

HUMAN GENETICS



Norman V. Rothwell

PRENTICE-HALL, INC. / ENGLEWOOD CLIFFS, N.J., 07632

NORMAN V. ROTHWELL

PROFESSOR OF BIOLOGY / LONG ISLAND UNIVERSITY

HUMAN GENETICS

Library of Congress Cataloging in Publication Data

Rothwell, Norman V (date)

Human genetics.

Bibliography: p.

Includes index.

1. Human genetics. I. Title.
QH431.R853 573.2 '1 76-26701
ISBN 0-13-445080-9

© 1977 by Prentice-Hall, Inc., Englewood Cliffs, N.J. 07632

All rights reserved.

No part of this book may be reproduced in any form
or by any means without permission in writing from
the publisher.

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Prentice-Hall International, Inc., *London*
Prentice-Hall of Australia, Pty. Limited, *Sydney*
Prentice-Hall of Canada, Ltd., *Toronto*
Prentice-Hall of India Private Limited, *New Delhi*
Prentice-Hall of Japan, Inc., *Tokyo*
Prentice-Hall of Southeast Asia Pte. Ltd., *Singapore*
Whitehall Books Limited, *Wellington, New Zealand*

HUMAN GENETICS

PRENTICE-HALL BIOLOGICAL SCIENCES SERIES

William D. McElroy and Carl P. Swanson, *Editors*

Cover photo: From a sculpture by Arpi Misserlian

To Robert F. Lewis / friend and colleague

PREFACE

The basic objective of this book is to present the major concepts and problems of human genetics in a manner that can be readily understood by a reader with little or no background in the subject. Specific topics and examples were selected with two major audiences in mind: First, for “non-science” college students who wish to become familiar with biological principles that will remain pertinent to their everyday affairs. To satisfy that need, several schools offer a variety of courses in specific areas of the life sciences, among them human genetics intended for the non-science undergraduate. The number of such courses is increasing because of a growing awareness of human genetics problems. This book is also written for persons preparing for careers as nurses, physicians’ associates, clinical technicians, and social workers concerned with communicating genetic information to community groups. The demand for physicians’ associates and other allied medical personnel continues to increase with advances in human genetics, particularly as related to prenatal diagnosis, detection of carriers in high-risk groups, and the manipulation of environmental factors.

In fact, any person who desires to understand the genetic and environmental components that interact to produce the human being will find this book of value. No attempt is made to satisfy the requirements for a course in general genetics; instead we deal almost completely with the human organism. Examples from other species are given only when they best serve to make a major point. No plant genetics is included nor are microorganisms explored as genetic systems. However, references to bacteria and viruses are made throughout the text because of the insights these groups provide as to the nature of the gene and molecular interactions. Phage replication and the prophage concept are also included to explain their relation to environmental and genetic interactions and the triggering of diseases.

Technical nomenclature is minimized but the reader is not “talked down to” by substituting awkward phrases in place of common genetic expressions. All the elementary genetic terms are given such as homozygous, heterozygous, genotype, allele. All terms are explained thoroughly and used continually so as

to integrate them with a reader's vocabulary without requiring rote memorization.

Certain elementary mathematical principles are stressed, mainly those applying to the concepts of probability. Nowhere are these concepts more important than in their application to problems in human genetics. Failure to understand the principles of probability as they relate to simple genetic ratios and gene frequencies in populations can lead to naive and unfortunate interpretations of the facts. The person who encounters genetic problems in daily life must understand the simple fundamentals of probability. The necessary, elementary mathematical concepts are carefully developed here and applied to specific examples of the human organism.

Genetic counseling is reviewed within the framework of recent ideas that attempt to define the role of counseling teams. The material on counseling is intended for the reader with a medical orientation or anyone who may be unaware of the role of this essential service. The chapter on pedigree analysis shows the dependence of the genetic counselor on probability.

Although the specific genetic disorders included are rather extensive this book is not a clinical text. These disorders are afflictions that are familiar to some persons (such as cystic fibrosis, sickle cell anemia, Tay-Sachs disorder). Others which may be less well known (such as glycogen storage diseases) are explained in regard to the information they provide on gene expression and the manipulation of the environment. Certain subjects are treated (homosexuality, for example) even though no genetic bases may have been established for them. The controversial topic of sex-role inheritance is also included. Such material is intended to answer questions which occur to a reader who often finds such topics omitted from basic genetics texts.

The presentation assumes no familiarity with biology or other sciences beyond that encountered in most high school curricula. Chemistry is kept to the essentials needed to appreciate the nature of gene action and of molecular disorders, their detection, and diagnosis. Mitosis and meiosis are stressed in relation to the transmission and maintenance of balanced sets of genetic information. Names of meiotic substages are not given nor are any other terms that are unnecessary for an appreciation of the biological significance of nuclear divisions. The concepts of linkage and crossing over, difficult ones for many students, cannot be eliminated from any text on human genetics without the danger of presenting a distorted viewpoint and an incomplete picture of the relationship between genes and chromosomes. Moreover, our knowledge of human linkage groups and chromosome maps is rapidly growing and will continue to be applied more routinely to the prenatal diagnosis of human afflictions. The treatment of these topics here is kept as simple as possible and is always tied to familiar situations and practical applications.

A glossary, which follows the last chapter, includes all terms defined and used in the text, as well as elementary biological expressions that may not be familiar to the student with little science background.

Norman V. Rothwell

Brooklyn, New York

ACKNOWLEDGMENTS

The author expresses his appreciation to the following individuals and sources for permission to reproduce the material cited below:

Figures

- 1-3 A. M. Winchester, *Human Genetics*, Charles E. Merrill Publishing Co., Columbus, Ohio, 1971.
- 1-10 Carolina Biological Supply Company.
- 2-4(A,B) Victor A. McKusick, *Human Genetics*, 2nd ed., Prentice-Hall, Inc., Englewood Cliffs, N.J., 1969.
- 2-5(A) Schreck, et al., *Proc. Nat. Acad. Sci. (U.S.)* 70: 804-807.
- 2-5(B) Frank H. Ruddle and Raju S. Kucherlapati, "Hybrid Cells and Human Genes," pp 40-41, *Scientific American*, July, 1974. Copyright © 1975 by *Scientific American*. All rights reserved.
- 2-6(A) Victor A. McKusick, *Human Genetics*, 2nd ed., Prentice-Hall, Inc., Englewood Cliffs, N.J., 1969.
- 2-6(B) The National Foundation: March of Dimes.
- 3-5 Dr. John Melnyk, City of Hope National Medical Center.
- 4-3(A,B) Malcolm A. Ferguson-Smith, "Chromosomal Abnormalities II: Sex Chromosome Defects," *Medical Genetics* (eds., McKusick and Claiborne) HP Publishing Co., Inc., New York, 1973.
- 4-3(C) The National Foundation: March of Dimes.
- 4-6(A) The National Foundation: March of Dimes.
- 5-6(A) Malcolm A. Ferguson-Smith, "Chromosomal Abnormalities II: Sex Chromosome Defects," *Medical Genetics* (eds., McKusick and Claiborne) HP Publishing Co., Inc., New York, 1973.
- 5-6(B) Carolina Biological Supply Company.
- 6-13 Kathleen and Eileen Murphy.
- 6-14 Elaine and Steven Scavelli.
- 6-16 N. V. Rothwell, *Understanding Genetics*, The Williams and Wilkins Co., Baltimore, Md., 1976.
- Table 8-2 T. Dobzhansky, *Mankind Evolving*, Yale University Press, New Haven, Conn., 1962.
- 8-12 L.S. Penrose.
- 9-12(A) James D. Watson, *Molecular Biology of the Gene*, 2nd ed., W. A. Benjamin, Inc., Menlo Park, Ca., 1970. Copyright © by James D. Watson.
- 10-4 Dr. Christian B. Anfinsen.
- 10-5 Vernon M. Ingram, *Nature* 180: 362, 1957.
- Table 14-2 M. Green, "Oncogenic Viruses," *Ann. Rev. Biochem.* 39: 701, 1970.
- 14-1 J. Cairns, *Cold Spring Harbor Symposium Quantitative Biology* 28: 44, 1963.
- 14-2 N. V. Rothwell, *Understanding Genetics*, The Williams and Wilkins Co., Baltimore, Md., 1976.
- 14-3 N. V. Rothwell, *Understanding Genetics*, The Williams and Wilkins Co., Baltimore, Md., 1976.
- 15-2 Monroe W. Strickberger, *Genetics*, Macmillan Publishing Co., Inc., New York, 1968.
- 15-4 Shapiro, et al., "Isolation of Pure *lac operon* DNA," *Nature* 224: 768-774, 1969.

CONTENTS

chapter 1:

SOME FUNDAMENTAL GENETIC PRINCIPLES, 1

- The Human and Other Species in Genetic Analysis, 1
- The Particulate Nature of the Hereditary Material, 5
- Mendelian Inheritance in Mice and the Human, 8
- Application of Mendel's First Law to Human Genetics, 17
- Variation in Gene Expression in the Human, 18
- The Environment and Gene Expression in the Human, 24

chapter 2:

THE PHYSICAL BASIS OF INHERITANCE, 30

- The Distribution of the Genetic Material, 30
- The Human Chromosome Complement, 36

chapter 3:

CHROMOSOME BEHAVIOR AND SEXUAL REPRODUCTION, 47

- The Need for a Reduction Division, 47
- Meiosis in the Male, 48
- Meiosis in the Female, 56
- Meiosis and the Generation of Variation, 59
- Meiosis and Mendel's Laws, 60

chapter 4:

SEX CHROMOSOMES AND THE GENES THEY CARRY, 68

Sex Determination, 68
Anomalies of the Sex Chromosomes, 71
Genes on the X Chromosome, 80
Blood Clotting and Genes Which Influence It, 86
Sex-linked Recessives and Autosomal Recessives, 90
Sex Chromosomes and Mendel's Laws, 92

chapter 5:

SEX AS A COMPLEX CHARACTERISTIC, 97

Sex-limited Genes, 97
Sex-influenced Genes, 99
Aspects of Hermaphroditism, 103
Sexual Preferences, 105
The Female and Mosaicism, 106
Evidence for the Lyon Hypothesis, 109
Practical Implications of a Knowledge of Sex Chromosome Constitution, 113

chapter 6:

LINKAGE, CROSSING OVER, AND HUMAN VARIABILITY, 117

Linked Genes Tend to Stay Together, 117
Linked Genes May Separate, 119
Gene Locations Can Be Mapped, 122
Assignment of Human Genes to Chromosomes, 127
Sexual Reproduction and the Generation of Variation, 130
The Biological Significance of Crossing Over, 135
Types of Twins and the Variation in a Twin Pair, 138
Effects of Inbreeding on Variation, 142

chapter 7:

GENES AND THE IMMUNE SYSTEM, 148

Antigens and Antibodies, 148
Inheritance of ABO Blood Types, 150
The MN Blood Groupings, 154
The Rh Types, 156
Blood Groups and Associated Effects, 161
Transplants and Grafting, 163

chapter 8:

SINGLE GENES, POLYGENES, AND POPULATIONS, 170

Types of Variation, 170
Inheritance of Skin Pigmentation, 173
Problems in Analysis of Polygenic Inheritance, 177
Populations, Species, and Gene Flow, 184
Factors in Variation Among Populations, 186
Differences Among Human Populations, 192
Human Races and Their Distinction, 194
Skin Pigment and Natural Selection, 197
Detrimental Genes in Human Populations, 198
The Role of Chance in Gene Frequency, 201

chapter 9:

CHEMICAL ASPECTS OF GENETICS, 207

Composition of the Hereditary Material, 207
The Watson-Crick Model and Some of Its Implications, 209
Genes and Protein Formation, 216
The Role of Messenger RNA, 219
Amino Acids and Steps in Protein Construction, 221
The Genetic Code, 227
Colinear Molecules and Their Significance for the Human, 230

chapter 10:

GENES, MOLECULES, AND DISEASE, 235

Genetic Blocks and Human Disorders, 235
Mutant Genes and Hemoglobins, 243
Genetic Disease and Early Detection, 251
Heredity and Environment in Expression of Disease, 256

chapter 11:

CHROMOSOME ANOMALIES AND APPROACHES TO THE PROBLEM OF GENETIC DISORDERS, 262

Inherited and Non-inherited Genetic Disorders, 262
Aneuploidy Involving Sex Chromosomes, 264
Aneuploidy Involving Autosomes, 265
Parental Age and the Origin of Chromosome Anomalies, 266
Polyploidy, 268

The Deletion, 269
The Translocation and the Inheritance of Chromosome Anomalies, 271
The Inversion, 275
Complications of Some Unusual Genetic Conditions, 277
The Increasing Challenge of Genetic Impairments, 280
Detection of Genetic Defects, 281
Genetic Counseling, 282

chapter 12:

PEDIGREES AND PROBABILITY, 287

The Geneticist and the Application of Probability, 287
Combining Simple Probabilities, 288
Probability and Degrees of Relationship, 292
Use of the Binomial Expansion in Genetics, 295
Representative Pedigrees and Genetic Counseling, 300
Linkage, Probability, and Prenatal Diagnosis, 305

chapter 13:

THE ORIGIN AND SIGNIFICANCE OF GENE MUTATION, 313

General Effects of Gene Mutation, 313
Spontaneous Mutation Rate and Some of Its Effects, 315
Mutation and the Degenerate Code, 319
Harmful Genes and the Calculation of Their Mutation Rate, 320
Some Mutagenic Factors, 322
Some Properties and Genetic Effects of Radiations, 323
Ultraviolet Light as a Mutagen, 325
Action of Radiation in Genetic Change, 329
Chemical Mutagens, 330
Mutant Genes in Populations, 332

chapter 14:

CONTROL MECHANISMS, 339

Cell Specialization and Gene Expression, 339
Control of Gene Expression, 342
The Jacob-Monod Model, 344
Control of Gene Activity in Higher Life Forms, 349
Gene Control and Virus Activity, 355
Viruses, Cancer, and Controlling Mechanisms, 358
A Consideration of Various Cancer Causing Factors, 364
Factors in Aging, 367

chapter 15:

HUMAN BEHAVIOR AND OTHER PROBLEMS, 373

Genetic and Environmental Components in Species Specific Behavior, 373
Human Sex Roles in Society, 376
Intelligence and Problems in Its Measurement, 379
The Use of Twin Studies in Genetic Analysis, 381
Heritability and the Intelligence Controversy, 384
Genes, Environment, and Mental Capacity, 387
Heredity and Environment in Mental Illness, 389
Ethical Considerations in Genetic Investigations, 391
Genetic Engineering and Problems for Society, 393

GLOSSARY, 401

REVIEW QUESTION ANSWERS, 419

INDEX, 423

chapter 1

SOME FUNDAMENTAL GENETIC PRINCIPLES

In some families, one child may combine features of both parents, whereas another resembles only the mother or the father. And then, there are those cases in which the offspring bear no physical resemblance to any family member. What accounts for such variations as these? Obviously, parents must transmit hereditary material to their children, but exactly what is being passed down? It must be something which carries the information required to guide the formation of a human being. All living things must carry specific information which can be transmitted to the next generation. This transfer of information insures that cats give rise to cats, dogs to dogs, oak trees to oak trees, and similarly for all forms of life. The science of *genetics* encompasses a study of the nature of the hereditary material, how it is transmitted, and how it interacts with the environment to bring about an effect on a cell or an individual. A knowledge of genetics helps us to explain why an individual may resemble both parents, one of them, or neither.

The Human and Other Species in Genetic Analysis

Most of the information on patterns of inheritance and the action of the hereditary material has been assembled from forms of life lower than the human. It is true that well before the turn of the century certain simple patterns of inheritance in humans were known. While it was appreciated that such traits as the presence of extra fingers (polydactyly) and colorblindness occur in a characteristic fashion in human pedigrees, the basis for the transmission was not well understood. Pioneer investigators utilized both plants and animals in their genetic studies. More recently, elegant analyses employ-

ing bacteria and viruses as genetic tools have provided an insight into the very nature of the hereditary material and the way in which it acts in the cell. The basic principles established in these lower groups have been found to apply to the human. Since it is the human species which concerns us most, why is it that biologists have not concentrated solely on the human to obtain fundamental genetic information? The human is not the ideal creature for such research, and the reasons become clear when we consider several factors which are essential to a detailed study of inheritance patterns.

Extremely important to such research is the need to follow not just one or two, but several generations in order to determine the way in which a particular trait occurs among members of a family line. The span of a human generation is long, in the vicinity of 25 years. Consequently, not many generations of one family can be followed in the lifetime of an investigator. Moreover, the average person can contribute little to a study of his family, since he knows little about his ancestors.

Another requirement for genetic analysis is the existence of a number of clear-cut traits in the organism being used as a genetic tool. Suppose we wanted to study the inheritance of eye color, a characteristic of all humans which occurs in many forms: blue, gray, brown, hazel, etc. Each of these alternatives is considered a *trait*, a variant form of a characteristic [Fig. 1-1(A)]. To gain information on the inheritance of any characteristic, it must exist in variant forms. If everyone had brown eyes, it might be appreciated that brown eye color has a hereditary basis; but lacking an alternative to brown, not much could be surmised about the transmission of information for the color characteristic. Moreover, the best traits for genetic study are those which are easy to recognize and to describe. Eye color in humans is a characteristic whose traits meet this requirement. In contrast, a characteristic such as height presents difficulties [Fig. 1-1(B)]. While persons may be classified into general categories such as tall, short, and medium, such groups are separated by ill-defined boundaries. Many persons would not fit precisely into any one of them. A further complication entails the influence of the environment on height. Poor diet can stunt the growth of any individual, who might otherwise be able to grow taller. A complex characteristic such as

Figure 1-1. Characteristics and traits. (A) A characteristic is a general attribute of an individual which may occur in 2 or more well-defined forms. Characteristics such as the first six noted above are obvious ones whose traits can be recognized by casual inspection. Many characteristics such as color vision or blood grouping demand closer inspection or special techniques before their variant forms can be recognized. Nonetheless, for each of these characteristics, rather sharply defined categories are apparent. (B) Height is a characteristic in which the variation is not distinct. No clear-cut traits exist. Instead, the variation describes a continuum from one extreme to the other. Such characteristics present more difficulties in genetic analysis than those in which the variant forms are clearly defined.

CHARACTERISTICS

TRAITS

Eye color:



Brown



Blue



Gray

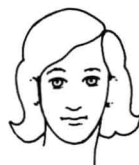
Hair color:



Black



Red



Blond

Hair form:

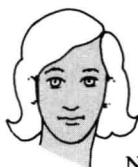


Straight



Wavy

Skin pigmentation:



Normal



Albino

Ear lobe form:



Attached



Free

Number of fingers:

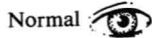


5



6

Color vision:



Normal



Red-green
colorblind

ABO blood grouping:

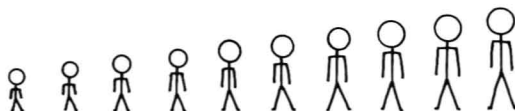
Type A

Type B

Type O

Type AB

(A)



(B)

Figure 1-1