Imprinting disorders	1–2

[a] Approximate estimates based on various sources.

The most important and frequent group of diseases is the group comprising multigenic or multifactorial diseases. These result from environmental influences interacting with the individual genetic makeup of the affected individual. Important examples are relatively common chronic diseases, such as high blood pressure, hyperlipidemia, diabetes mellitus, gout, psychiatric disorders, disorders with intellectual impairment, aging disorders, and certain congenital malformations. Their cause is not a mutation in a single gene, but rather specific variants in several genes with predisposition to a particular disorder. Another common category is cancer, a large, heterogeneous group of nonhereditary genetic disorders resulting from mutations in somatic cells or hereditary changes in germ cells.

Numerous subspecialties of human genetics have arisen, such as *biochemical genetics*, *immunogenetics*, *somatic cell genetics*, *cytogenetics*, *clinical genetics*, *population genetics*, *teratology*, mutational studies, and others. The development of human genetics has been well summarized by McKusick (1992), McKusick and Harper (2013), and Vogel and Motulsky (1997).

The enormous progress in the medical aspects of human genetics (*medical genetics*), in particular for monogenic disorders, is best documented in *Mendelian Inheritance in Man* (MIM), a catalog of human genes and genetic disorders (McKusick, 1998). It is freely available online: *Online Mendelian Inheritance in Man* (OMIM). It was first established in 1966 by Victor A. McKusick (1921–2008) at the Johns Hopkins University in Baltimore and went through 12 printed editions (1968–1998, see p. 398 in CAG). Each entry carries a six-digit number. The first digit indicates the mode of inheritance or status of molecular knowledge (1, autosomal dominant; 2, autosomal recessive; 3, X-chromosomal; 4, Y-chromosomal; 5, mitochondrial; 6, additional molecular information [OMIM, Online Mendelian Inheritance in Man, see p. 392]). All diseases mentioned are designated with their 6-digit OMIM number throughout this book.

The Human Genome Project and other International Initiatives

A new dimension in genomics was introduced into biomedical research in 1990 by the Human Genome Project (HGP) and related programs in many other organisms (Lander and Weinberg, 2000; Green and Guyer, 2011). It ended in 2003 with the publication of the sequence of human DNA in a reference sequence (IHGSC, 2004). The HGP was an international organization representing several countries under the leadership of biomedical centers in the United States and the United Kingdom. The main goal of the HGP was to determine the entire sequence of the 3 billion nucleotide pairs in the DNA of the human genome. At the time, this was a daunting task, as it was comparable to deciphering each individual 1-mm wide letter of a strip of text 3,000 km long. The first draft of a sequenced human genome covering approximately 90% of the genome was announced in June 2000 (IHGSC, 2001; Venter et al, 2001). The complete DNA sequence of human genome was published in 2004 (IHGSC, 2004). All human chromosomes have been sequenced (see Selected Websites for Access to Genetic and Genomic Information: Nature Web Focus: Human Genome Collection and OMIM). Several other international

Victor A. McKusick (1921–2010)
(www.hopkinsmedicine.org)

initiatives have formed to investigate a defined area of research. Two examples are the HapMap Project and ENCODE.

The International HapMap Project was initiated in 2002 as an international multi country project aimed at identifying all individual genetic variants in the DNA sequence. These variants may have important influences on the causes of diseases or responses to therapeutic drugs (see Website for Access to Genetic and Genomic Information: International HapMap Project).

ENCODE (Encyclopedia of DNA Elements) is an international consortium studying all functional elements in the human genome (see Selected Websites for Access to Genetic and Genomic Information: Encyclopedia of DNA Elements).

The Human Epigenome Project (HEP) aims to identify and catalog all variable methylation positions in the human genome.

A Misconception in Genetics: Eugenics

Eugenics, a term coined by Francis Galton in 1882, aims to improve humans by genetic means. Between about 1900 and 1935, many countries adopted policies and laws that were assumed to reduce or eliminate an accumulation of "undesired" genetic traits in a population. It was believed that the "White race" was superior to others, but proponents did not realize that genetically defined human races do not exist. Eugenics assumed that sterilizing individuals with diseases considered hereditary would improve the human society. By 1935, sterilization laws had been passed in Denmark, Norway, Sweden, Germany, and Switzerland, as well as in 27 states of the United States. Individuals with mental impairment of variable degree or epilepsy and criminals and homosexuals were the prime targets. Although in most cases, the stated purpose was eugenic, sterilizations were performed for social rather than genetic reasons.

The complete lack of knowledge of the structure and function of genes might have contributed to the eugenic misconceptions, which assumed that "bad genes" could be eliminated from human populations. However, the disorders targeted are either not hereditary or have a complex genetic background. Sterilization simply will not reduce the frequency of genes contributing to mental retardation and other disorders. In Nazi Germany from 1933 until the end of World War II in 1945, eugenics was used as a pretext for widespread discrimination and the murder of millions of innocent human beings claimed to be "worthless" (Müller-Hill, 1988; Vogel and Motulsky, 1997; Strong, 2003). However, all such reasons supposedly based on genetics have no scientific basis. Modern genetics has shown that the ill-conceived eugenic approach cannot eliminate or reduce the frequency of human genetic diseases. Thus, incomplete genetic knowledge was applied to human individuals at a time when nothing was known about the structure of genes. Indeed, up to 1949, no fundamental advances in genetics had been obtained by studies in humans. Quite the opposite holds true today. It is evident that genetically determined diseases cannot be eradicated and the society has to adjust to their occurrence. No one is free from a genetic burden. Every individual carries approximately 10 or more potentially harmful changes in the genome that under certain circumstances could manifest as a genetic disease unexpectedly in any family.

Ethical and Societal Issues, Education

The HGP also devoted attention and resources to ethical, legal, and social issues (the Ethical, Legal and Social Implications [ELSI] Research program). This constituted a significant part of the HGP, in view of the far-reaching consequences of the current and expected knowledge about human genes and the genome. Depending on the family history and the type of disease, it is now often possible to obtain diagnostic information about a disease years or even decades prior to its manifestation. This widens the time frame of a diagnosis. Furthermore, not only the affected individual, the patient, but also other, i.e., the unaffected family members may seek information about their own risk for a disease or the risk for a disease in their offspring. The ability to perform presymptomatic or predictive genetic testing raises new questions about the use of genetic data. The decision to perform a genetic test has to take into account a person's view on an individual basis, and informed consent be obtained only after the individuals involved have been properly counseled about the purpose, validity, and reliability, and the possible consequences of the test result. In some countries, laws have been introduced to ensure that

any genetic information generated is used in the best interests of the individual involved, informed consent is obtained, and the confidentiality of data is assured.

The completion of the HGP and the introduction of new tools for genomic research, in particular the relatively inexpensive high-capacity methods of sequencing DNA (massive parallel sequencing, "second generation," p. 64), since 2005 have ushered in a new era of genomic medicine (Green and Guyer, 2011; Lupski et al, 2011). In addition, the whole genome can now be subjected to a search for genetic factors that contribute to the causes of a given disorder (genome-wide association studies, p. 220). Genetic and nongenetic bases of disease can be distinguished and individual risk factors determined. Individual adverse responses to therapeutic agents (pharmacogenetics) can now be defined at the level of the whole genome (pharmacogenomics). Any new, often unsuspected, genomic information has to be channeled into individual counseling and decision making.

Literature Cited in the Text

Bateson W. Mendel's Principles of Heredity. Cambridge: University of Cambridge Press; 1909

Bearn AG. Archibald Garrod and the Individuality of Man. Oxford: Oxford University Press, Oxford; 1993

Cairns J, Stent GS, Watson JD, eds. Phage and the Origins of Molecular Biology. New York: Cold Spring Harbor Laboratory Press; 1978

Chargaff E. Heraclitean Fire: Sketches from a Life before Nature. New York: Rockefeller University Press; 1978

Childs B. Genetic Medicine. A Logic of Disease. Baltimore: Johns Hopkins University Press; 1999

Childs B. A Logic of Disease. The Online Metabolic and Molecular Bases of Inherited Disease. 6th ed. Elsevier; Chap 2

Childs B, Pyeritz RE. Medicine in a genetic context. In: Rimoin DL, Pyeritz R, Korf B, eds. Emery and Rimoin's Principles and Practice of Medical Genetics. 6th ed. New York: Elsevier; 2013. Chap 2

Crick F. What Mad Pursuit: A Personal View of Scientific Discovery. New York: Basic Books; 1988

Demuth JP, De Bie T, Stajich JE, Cristianini N, Hahn MW. The evolution of mammalian gene families. PLoS One 2006;1:e85 PubMed

Dobzhansky T. Nothing in biology makes sense except in the light of evolution. Am Biol Teach 1973;35(3):125–129

Dubos RJ. The Professor, the Institute, and DNA: Oswald T. Avery, his Life and Scientific Achievements. New York: Rockefeller University Press; 1976

Fedoroff N, Botstein D, eds. The Dynamic Genome: Barbara McClintock's Ideas in the Century of Genetics. New York: Cold Spring Harbor Laboratory Press; 1992

Fox Keller EA. A Feeling for the Organism: the Life and Work of Barbara McClintock. New York: W. H. Freeman; 1983

Franklin RE, Gosling RG. Molecular configuration in sodium thymonucleate. Nature 1953;171(4356): 740–741 PubMed

Garrod AE. The Inborn Factors in Disease: an Essay. Oxford: Clarendon Press; 1931

Green ED, Guyer MS; National Human Genome Research Institute. Charting a course for genomic medicine from base pairs to bedside. Nature 2011;470(7333):204–213 PubMed

Haws DV, McKusick VA. Farabee's brachydactylous kindred revisited. Bull Johns Hopkins Hosp 1963;113:20–30 PubMed

Lander ES, Linton LM, Birren B, et al; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 2001;409(6822):860–921 PubMed

International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Nature 2004;431(7011):931–945 PubMed

Judson HF. The Eighth Day of Creation. Makers of the Revolution in Biology, expanded edition. New York: Cold Spring Harbor Laboratory Press; 1996

Lander ES, Weinberg RA. Genomics: journey to the center of biology. Science 2000;287(5459):1777–1782 PubMed

Lupski JR, Belmont JW, Boerwinkle E, Gibbs RA. Clan genomics and the complex architecture of human disease. Cell 2011;147(1):32–43 PubMed

Maddox B. Rosalind Franklin. Dark Lady of DNA. New York: HarperCollins; 2002

McCarty M. The Transforming Principle. New York: W. W. Norton; 1985

McClintock B. The significance of responses of the genome to challenge. Science 1984;226(4676):792–801 PubMed

McKusick VA. Human genetics: the last 35 years, the present, and the future. Am J Hum Genet 1992;50 (4):663–670 PubMed

McKusick VA, Harper P. History of medical genetics. In: Rimoin D, Pyeritz R, Korf B, eds. Emery and Rimoin's Principles and Practice of Medical Genetics. 6th ed. New York: Elsevier; 2013. Chap 1

McKusick VA. Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders. 12th ed. Baltimore: Johns Hopkins University Press; 1998

Mendel G. Versuche über Pflanzen-Hybriden. Verh Naturforsch Ver Brünn 1866;4: 3–47

Morgan TH. The Theory of the Gene. Enlarged and Revised Edition. New Haven: Yale University Press; 1926

Müller-Hill B. Murderous Science. Oxford: Oxford University Press; 1988

Ohno S. Evolution by Gene Duplication. New York, Berlin Heidelberg: Springer-Verlag; 1970

OMIM. Online Inheritance in Man. A Catalog of Human Genes and Genetic Disorders. Available at: http://www.ncbi.nlm.nih.gov/omim

Reilly MT, Faulkner GJ, Dubnau J, Ponomarev I, Gage FH. The role of transposable elements in health and diseases of the central nervous system. J Neurosci 2013;33(45):17577–17586 PubMed

Schrödinger E. What Is Life? The Physical Aspect of the Living Cell. New York: Penguin Books; 1944

Watson JD. The Double Helix: A Personal Account of the Discovery of the Structure of DNA. Stent GS, ed. London: Weidenfeld & Nicolson; 1981

Stern C. Principles of Human Genetics. 3rd ed. San Francisco: W. H. Freeman; 1973

Strong C. Eugenics. In: Cooper DV, ed. Encyclopedia of the Human Genome. Vol. 2. London: Nature Publishing Group; 2003:335–340

Sudmant PH, Rausch T, Gardner EJ, et al; 1000 Genomes Project Consortium. An integrated map of structural variation in 2,504 human genomes. Nature 2015;526(7571):75–81 PubMed

Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science 2001;291(5507):1304–1351 PubMed

Vogel F, Motulsky AG. Human Genetics: Problems and Approaches. 3rd ed. Heidelberg: Springer-Verlag; 1997

Watson JD. The Double Helix. A Personal Account of the Discovery of the Structure of DNA. New York: Atheneum; 1968

Watson JD. A Passion for DNA. Genes, Genomes, and Society. New York: Cold Spring Harbor Laboratory Press; 2000

Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature 1953;171(4356):737–738 PubMed

Watson JD, Tooze J. The DNA Story: a documentary history of gene cloning. San Francisco: W. H. Freeman; 1981

Wilkins MH, Stokes AR, Wilson HR. Molecular structure of deoxypentose nucleic acids. Nature 1953;171(4356):738–740 PubMed

Wilkins M. The Third Man of the Double Helix. Oxford: Oxford University Press; 2003

(revised 8 June 2017)

Further Reading

Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 6th ed. New York: Garland Publishing Co; 2015

Brown TA. Genomes. 3rd ed. New York: Garland Science; 2007

Dobzhansky T. Genetics of the Evolutionary Process. New York: Columbia University Press; 1970

Dunn LC. A Short History of Genetics. New York: McGraw-Hill; 1965

Erickson RP, Wynshaw-Boris AJ, eds. Epstein's Inborn Errors of Development: The Molecular Basis of Clinical Disorders of Morphogenesis. 3rd ed. Oxford: Oxford University Press; 2016

Gilbert SF, Barresi MJF. Developmental Biology. 11th ed. Sunderland: Sinauer; 2016

Harper PS. Practical Genetic Counselling. 7th ed. London: Edward Arnold; 2010

Griffiths AJF, Wessler SR, Lewontin RC. Carroll SB. Introduction to Genetic Analysis. 10th ed. San Francisco: W. H. Freeman; 2014

Domchek SM, Jameson JL, Miesfeldt S. The Practice of Genetics in Clinical Medicine. Harrison's Principles of Internal Medicine. 10th ed. New York: McGraw-Hill Medical; 2015. Chap 84

Jobling MA, Hollox E, Hurles M, Kivisild T, Tyler-Smith C. Human Evolutionary Genetics. 2nd ed. New York: Garland Science; 2014

Jorde LB, Carey JC, Bamshad MJ. Medical Genetics. 5th ed. Philadelphia: Elsevier; 2015

King R, Rotter J, Motulsky AG, eds. The Genetic Basis of Common Disorders. 2nd ed. Oxford: Oxford University Press; 2002

King RC, Mulligan PK, Stansfield WD. A Dictionary of Genetics. 8th ed. Oxford: Oxford University Press; 2013

Jan K, Naoyuki T. Where Do We Come From? The Molecular Evidence for Human Descent. Heidelberg: Springer-Verlag; 2002

Krebs JE, Kilpatrick ST, Goldstin ES. Lewin's Genes XI. Sudbury: Jones & Bartlett; 2013

Lodish H, Berk A, Kaiser CA, et al. Molecular Cell Biology. 8th ed. New York: W. H. Freeman; 2016

Lupski JR, Stankiewicz P, eds. Genomic Disorders. The Genomic Basis of Disease. Totowa: Humana Press; 2006

McCLINTOCK B. Chromosome organization and genic expression. Cold Spring Harb Symp Quant Biol 1951;16:13–47 PubMed

McClintock B. Induction of instability at selected loci in maize. Genetics 1953;38(6):579–599 PubMed

Morgan TH. The Theory of the Gene. New Haven: Yale University Press; 1926

Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine. 8th ed. Philadelphia: W. B. Saunders; 2016

Rimoin DL, Connor JM, Pyeritz RE, Korf BR, eds. Emery and Rimoin's Principles and Practice of Medical Genetics. 7th ed. Edinburgh: Elsevier; 2013

Scriver CR, Beaudet AL, Sly W, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001. Available at: http://www.ommbid.org. Accessed June 6, 2017

Stankiewicz P, Lupski JR. Structural variation in the human genome and its role in disease. Annu Rev Med 2010;61:437–455 PubMed

Speicher MR, Antnonarakis SE, Motulsky AG, eds. Vogel and Motulsky's Human Genetics. Problems and Approaches. 4th ed. Heidelberg: Springer-Verlag; 2010

Stebbins GL. Darwin to DNA. Molecules to Humanity. San Francisco: W. H. Freeman; 1982

Stent G, Calendar R. Molecular Genetics. An Introductory Narrative. 2nd ed. San Francisco: W. H. Freeman; 1978

Strachan T, Goodship J. Chinnery P Genetics and Genomics in Medicine. London: Garland Science; 2015

Sturtevant AH. A History of Genetics. New York: Harper & Row; 1965

Turnpenny PD, Ellard S. Emery's Elements of Medical Genetics. 14th ed. Edinburgh, Philadelphia: Elsevier-Churchill Livingstone; 2011

Watson JD, Baker TA, Bell SP, Gann A, Levine M, Losick R. Molecular Biology of the Gene. 6th ed. New York: Pearson/Benjamin Cummings and Cold Spring Harbor Laboratory Press; 2008

Weinberg RA. The Biology of Cancer. 2nd ed. New York: Garland Science; 2013

Weatherall DJ. The New Genetics and Clinical Practice. 3rd ed. Oxford: Oxford University Press; 1991

Whitehouse HLK. Towards an Understanding of the Mechanism of Heredity. 3rd ed. London: Edward Arnold; 1973

Selected Websites for Access to Genetic and Genomic Information

Cancer Genome Atlas NIH. https://cancergenome.nih.gov/. Accessed June 6, 2017

Cancer Genome Projects ICGC. http://icgc.org/. Available at: http://www.icgc.org and http://www.sanger.ac.uk/perl/genetics/CGP/cosmic. Accessed January 24, 2012

Deciphering human disease. Database of causes of illness. Available at: http://www.sanger.ac.uk/. Accessed June 6, 2017

Encyclopedia of DNA Elements. ENCODE. Available at: http://www.genome.gov/encode. Accessed June 6, 2017

GeneTests, a clinical information resource relating genetic testing to the diagnosis, management, and genetic counseling of individuals and families with specific inherited disorders. At: https://www.genetests.org. Accessed June 6, 2017

Genome Bioinformatics UCSC Genome Browser. Available at: http://genome.ucsc.edu/. Accessed June 6, 2017

Genome-wide Association Studies. Available at: http://www.genome.gov/GWAStudies/. Accessed June 6, 2017

Human Epigenome Project (HEP). Available at: http://www.epigenome.org/. Accessed June 11, 2017

International HapMap Project. Available at: www.hapmap.ncbi.nlm.nih.gov. Accessed June 6, 2017

National Human Genome Research Institute. Available at: http://www.genome.gov/Planning/. Accessed June 6, 2017

MITOMAP. A human mitochondrial genome database. Available at: http://www.gen.emory.edu/mitomap.html. Accessed June 6, 2017

National Center for Health Statistics at Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/. Accessed June 6, 2017

Nature Web Focus: Human Genome Collection. Available at: http://www.nature.com/nature/supple-ments/collections/humangenome/. Accessed January 24, 2012

OMIM. Online Mendelian Inheritance of Man. Available at: http://www.ncbi.nlm.nih.gov/omim. Accessed June 6, 2017

Online Metabolic and Molecular Bases of Inherited Disease. Available at: www.ommbid.com/. Accessed June 6, 2017

Thousand Genomes Project. Available at: http://www.1000genomes.org. Accessed June 6, 2017

Important Advances that Contributed to the Development of Genetics

(This list represents a selection and should not be considered complete; apologies to all authors not included.)

1665 Cells described and named (*Robert Hooke)*

1827 Human egg cell described *(Karl Ernst von Baer)*

1839 Cells recognized as the basis of living organisms *(Schleiden, Schwann)*

1859 Concept and facts of evolution *(Charles Darwin)*

1866 Rules of inheritance by distinct "factors" acting dominantly or recessively (*Gregor Mendel)*

1869 "Nuclein": a new acidic, phosphorus-containing, long molecule (F. *Miescher)*

1874 Monozygotic and dizygotic twins distinguished *(C. Dareste)*

1876 "Nature and nurture" (*F. Galton)*

1879 Chromosomes in mitosis *(W. Flemming)*

1883 Quantitative aspects of heredity (*F. Galton)*

1888 Term "chromosome" *(W. Waldeyer)*

1889 Term "nucleic acid" (*R. Altmann)*

1892 Term "virus" (*R. Ivanowski)*

1897 Enzymes discovered (*F. Biichner)*

1900 Mendel's discovery recognized *(H. de Vries, E. Tschermak, K. Correns,* independently). ABO blood group system *(Landsteiner)*

1901 Term "Mutation" coined *(H. deVries)*

1902 Some diseases in man inherited according to Mendelian rules *(W. Bateson, A. Garrod). Sex chromosomes (McClung). Chromosomes and Mendel's factors are related (W. Sutton). Individuality of chromosomes (T. Boveri)*

1906 Term "genetics" proposed *(W. Bateson)*

1907 Amphibian spinal cord culture *(Harrison)*

1908 Population genetics (*G. H. Hardy, W. Weinberg)*

1909 Inborn errors of metabolism (*A. Garrod). Terms "gene," "genotype," and "phenotype" proposed (W. Johannsen). Chiasma formation during meiosis (Janssens) First inbred mouse strain, DBA (C. Little)*

1910 Beginning of *Drosophila* genetics (*T. H. Morgan). First Drosophila mutation (white eyed)*

1911 Sarcoma virus (*Peyton Rous)*

1912 Crossing over (*T. H. Morgan and E. Cattell). Genetic linkage (T. H. Morgan and C. J. Lynch). First genetic map (A. H. Sturtevant)*

1913 First long-term cell culture (*A. Carrel). Nondisjunction (C. B. Bridges)*

1915 Genes located on chromosomes (chromosomal theory of inheritance; *Morgan, Sturtevant, Muller, Bridges). Bithorax mutant (C. B. Bridges). First genetic linkage in vertebrates (J. B. S. Haldane, A. D. Sprunt, N. M. Haldane). Term "intersex" (R. B. Goldschmidt)*

1917 Bacteriophage discovered (*F. d'Herrelle)*

1922 Characteristic phenotypes of different trisomies in the plant. *Datura stramonium* (*F. Blakeslee)*

1923 Chromosome translocation in *Drosophila* (*C. B. Bridges)*

1924 Blood group genetics (*Bernstein). Statistical analysis of genetic traits (R. A. Fisher)*

1926 Enzymes are proteins (*J. Sumner)*

1927 Mutations induced by X-rays (*H. J. Muller). Genetic drift (S. Wright)*

1928 Euchromatin/heterochromatin (*E. Heitz). Genetic transformation in bacteria (F. Griffith)*

1933 Pedigree analysis (*Haldane, Hogben, Fisher, Lenz, Bernstein). Polytene chromosomes (Heitz and Bauer, Painter)*

1934 Term "aneuploidy" coined *(A. F Blakeslee)*

1935 First cytogenetic map in *Drosophila (C B. Bridges). First estimate of human mutation rate (JBS Haldane)*

1937 Mouse H2 gene locus *(P. Gorer).* First human linkage group hemophilia A-colorblindness *(J. Bell and J. B. S. Haldane)*

1938 Telomere defined *(H J. Mutter)*

1940 Polymorphism (*E. B. Ford).*
Rhesus blood groups (Landsteiner and Wiener)

1941 Evolution through gene duplication (*E. B. Lewis). Genetic control of enzymatic biochemical reactions (Beadle and Tatum). Mutations induced by mustard gas*
(C Auerbach and M. Robson)

1942 Concept of epigenetics *(C. H. Waddington)*

1943 Mutations in bacteria *(S. E. Luria and M. Delbrück)*

1944 DNA as the material basis of genetic information *(Avery, MacLeod, McCarty).*
What is Life? The Physical Aspect of the Living Cell.
An influential book (*E. Schrödinger)*

1946 Genetic recombination in bacteria *(Lederberg and Tatum)*

1947 Genetic recombination in viruses *(Delbrück and Bailey, Hershey)*

1949 Sickle cell anemia, a genetically determined molecular disease *(Neel, Pauling).*
Hemoglobin disorders prevalent in areas of malaria *(J. B. S. Haldane).*
X chromatin *(Barr and Bertram)*

1950 Defined relation of the four nucleotide bases (*E. Chargaff)*

1951 Mobile genetic elements in Indian corn, *Zea mays (B. McClintock).*
α-helix and β-sheet in proteins (I. *Pauling and R. B. Corey)*

1952 Genes consist of DNA *(Hershey and Chase).* Plasmids *(Lederberg).* Transduction by phages *(Zinder and Lederberg).*
First enzyme defect in man (*Cori and Cori). First linkage group in man (Mohr). Colchicine and hypotonic treatment in chromosomal analysis (Hsu and Pomerat). Exogenous factors as a cause of congenital malformations (J. Warkany)*

1953 DNA structure (*Watson and Crick, Franklin, Wilkins). Conjugation in bacteria (W. Hayes, L. L. Cavalli, J. and E. Lederberg, independently). Non-Mendelian inheritance (Ephrussi). Cell cycle (Howard and Pelc). Dietary treatment of phenylketonuria (Bickel)*

1954 DNA repair (*Muller). HLA system (J. Dausset). Leukocyte drumsticks (Davidson and Smith). Cells in Turner syndrome are X-chromatin negative (P. Polani). Cholesterol biosynthesis (K. Bloch)*

1955 First genetic map at the molecular level (*S. Benzer). First amino acid sequence of a protein, insulin (F. Sanger). Lysosomes (C. de Duve). Buccal smear (Moore, Barr, Marberger). 5-Bromouracil, an analogue of thymine, induces mutations in phages (A. Pardee and R. Litman)*

1956 46 Chromosomes in man (*Tijo and Levan, Ford and Hamerton). Amino acid sequence of hemoglobin molecule (V. Ingram). DNA synthesis in vitro (S. Ochoa, A. Kornberg). Synaptonemal complex, the area of synapse in meiosis (M. J. Moses, D. Fawcett). Genetic heterogeneity (H. Harris, C. F. Fraser)*

1957 Genetic complementation (*Fincham). Genetic analysis of radiation effects in man (Neel and Schull)*

1958 Semiconservative replication of DNA (*M. Meselson and F. W. Stahl). Somatic cell genetics (G. Pontecorvo). Ribosomes (Roberts, Dintzis). Cloning of single cells (Sanford, Puck)*

1959 First chromosomal aberrations in man: trisomy 21 (*Lejeune, Gautier, Turpin). Turner syndrome, 45, XO (C. E. Ford). Klinefelter syndrome: 47 XXY (Jacobs and Strong). DNA polymerase (A. Kornberg). Isoenzymes (Vesell, Markert). Pharmacogenetics (Motulsky, Vogel)*

1960 Phytohemagglutinin-stimulated lymphocyte cultures (*Nowell, Moorhead, Hungerford*). Philadelphia chromosome (*Nowell and Hungerford)*

1961 The genetic code is read in triplets (*Crick, Brenner, Barnett, Watts-Tobin). The genetic code determined (Nirenberg, Mathaei, Ochoa). X-chromosome inactivation (M. F. Lyon, confirmed by Beutler, Russell, Ohno). Gene regulation, concept of operon (Jacob and Monod). Galactosemia in cell culture (Krooth). Cell hybrid-*

ization (Barski, Ephrussi). Thalidomide embryopathy (Lenz, McBride)

1962 Molecular characterization of immunoglobulins (*Edelman, Franklin). Identification of individual human chromosomes by ^{3}H-autoradiography (J. German, O. J. Miller). Term "codon" for a triplet of (sequential) bases (S. Brenner). Replicon (Jacob and Brenner). Cell culture (W. Szybalski and E. K. Szybalska). Xg, the first X-linked human blood group (Mann, Race, Sanger). Screening for phenylketonuria (Guthrie, Bickel)*

1963 Lysosomal storage diseases (*C. de Duve). First autosomal deletion syndrome (cri-du-chat syndrome, J. Lejeune)*

1964 Colinearity of gene and protein gene product (*C. Yanofsky). Excision repair (Setlow). MLC test (Bach and Hirschhorn, Bain and Lowenstein). Microlymphotoxicity test (Terasaki and McClelland). Selective cell culture medium HAT (J. Littlefield). Spontaneous chromosomal instability (J. German, T. M. Schröder). Cell culture from amniotic fluid cells (H. P. Klinger). Hereditary diseases studied in cell cultures (Danes, Bearn, Krooth, Mellman). Population cytogenetics (Court Brown). Fetal chromosomal aberrations in spontaneous abortions (Carr, Benirschke)*

1965 Sequence of alanine transfer RNA from yeast (*R. W. Holley). Limited life span of cultured fibroblasts (Hayflick, Moorhead). Crossing over in human somatic cells (J. German). Cell fusion with Sendai virus (H. Harris and J. F. Watkins)*

1966 Genetic code complete. Catalog of Mendelian phenotypes in man (*V. A. McKusick)*

1968 Restriction endonucleases (*H. O. Smith, Linn and Arber, Meselson and Yuan). Okazaki fragments in DNA synthesis (R. T. Okazaki). HLA-D the strongest histocompatibility system (Ceppellini, Amos). Repetitive DNA (Britten and Kohne). Biochemical basis of the ABO blood group substances (Watkins). DNA excision repair defect in xeroderma pigmentosum (Cleaver). First assignment of an autosomal gene locus in man (Donahue, McKusick). Synthesis of a gene in vitro (H. G. Khorana). Neutral gene theory of molecular evolution (M. Kimura)*

1970 Reverse transcriptase (*D. Baltimore, H. Temin, independently). Synteny, a new term to refer to all gene loci on the same chromosome (Renwick). Enzyme defects in lysosomal storage diseases (Neufeld, Dorfman). Individual chromosomal identification by specific banding stains (Zech, Casperson, Lubs, Drets and Shaw, Schnedl, Evans). Y chromatin (Pearson, Bobrow, Vosa). Thymus transplantation for immune deficiency (van Bekkum)*

1971 Two-hit theory in retinoblastoma (*A. G. Knudson)*

1972 High average heterozygosity (*Harris and Hopkinson, Lewontin). Association of HLA antigens and diseases*

1973 Receptor defects in the etiology of genetic defects, genetic hyperlipidemia (*Brown, Goldstein, Motulsky). Demonstration of sister chromatid exchanges with BrdU (S. A. Latt). Philadelphia chromosome as translocation (J. D. Rowley)*

1974 Chromatin structure, nucleosome (*Kornberg, Olins and Olins). Dual recognition of foreign antigen and HLA antigen by T lymphocytes (P. C. Doherty and R. M. Zinkernagel). Clone of a eukaryotic DNA segment mapped to a specific chromosome location (D. S. Hogness)*

1975 Southern blot hybridization (*E. Southern). Monoclonal antibodies (Köhler and Milstein). First protein signal sequence identified (G. Blobel). Model for promoter structure and function (D. Pribnow). First transgenic mouse (R. Jaenisch). Asilomar conference about recombinant DNA*

1976 Overlapping genes in phage ΦX174 (*Barell, Air, Hutchinson). Loci for structural genes on each human chromosome known (Baltimore Conference on Human Gene Mapping). First diagnosis using recombinant DNA technology (W. Kan, M. S. Golbus, A. M. Dozy)*

1977 Genes contain coding and noncoding DNA segments (*R. J. Roberts, P. A. Sharp,*

independently). First recombinant DNA molecule that contains mammalian DNA. Methods to sequence DNA (F. Sanger, Maxam and Gilbert). Sequence of phage ΦX174 (F. Sanger). X-ray diffraction analysis of nucleosomes (Finch and coworkers)

1978 Terms "exon" and "intron" for coding and noncoding parts of eukaryotic genes (*W. Gilbert*).
β-globulin gene structure (Leder, Weissmann, Tilghman and others). Mechanisms of transposition in bacteria. Production of somatostatin with recombinant DNA. Introduction of "chromosome walking" to find genes. First genetic diagnosis using restriction enzymes (Y. H. Kan and A. M. Dozy). DNA tandem repeats in telomeres (E. H. Blackburn and J. G. Gall)

1979 Small nuclear ribonucleoproteins ("snurps," *M R. Lerner and J. A. Steitz*). Alternative genetic code in mitochondrial DNA (*B G. Barell, A. T. Bankier, J. Drouin). p53 protein (D. P. Lane, A. Levine, L. Crawford, L. Old)*

1980 Restriction fragment length polymorphism for mapping *(D. Botstein and coworkers).* Genes for embryonic development in *Drosophila* studied by mutational screen (*C. Nüsslein-Volhard and E. Wieschaus). First transgenic mice by injection of cloned DNA (J. W. Gordon). Transformation of cultured mammalian cells by injection of DNA (M. R. Capecchi). Structure of 16S ribosomal ribonucleoprotein (C. Woese)*

1981 Sequence of a mitochondrial genome (*S. Anderson, S. G Barrett, A. T. Bankier)*

1982 Tumor suppressor genes *(H. P. Klinger).* Prions (proteinaceous infectious particles) as cause of central nervous system diseases (kuru, scrapie, Creutzfeldt-Jakob disease; *S. B. Prusiner). Insulin made by recombinant DNA marketed (Eli Lilly)*

1983 Cellular oncogenes *(H. E. Varmus and others).* HIV virus (*I. Montagnier, R. Gallo). Molecular basis of chronic myelocytic leukemia (C. R. Bartram, D. Bootsma and coworkers). First recombinant RNA molecule (E. A. Miele, D. R. Mills, F. R. Kramer). Bithorax complex of Drosophila sequenced (W. Bender)*

1984 Identification of the T cell receptor (*Tonegawa) Homeobox (Hox) genes in Drosophila and mice (W. McGinnis). Localization of the gene for Huntington disease (Gusella). Description of Helicobacter pylori (B. Marshall and R. Warren)*

1985 Polymerase chain reaction (*K. B. Mullis, R. K. Saiki). Hypervariable DNA segments as "genetic fingerprints" (A. Jeffreys). Hemophilia A gene cloned (J. Gietschier). Sequencing of the HIV-1 virus linkage analysis of the gene for cystic fibrosis (H. Eiberg and others). Isolation of telomerase from Tetrahymena (C. W. Greider and E. H. Blackburn). Isolation of a zinc finger protein from Xenopus oocytes (J. R. Miller, A. D. McLachlin, A. Klug). Insertion of DNA by homologous recombination (O. Smithies). Genomic imprinting in the mouse (B. Cattanach)*

1986 First cloning of human genes. Human visual pigment genes characterized (*J. Nathans, D. Thomas, D. S. Hogness). RNA as catalytic enzyme (T. Cech). First identification of a human gene based on its chromosomal location (positional cloning) (B. Royer-Pokora and coworkers)*

1987 Fine structure of an HLA molecule (*Björkman, Strominger and coworkers). Knockout mouse (M. Capecchi). A genetic map of the human genome (H. Donis-Keller and coworkers). Mitochondrial DNA and human evolution (R. L. Cann, M. Stoneking, A. C. Wilson)*

1988 Start of the Human Genome Project. Molecular structure of telomeres at the ends of chromosomes (*E. H. Blackburn and others). Cloning of the gene for Duchenne muscular dystrophy (L. M. Kunkel and others). Mutations in human mitochondrial DNA (D. C. Wallace). Transposable DNA as rare cause of hemophilia A (H. H. Kazazian). Successful gene therapy in vitro*

1989 Identification of the gene causing cystic fibrosis (*L. C. Tsui and others). Microdissection and cloning of a defined region of a human chromosome (Lüdecke, Senger, Claussen, Horsthemke)*

1990 Mutations in the *p53* gene as cause of Li–Fraumeni syndrome (*D. Malkin). Mutations in the gene wrinkled seed used by Mendel (M. K. Bhattacharyya). A defective gene as cause of inherited breast cancer (Mary-Claire King)*

1991 Odorant receptor multigene family (*Buck and Axel). Complete sequence of a yeast chromosome. Increasing use of microsatellites as polymorphic DNA markers. Trinucleotide repeat expansion as a new class of human pathogenic mutations*

1992 High-density map of DNA markers on human chromosomes. X chromosome inactivation center identified. p53 knockout mouse (*O. Smithies)*

1993 Gene for Huntington's disease cloned (*M. E. MacDonald). Developmental mutations in zebra fish (M. C. Mullins and C. Nüsslein-Volhard)*

1994 First physical map of the human genome in high resolution. Mutations in fibroblast growth factor receptor genes as cause of achondroplasia and other human diseases (*M. Muenke). Identification of genes for hereditary breast cancer*

1995 Cloning of the *BLM* (Bloom syndrome) gene (*N. A. Ellis, J. Groden, J. German and coworkers). First genome sequence of a free-living bacterium, Haemophilus influenzae (R. D. Fleischmann, J. C. Venter and coworkers). Master gene of the vertebrate eye, sey (small eye; G. Halder, P. Callaerts, W. J. Gehring). STS map of the human genome (T. J. Hudson and coworkers)*

1996 Yeast genome sequenced (*A. Goffeau and coworkers). Mouse genome map with more than 7,000 markers (E. S. Lander)*

1997 Sequence of *E. coli* (*F. R. Blattner and coworkers). Helicobacter pylori (J. F. Tomb). Neanderthal mitochondrial DNA sequences (M. Krings, S. Pääbo and coworkers). Mammal ("Dolly, the sheep") cloned by transfer of an adult cell nucleus into an enucleated oocyte (I. Wilmut)*

1998 RNA interference (RNAi; *A. Fire and coworkers). Nematode Caenorhabditis elegans genome sequenced human embryonic stem cells (Thomson and Gearhart)*

1999 First human chromosome (22) sequenced. Ribosome crystal structure

2000 *Drosophila* genome sequenced (*M. D. Adams). First complete genome sequence of a plant pathogen (Xylella fastidiosa). Arabidopsis thaliana, the first plant genome sequenced*

2001 First draft of the complete sequence of the human genome (*F. H. Collins, J. C. Venter and coworkers)*

2002 Genome sequence of the mouse (*R. H. Waterston and coworkers). Sequence of the genome of rice, Oryza sativa (J. Yu, S. A. Goff and coworkers). Sequence of the genomes of malaria parasite, Plasmodium falciparum and its vector, Anopheles gambiae. Earliest hominid, Sahelanthropos tchadensis (M. Brunet)*

2003 International HapMap Project and ENCODE launched sequence of the human Y chromosome (*H. Skaletsky, D. C. Page and coworkers). Homo sapiens idaltù, the oldest anatomically modern man from Pleistocene 154–160 years ago (T. D. White and coworkers)*

2004 Genome sequence of the Brown Norway rat. A new small-bodied hominin from Flores island, Indonesia *(P. Brown and coworkers)*

2005 Massive parallel DNA sequencing methods ("next generation sequencing") introduced genome sequence of the chimpanzee (*R.H. Waterston, E. S. Lander, R. K. Watson and coworkers). A total of 1.58 million human single-nucleotide polymorphisms mapped (D. A. Hinds, D. R Cox and coworkers). Human haplotype map. Sequence of the human X chromosome (M. T. Ross and coworkers). Inactivation profile of the human X chromosome (L Carrel and H. F. Willard)*

2006 All human chromosomes sequenced. Induced pluripotent stem cells (iPS), Takahashi & Yamanaka (Nobel 2012)

2007 Genome-wide studies applied to find predisposing factors for certain diseases. Genomic disorders recognized

2008 Synthetic bacterial genome (*C. Venter and coworkers.)*
Sequencing of individual human genomes

2009 Whole genome analysis by microarrays cancer genomes sequenced. *Ardipithecus ramidus* defines new stages in human evolution *(T. White and others)*

2010 Exome Sequencing Neanderthal genome sequence. Induced pluripotent stem (iPS) cells

2011 Genome structural variation (*E. E. Eichler and coworkers).*
Chromothripsis, a catastrophic event in oncogenesis (PJ Stephens and coworkers).

2012 Whole genome sequencing. Cancer epigenetics. Genome of a Denisovan.

Topologically associated domains (TADs) in chromatin.

2013 ENCODE project (**En**cyclopedia **O**f **D**NA **E**lements) launched. Genome editing CRISPR-Cas (*M. Jinek and coworkers, Charpentier & Doudna).*

2014 Nucleosome remodeling, SWI/SNF complex. Hallmarks of aging (*López-Otin).* Next generation sequencing. Complete Neandertal sequence (*K. Prüfer and coworkers). Lung cancer genome landscape.*

2015 Epigenome roadmap. *Homo naledi* (*L. Berger*). 1,000 Genomes Project. *Cancer Genome Atlas.*

2016 New telomere lengthening mechanism (*Dilley and coworkers). Mitochondrial replacement.*

2017 (first half) Liquid biopsy for ctDNA (circulating tumor DNA)

References for the Chronology

In addition to personal notes, dates are based on the following main sources:

Dunn LC. A Short History of Genetics. New York: McGraw-Hill; 1965

King RC, Mulligan PK, Stansfield WD. A Dictionary of Genetics. 8th ed. Oxford: Oxford University Press; 2013

Lander ES, Weinberg RA. Genomics: journey to the center of biology. Science 2000;287(5459):1777–1782 PubMed

McKusick VA. Human genetics: the last 35 years, the present, and the future. Am J Hum Genet 1992;50 (4):663–670

McKusick VA, Harper PS. History of Medical Genetics. In: Rimoin D, Pyeritz R, Korf B, eds. Emery and Rimoin's Principles and Practice of Medical Genetics. 6th ed. New York: Elsevier; 2013. Chap 1

Watson JD. The Double Helix: A Personal Account of the Discovery of the Structure of DNA. Stent GS, ed. London: Weidenfeld & Nicolson; 1981

Sturtevant AH. A History of Genetics. New York: Cold Spring Harbor Press; 2001

The New Encyclopaedia Britannica. 15th ed. Chicago: Encyclopaedia Britannica; 2010

Vogel F, Motulsky AG. Human Genetics: Problems and Approaches. 3rd ed. Heidelberg: Springer-Verlag; 1997

Whitehouse HLK. Towards an Understanding of the Mechanism of Heredity. 3rd ed. London: Edward Arnold; 1973

Fundamentals

Phylogenetic Tree of Living Organisms

A phylogenetic tree attempts to show inferred evolutionary relationships of living organisms. The first example of such a tree was presented by Lamarck in 1809. It is the only figure in the *Origin of Species*, in which Charles Darwin in 1859 wrote, "Probably all of organic beings which have ever lived on this Earth have descended from some primordial form." There is an overall agreement that the earth is a little more than 4.5 billion years old and that early forms of life date back to approximately 3.5 billion years.

A. Three primary branches of the tree of life

The formal evolutionary hierarchy of groups of organisms proceeds from the largest to the smallest groups: domain → kingdom → phylum → order → class → family → genus → species. Living organisms are grouped according to the type of cells they consist of, either *prokaryotic* cells or *eukaryotic* cells. A third group of living organisms was recognized in the late 1960s, the Archaea (also called *archaebacteria*). They are assigned to two classes: Euryarchaeota and Crenarchaeota. Recent data indicate that the three-domain evolutionary tree actually consists of two domains: archaea and bacteria. Eukaryotes arose through a partnership between them, approximately 1.8 billion years ago (Williams et al., 2013).

Archaea can sustain without molecular oxygen at high (70–110°C, *thermophiles*) or low temperatures (*psychrophiles*), in water with high concentrations of sodium chloride (*halophiles*) or sulfur (*sulfothermophiles*), a highly alkaline environment (pH 11.5, alkaliphiles), in acid conditions (acidophiles), or in a combination of such adverse conditions that would boil or dissolve ordinary bacteria. Eukaryotes consist of several kingdoms, including animals, fungi, plants, algae, protozoa, and others. All domains have a presumed common progenitor called the *last universal common ancestor*.

B. Phylogeny of metazoa (animals)

The phylogeny of metazoa differs depending on whether it is based on the traditional interpretation or on molecular evidence as revealed mainly by ribosomal RNA sequence comparisons.

C. Mammalian phylogeny

Mammals arose approximately 100 to 120 million years ago in the late Mesozoic period of the earth. The timescale is only approximate. Of the 4,629 known mammalian species, 4,356 are placentals, and these fall into 12 orders. The first five placental orders according to their number of species are rodents (2015), followed by bats (925), insectivores (385), carnivores (271), and primates (233). DNA sequence data have resulted in some rearrangements of the phylogeny. (Figures adapted from Klein & Takahara, 2001)

Further Reading

Alberts B, et al. Molecular Biology of the Cell. 6th ed. New York, NY: Garland Science, 2015

Allers T, et al. Archaeal genetics - the third way. Nat Rev Genet 2005; 6(1): 58–73

Delsuc F, et al. Phylogenomics and the reconstruction of the tree of life. Nat Rev Genet 2005; 6(5): 361–375

Delsuc F, et al. Tunicates and not cephalochordates are the closest living relatives of vertebrates. Nature 2006; 439(7079): 965–968

Telford MJ. The animal tree of life. Science 2013; 339: 764–766

Klein J, Takahara N. Where Do We Come From? The Molecular Evidence for Human Descent. Berlin, Heidelberg: Springer-Verlag, 2001

Murphy WJ, et al. Molecular phylogenetics and the origins of placental mammals. Nature 2001; 409 (6820): 614–618

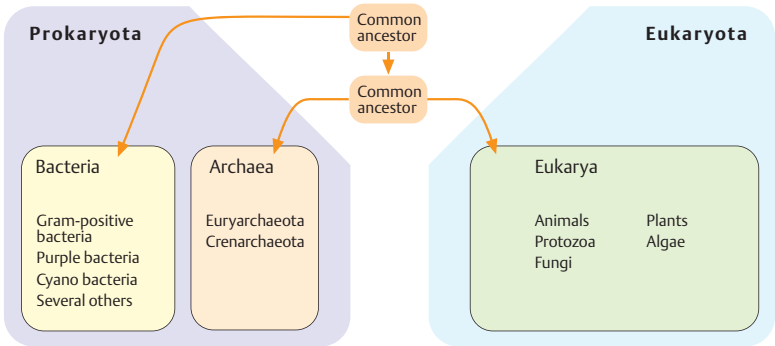
Rivera MC, Lake JA. The ring of life provides evidence for a genome fusion origin of eukaryotes. Nature 2004; 431(7005): 152–155

Williams TA, et al. An archaeal origin of eukaryotes supports only two primary domains of life. Nature 2013; 504: 231–236

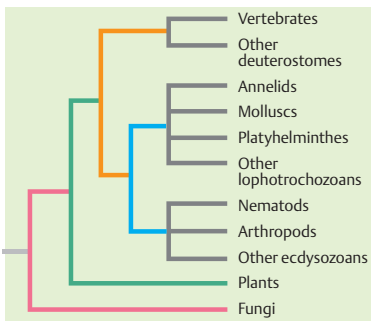
Woese CR. Interpreting the universal phylogenetic tree. Proc Natl Acad Sci U S A 2000; 97(15): 8392–8396

Woese CR. On the evolution of cells. Proc Natl Acad Sci U S A 2002; 99(13): 8742–8747

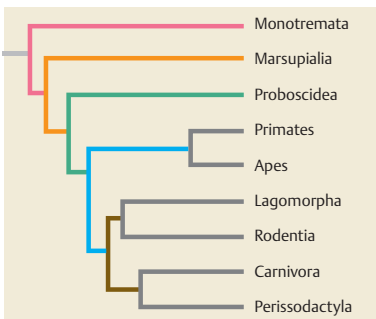
Woese CR. A new biology for a new century. Microbiol Mol Biol Rev 2004; 68(2): 173–186



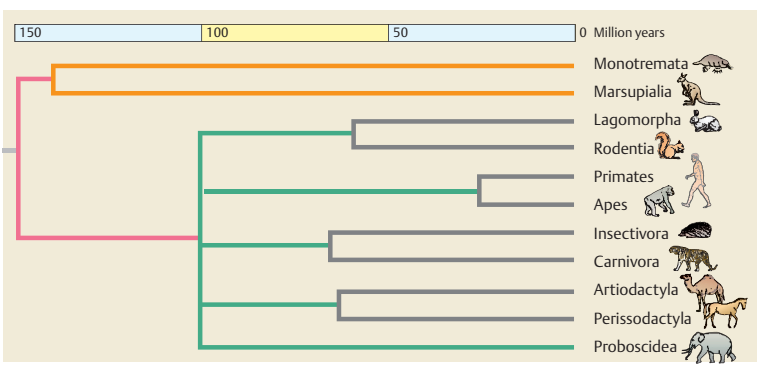
A. Three domains of living organisms (simplified version)



B. Phylogeny of metazoa, simplified



2. The molecular interpretation



1. The traditional view

C. Mammalian phylogeny (simplified)

Origins of Humans

Human and chimpanzee lineages separated from a common ancestor approximately 6 to 7 million years ago (mya). Several extinct species related to human evolution are collectively referred to as *hominids*, although the term *hominin* also is used. A complex pattern of human evolution has emerged during the past 10 to 15 years based on new fossils and genetic data derived from sequence analysis of ancient DNA. Important sites of hominids in Africa are along the Rift Valley in East Africa in the Afar and Hadar regions (north-East Ethiopia), the region on both sides of Lake Turkana in Kenya, Olduvai Gorge and Laetoli (Tanzania), two sites in Central Africa (Bar-el-Ghazal and Toros-Menalla, both in Chad), and several sites in South Africa (Sterkfontein, Kromdraai, Swartkrans, and Taung).

A. Time chart of hominid origins

Four hominid evolutionary age-related phases are distinguished: archaic hominids, transient forms including robust hominids, premodern humans, and anatomically modern man (AMM). Each group consists of different members with a relationship indicated by an arrow, however, it is often not known in detail. Of the early stages, only parts of a skeleton or teeth are available in most cases.

Archaic hominids: the oldest member of this group is *Sahelanthropus tchadensis* (6–7 mya), found in Central Africa, 2,500 km west of the Rift Valley. The size of the brain is that of a chimpanzee (360–370 cm^3), but the face is relatively flat, and enamel thickness is intermediate between a human and a chimpanzee. Two genera from approximately 5 to 6 mya are *Orrorin tugenensis* ("original man from the Tugen hills," Baringo region of central Kenya) and *Ardipithecus ramidus kadabba* (from Middle Awash, Afar, Ethiopia).

Transient hominids: this group comprises a subfamily of Hominidae, *Australopithecinae*, with a possible ancestral role for the early hominin species. Bipedal gait with concomitant anatomical changes of hands and feet, reduction of tooth size, and progressive development of the brain are main characteristics of this group. The member of this group, discovered first by Dart in 1924 (Taung child) in South Africa, was *Australopithecus africanus* with an apparent ability to walk upright. Best known of this group is *A. afarensis* (3–4 mya) with upright gait and other hominid features. "Lucy" is its most prominent representative. The robust hominids with a large jaw and teeth became extinct and are not considered to be ancestral to the genus *Homo*.

Premodern Man: the major representative of premodern man is *Homo erectus*. It originated in Africa approximately 1.9 mya and is the first earliest hominid to be found outside Africa in Asia and the Caucasus (1.6–1 mya in Georgia). *Homo habilis* (2.4–1 mya), "handy man," was not anagenetic to *H. erectus* but overlapped in time. The origin of the genus *Homo* coincides with the distinctive use of stone tools. Early *H. erectus* specimens from Africa are sometimes referred to as *H. ergaster* (2.3–1.4 mya). *Homo heidelbergensis* (0.6–0.1 mya) is an extinct *Homo* species that may be an ancestor of both *H. neanderthalensis* and *H. sapiens* in Europe. *Homo antecessor* (0.8 mya) is an extinct human species discovered 10 years ago in Gran Dolina, Spain. *Homo floresiensis* is a 60 mya extinct species with small stature (1 m adult height) discovered on Flora island, Indonesia (for Denisovans, see next page).

AMM: all humans living today belong to one species, *Homo sapiens. Homo sapiens* is derived from *H. erectus* in Africa approximately 200–100,000 years ago. AMM left Africa approximately 50,000 years ago and migrated to all continents at different times. (Data based on Wood, 2005; and Stringer, 2005.)

Further Reading

Brumm A, et al. Age and context of the oldest known hominin fossils from Flores. Nature 2016; 534 (7606): 249–253

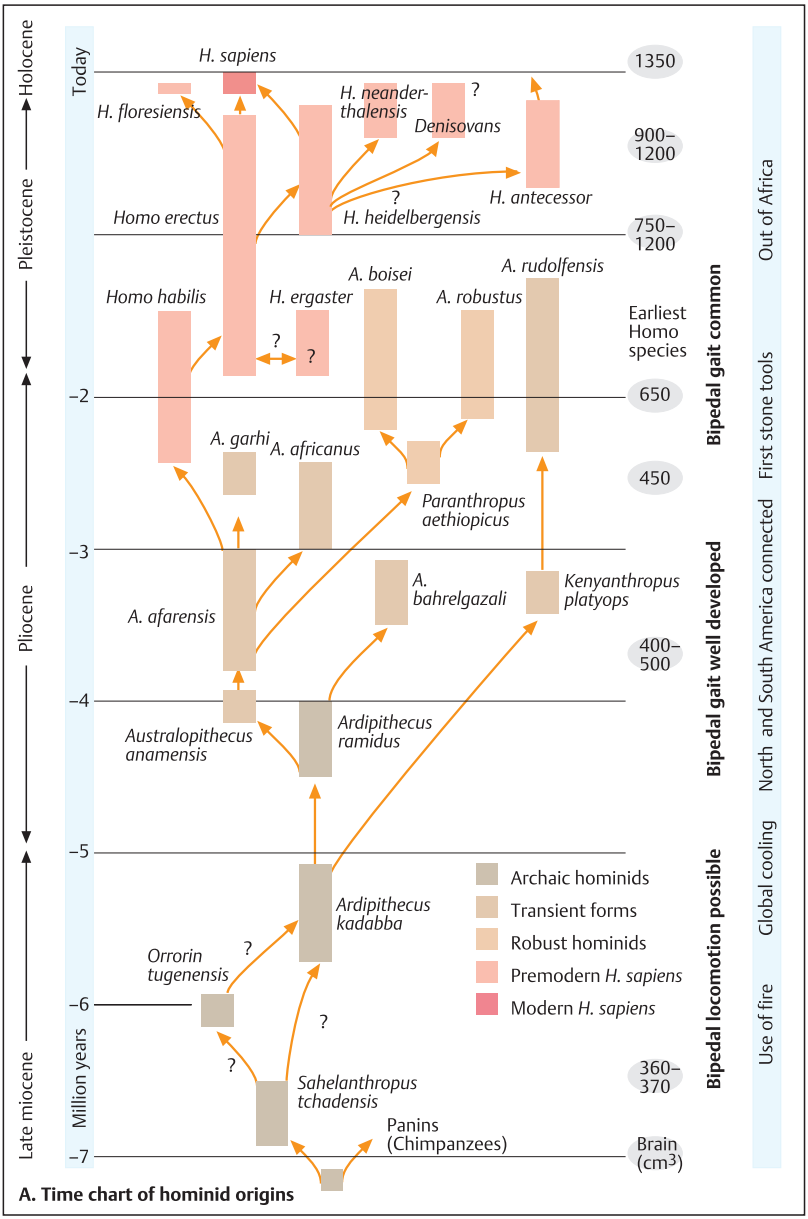
Jobling MA, et al. Human Evolutionary Genetics. 2nd ed. New York, NY: Garland, 2014

Kuhlwilm M, et al. Ancient gene flow from early modern humans into Eastern Neanderthals. Nature 2016; 530(7591): 429–433

Slatkin M, et al. Ancient DNA and human history. Proc Natl Acad Sci U S A 2016; 113(23): 6380–6387

Stringer C. The Origin of Our Species. London: Penguin Books, 2012

Wood B. Human Evolution. Oxford: Oxford University Press, 2005



A. Time chart of hominid origins

Out of Africa: Toward Modern Humans

Modern humans evolved in Africa approximately 0.2 mya. From there, several groups migrated out of Africa into Asia. DNA of all non-African human populations living today has been linked recently to one exodus. Modern humans arriving in Europe, approximately 50,000 years ago, met an older population that had been living there for approximately 0.4 my, the Neandertals. For the most part, they occupied different sites and developed different, albeit, overlapping forms of early culture, referred to as *Mousterian* for the Neandertals and *Acheulian* for the early humans, named after sites in France. In Asia, modern humans met an additional archaic hominin group, Denisovans, approximately 100 to 60,000 years ago.

A. Origins of humans in relation to Neandertals

Modern humans and Neandertals have shared a common ancestor approximately 0.8 mya. The population split occurred 270,000 to 440,000 years ago. For approximately 14,000 years, Neandertals and modern humans coexisted in regions extending from South-East Europe to Siberia. Even though Neandertals became extinct approximately 28,000 years ago, approximately 4% of European and Asian genomes share nuclear DNA with Neandertals, but African populations do not. A third group, named *Denisovans*, has been discovered from the Denisovan cave in the Altai Mountains, Siberia. Neandertals and Denisovans are more closely related to each other than to modern humans (Prüfer et al., 2014). Approximately 0.5% of the Denisovan genome was contributed by Neanderthals. (Figure adapted from Nonnan et al, 2006).

B. Dispersal of modern humans out of Africa

For the exodus out of Africa, approximately 60,000 years ago, northern and southern routes have been recognized. Asia was reached first (50,000–70,000 years ago), then Australia, and Europe somewhat later (40,000 years ago). The Americas were reached last (~13,000 years ago). The dispersal from Africa coincides with the growth of local populations and scarcity of resources. The climate must have been a main influence on the human populations that arrived in Europe. The use of tools developed rapidly, but cultural artifacts without practical use were also fabricated. The oldest tools for producing clothing, such as bone needles, are approximately 40,000 years old. Agriculture and domesticated animals were introduced approximately 12,000 years ago. (Figure modified from Jones, 2007).

C. Tools and art of early modern humans

Modern humans in the Upper Paleolithic age (17–33,000 years ago) were sophisticated makers of tools and art. Four stages of development have been identified: Magdalenian, Solutrean, Gravettian, and Aurignacian/Châtelperronian. The examples show a 26,000-year-old bone needle (**1**) and 38,000-year-old flutes made out of swan bone (**2**). (Photographs Conard et al, 2009).

Medical relevance

The field of evolutionary medicine deals with scientific and practical questions concerning the evolutionary background of many diseases in modern humans. Examples of such disorders are obesity, arteriosclerosis, hypertension, coronary heart disease, autoimmune diseases, and others. (Gluckman et al., 2009.)

Further Reading

Conard NJ, et al. New flutes document the earliest musical tradition in southwestern Germany. Nature 2009; 460(7256): 737–740

Gluckman P, et al. Principles of Evolutionary Medicine. Oxford: Oxford University Press, 2009

Jones D. Going global: how humans conquered the world. New Scientist, October 24, 2007

Meyer M, et al. Nuclear DNA sequences from the Middle Pleistocene Sima de los Huesos hominins. Nature 2016; 531(7595): 504–507

Noonan JP. Neanderthal genomics and the evolution of modern humans. Genome Res 2010; 20(5): 547–553

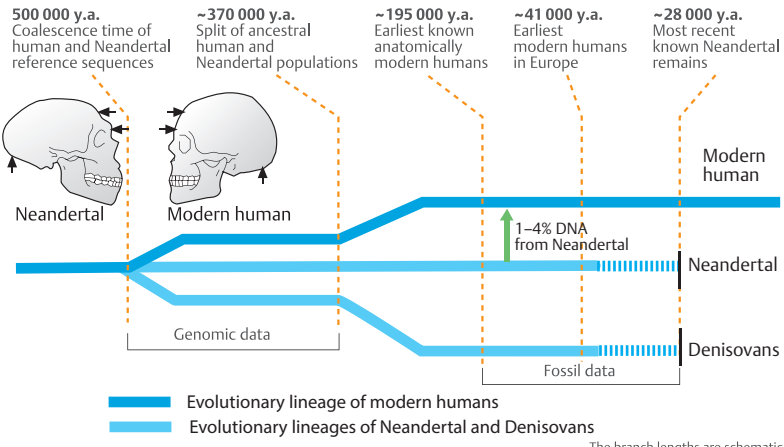
Noonan JP, et al. Sequencing and analysis of Neanderthal genomic DNA. Science 2006; 314(5802): 1113–1118

Prüfer K, et al. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 2014; 505(7481): 43–49

Reich D, et al. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 2010; 468(7327): 1053–1060

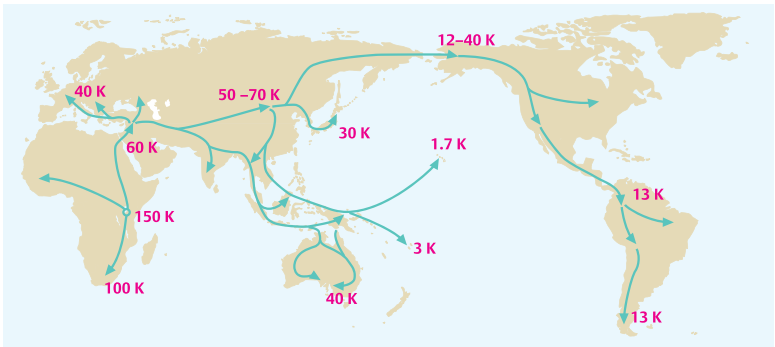
Roebroeks W, Soressi M. Neandertals revisited. Proc Nat Acad Sci 2016; 113: 6372–6379

Tucci S, et al. Population genetics: a map of human wanderlust. Nature 2016; 538(7624): 179–180

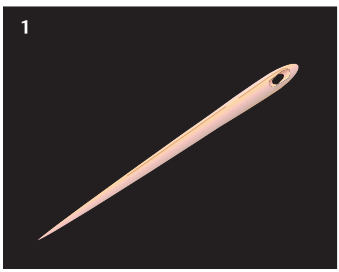


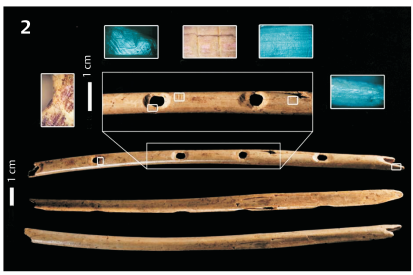
A. Origins of humans in relation to Neandertals

The branch lengths are schematic and not to scale. (y.a.: years ago)



B. Dispersal of modern humans out of Africa





C. Tools and art of early modern humans

The Cell and Its Components

Cells are the smallest organized structural units of living organisms, surrounded by a membrane, they are able to carry out a wide variety of functions during a limited life span. Each cell originates from another living cell, as postulated by Rudolf Virchow in 1855 (omnis celtula e cellula). Three basic types of cells exist: (1) *prokaryotic cells*, which carry their functional information in a circular genome without a nucleus, (2) the bacteria (or eubacteria) and archaea (or archaebacteria), and (3) *eukaryotic cells*, which contain their genome in individual chromosomes in a nucleus. They have a well-organized internal structure. Robert Hooke introduced the word *cell* in 1665 for the tiny cavities in cork, as they reminded him of the small rooms in which monks sleep. Cells were recognized as the "elementary particles of organisms," animals, and plants by Mathias Schleiden and Theodor Schwann in 1839. Today, we understand most of the biological processes in cells at the molecular level.

A. Scheme of a prokaryotic cell

Prokaryotic cells (bacteria) are typically rod-shaped or spherical, a few micrometers in diameter, and without a nucleus or special internal structures. Within a cell wall consisting of a bilayered cell membrane, bacteria contain on average 1,000 to 5,000 genes tightly packed in a circular molecule of DNA. In addition, they usually contain small circular DNA molecules named *plasmids*. These *plasmids* replicate independently of the main chromosome and generally contain genes that confer antibiotic resistance.

B. Scheme of a eukaryotic cell

A eukaryotic cell consists of cytoplasm and a nucleus, enclosed by a plasma membrane. The eukaryotic cell nucleus contains the genetic information. Nucleoli are nonmembrane-bound sites of ribosome synthesis. The nuclear membrane separates the nucleus from the cytoplasm, which harbors a complex system of inner membranes, that form discrete structures (organelles). These are the *mitochondria* (in which important energy-delivering chemical reactions take place), the *endoplasmic reticulum* (a series of membranes in which important molecules are formed), the *Golgi apparatus* (for transport functions), *lysosomes* (in which some proteins are broken down), and *peroxisomes* (for the formation or degradation of certain molecules).

Animal cells (**1**) and plant cells (**2**) share several features, but differ in important structures. A plant cell contains chloroplasts for photosynthesis, surrounded by a rigid wall of cellulose and other polymeric molecules, and contains vacuoles for water, ions, sugar, nitrogen-containing compounds, or waste products. Vacuoles are permeable to water but not to the other substances enclosed within them.

C. Plasma membrane of the cell

Cells are surrounded by a plasma membrane composed of bipartite molecules of fatty acids, water-repellent phospholipids arranged in a double layer (bilayer). Numerous molecules traverse the plasma membrane for special functions in cell communication. Different types of membrane proteins can be distinguished: (1) transmembrane proteins used as channels to transport molecules into or out of the cell, (2) proteins connected with each other to provide stability, (3) receptor molecules involved in signal transduction, (4) molecules with enzyme function to catalyze internal chemical reactions in response to an external signal, and (5) gap junctions in specialized cells forming pores between adjacent cells. Gap junction proteins are composed of connexins. They allow the passage of molecules as large as 1.2 nm in diameter. Cells contain four major families of organic molecules: carbohydrates, fatty acids, amino acids, and nucleotides.

Further Reading

Alberts B, et al. Molecular Biology of the Cell. 6th ed. New York, NY: Garland Science, 2015

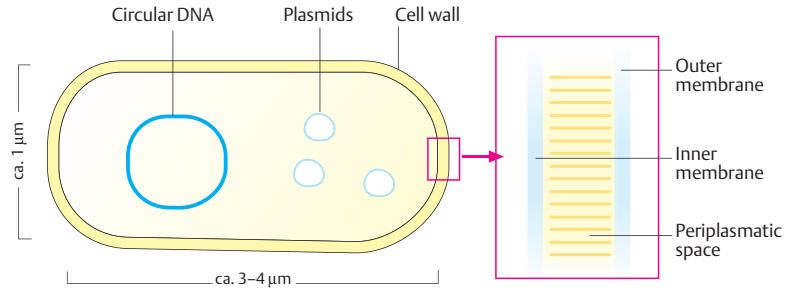
Challoner J. The Cell: A Visual Tour of the building Block of Life. Chicago, IL: University of Chicago Press, 2015

de Duve C. A Guided Tour of the Living Cell. Vols. 1 and 2. New York, NY: Scientific American Books, 1984

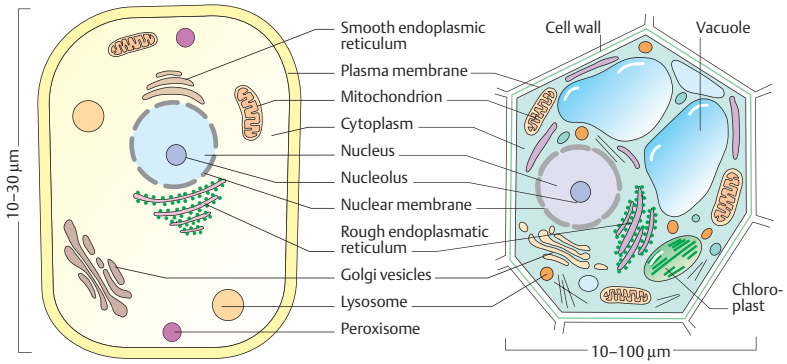
The Human Protein Atlas. Available at http://www.proteinatlas.org. Accessed 30 August, 2017

Lodish H, et al. Molecular Cell Biology. 8th ed. New York, NY: W. H. Freeman, 2016

The Human Cell. Poster in Science. November 25, 2016. Available at http://science.sciencemag.org/content/354/6315/1055.3. Accessed 30 August, 2017

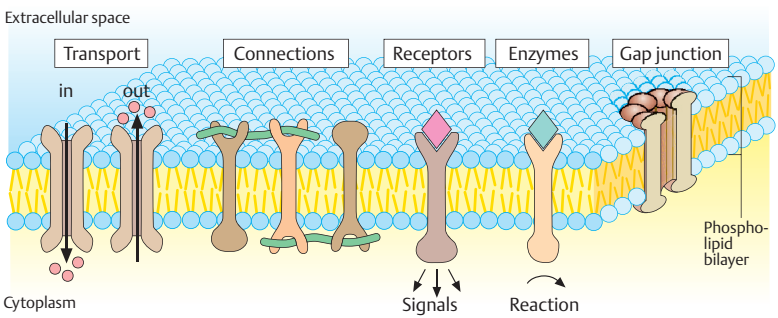


A. Scheme of a prokaryotic cell



1. Animal cell **2.** Plant cell

B. Scheme of an eukaryotic cell



C. Plasma membrane

Genetic Background of Aging Processes

Aging is the result of time-dependent processes affecting cellular, genetic, and metabolic homeostasis, including stem cell regenerative capacity. Organisms age within a species-specific *life span*, which suggests that aging not only involves damage but also genetically programmed factors. Certain gene mutations can extend life span in nematodes, Drosophila, and mice. Some human genetic disorders are associated with premature aging and a reduced life span.

A. Phenotypic manifestations of aging

Gustav Klimt (1862–1918) illustrated how human phenotypes appear at different ages (**1**). At the cellular level, the life span of cultured human fibroblasts is limited to approximately 40 to 60 cell divisions, depending on the age of the donor, referred to as Hayflick phenomenon. Initially (phase I) cells grow as long as there is sufficient surface (phase II). Then they reach phase III and no longer divide (**2**). This quiescent, nondividing state is called *cellular senescence*. In contrast, cancer cells in culture continue to divide. At the organismal level, aging affects almost all functions of the body, cognitive abilities, and reproductive success. It also increases the risk for common diseases such as atherosclerosis and cancer. Seven pillars of areas of research in aging involving different mechanisms in aging processes have been suggested (**3**). (Illustrations: 1, Galleria Nazionale d'Arte Moderna, Roma; 2, Hayflick and Moorhead, 1961; 3, Kennedy et al., 2014.)

B. Age-related changes in the cell

Aging is associated with DNA damage and telomere shortening. In addition, other cellular structures and processes are impaired, including nuclear architecture, mitochondrial function and stability, epigenetic regulation, maintenance of proteins, and intercellular communication. (Figure adapted from López-Otín et al, 2013).

C. Genetic premature aging disorders

Adult progeria or Werner syndrome, WS (OMIM 277700), first described in 1904, is an autosomal recessive disorder of multiple premature aging manifestations with onset during the second and third decades of life. WS is caused by homozygous mutations in the DNA helicase gene *WRN* (OMIM 604611) encoding RECQL2. Other helicase disorders are Bloom syndrome (OMIM 210900) due to mutations in RECQL3 (*BLM* gene 604610), and Rothmund-Thomson syndrome (OMIM 277700) due to mutations in RECQL4 (603780). Helicases unwind the DNA and are important for DNA replication, recombination, repair, and transcription (see p. 52). Loss of helicase function leads to genome instability. (Illustration: Werner Syndrome International Registry, http://www.wernersyndrome.org/).

Further Reading

Criscione SW, et al. The chromatin landscape of cellular senescence. Trends Genet 2016; 32(11): 751–761

Dong X, et al. Evidence for a limit to human lifespan. Nature 2016; 538(7624): 257–259

Hayflick L, et al. The serial cultivation of human diploid cell strains. Exp Cell Res 1961; 25: 585–621

Hayflick L. The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 1965; 37: 614–636

Kennedy BK, et al. Geroscience: linking aging to chronic disease. Cell 2014; 159(4): 709–713

Kenyon CJ. The genetics of ageing. Nature 2010; 464 (7288): 504–512

López-Otín C, et al. The hallmarks of aging. Cell 2013; 153(6): 1194–1217

Martin GM. The biology of aging. In: Longo DL, et al., eds. Harrison's Principles and Practice of Internal Medicine. 18th ed. New York, NY: McGrawHill Medical, 2012: 562–569

Oberdoerffer P, et al. The role of nuclear architecture in genomic instability and ageing. Nat Rev Mol Cell Biol 2007; 8(9): 692–702

OMIM: Online Mendelian Inheritance in Man. A Catalog of Human Genes and Genetic Disorders. Available at www.ncbi.nlm.nih.gov/Omim

Oshima J, et al. Werner syndrome: clinical features, pathogenesis and potential therapeutic interventions. Aging Res Rev 2017; 33: 105–114

Zhang W, et al. Aging stem cells. A Werner syndrome stem cell model unveils heterochromatin alterations as a driver of human aging. Science 2015; 348(6239): 1160–1163

Zhang H, et al. NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice. Science 2016; 352(6292): 1436–1443