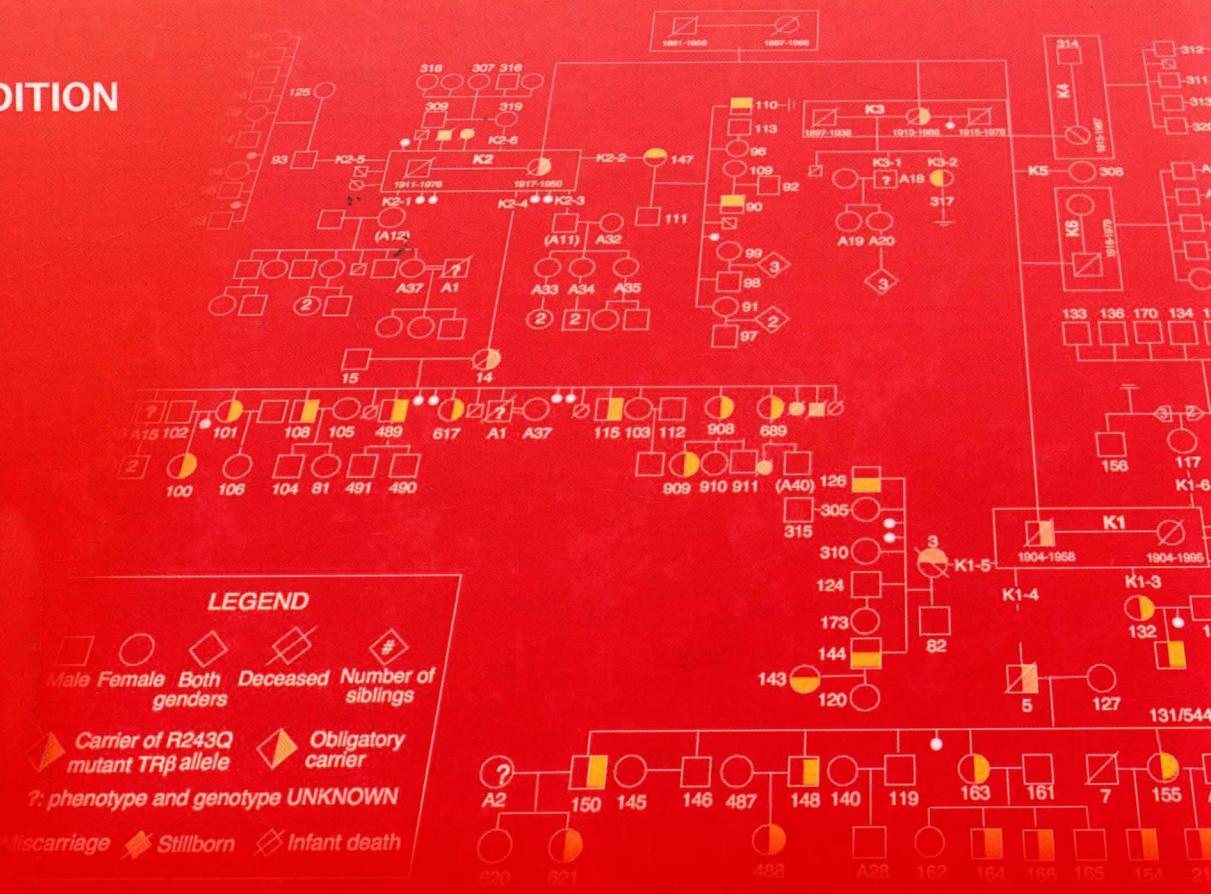
GENETIC DIAGNOSIS OF ENDOCRINE DISORDERS

SECOND EDITION



EDITED BY
ROY E. WEISS
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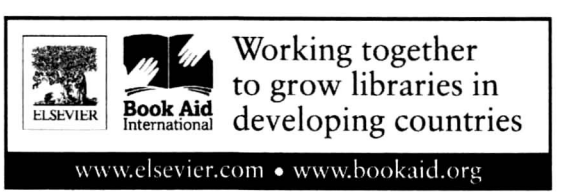

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Preface to the First Edition

Imagine the skepticism of a physician of the 1950s or 1960s if told that genetic testing would be used to diagnose specific complex endocrine disorders. Until relatively recently major abnormalities of the endocrine system were diagnosed, treated, and monitored with clinical assessment only. It was the clinical acumen of the astute physician that enabled correct diagnosis and determined which gland was responsible for producing too much or too little of a given hormone. The clinically pertinent markers of endocrine diseases were physiological measurements of basal metabolic rates, body weight, and urine output, which we now term the "physiologic" era of endocrinology.

Despite the discovery of insulin by Banting, Best, Macleod, and Collip in 1921 and its use for humans in 1923, it was only with Rosalyn Yalow and Salomon Berson's seminal report on the immunoassay of endogenous plasma insulin in 1960 that the "assay" period of endocrinology was introduced. This momentous methodological breakthrough enabled the endocrinologist to assay hormones previously impossible to measure at physiologically or pathologically relevant levels. The competitive protein-binding assay facilitated measurement of nanomolar or picomolar concentrations of hormones in plasma and tissues. Adaptation for other compounds further extended the field until 20 years ago, when "molecular" or "genetic" endocrinology evolved with the discovery of genes for insulin and growth hormone. Despite Paul Wermer's 1954 publication of the first clearly inherited endocrine disease "familial adenomatosis" (*American Journal of Medicine*, 1954, pp. 363–371), it is only with access to the genetic tools of the new millennium that the clinician can now precisely identify the genetic defects causing a disease and apply rational therapy. In *Genetic Diagnosis of Endocrine Disorders* we present to the clinician a straightforward, clinically relevant review of important genetic tests currently in use for the diagnosis of endocrine disorders, and practical information as to where these tests are performed.

Some endocrine disorders follow familial patterns of inheritance, while others may represent sporadic mutations. In both cases, identification of the mutation associated with the particular disease ideally allows the physician to test other family members, who may be asymptomatic. For example, in the case of a mutation with potential for adverse outcome such as medullary thyroid cancer. Physician and patient can now consider prophylactic thyroidectomy, for harboring such a gene prior to actual presentation of clinical disease; an approach possible only with the endocrine "genetic" revolution. Correlation of phenotype and genotype is frequently concordant, though in some instances the same genotype may cause different subtle or obvious phenotypes. An example would be patients with resistance to thyroid hormone who, despite identical mutations in the thyroid hormone receptor gene, may present with different phenotypes. The contrary example would be where the same phenotype may be due to different genotypes, as is occasionally the case in adrenal hyperplasias. Even in "truly" monogenic diseases, the genetic background of affected individuals may substantially modulate the phenotype. Thus, while genetic diagnosis is a critical part of the armamentarium of the modern-day Banting and Best, correlation of the genetic abnormality with its physiological manifestations remains crucial. Knowledge of which genetic tests to order must be supported by a full understanding of the genetic information they provide. The health care team responsible for diagnosis and follow-up, should ensure inclusion of the patient's family/primary care physician and a genetic counselor.

Genetic Diagnosis of Endocrine Disorders was initially conceived for purely selfish reasons. For our own use we needed a comprehensive clinical practice handbook for the genetic diagnoses of endocrine diseases. We therefore invited world experts to summarize the full range of currently available genetic endocrine diagnoses for our text. Initially we had to justify to ourselves taking time from our research to edit yet another endocrine book. However, the real advantage of editing this compilation of excellent reviews by renowned experts is the knowledge we have acquired in doing so. We hope that the reader will as well.

Our many thanks to those who have so graciously contributed to *Genetic Diagnosis of Endocrine Disorders* as well as to Fay, Heather, and our children who have been unswerving in their support of our careers. We would also like to acknowledge the support of the National Institute of Health (grants DK15070, DK07011, DK20595, and RRO4999), the Abrams and Esformes Endowments, and the Sherman family.

Roy E. Weiss, MD, PhD, FACP, FACE
Samuel Refetoff, MD, PhD

Preface to the Second Edition

The first edition of Genetic Diagnosis of Endocrine Disorders was published five years ago. Since then, the revolution of Precision Medicine has taken center stage in medical diagnosis, and those treating endocrine diseases need the appropriate ammunition to approach their patient's problems. There is rarely an article in the medical literature involving endocrine diseases, which does not mention a new gene or mutation. An encyclopedic compilation of the totality of genes involved in endocrine diagnosis does not lend itself to a printed text, which by nature is static. Therefore, the purpose of this book is to present emerging concepts to practicing pediatric and adult endocrinologists, students in the field, and genetic counselors, and review the most common genetic causes for endocrine disorders. Given the increasing affordability and availability of whole exome sequencing, the genetic cause of many more diseases will be identified, and there will be additional genes to know. New genetic conditions will emerge. In addition the role of epigenetics miRNAs, and enhancers in the cause of genetic endocrine disorders is quickly being recognized.

The purpose of having a genetic diagnosis should enable the patient and physician to understand the basis for the disease and thereby apply rationale and targeted therapy. In addition, based on the genetic information, decisions can be made regarding risks in asymptomatic relatives, allowing for preemptive.

Another reason for the second edition was based on the favorable reviews of the first edition and being urged by those reviewers to write a new edition.

We thank our returning and new authors for their outstanding contributions to this second edition.

Roy E. Weiss, Miami
Samuel Refetoff, Chicago

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PART I

INTRODUCTION

CHAPTER

1

Mechanisms of Mutation

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INTRODUCTION

Darwin realized the need for variation to provide a basis for natural selection, but he had no way of understanding the mechanisms by which such variation arose. Vague ideas of the origin of variation in the late nineteenth century gave way to the term mutation, coined by deVries to describe the discontinuous variation associated with Mendelian traits.[1] Genes were first recognized and defined by mutations with an extreme phenotype (see Table 1.1). Further progress led to conceptualizing the gene as a more complex structure with multiple "sites" for mutation available within the same gene. The nature of such sites was not clear, nor was the relationship between the physiological effects of gene mutations and the structural change involved. A typical pre-Watson–Crick examination question, "what is a gene?" could be answered in terms of function, of mutation, or of recombination and the question for geneticists was the relationship between these definitions.

Modern understanding of the mechanism of mutation is based on the Watson–Crick DNA structure. Recognizing the importance of nucleotide sequence followed by the deciphering of the genetic code led to a change from a biological and formalistic or mathematical view of mutation to a more biochemical approach. This chapter presents the problem of mutation as mainly one of biochemistry.

The immediate response of investigators to the Watson–Crick structure was to focus attention on the base changes that resulted in mutation and on the chemical changes that might alter base pairing.[2] The specificity of particular mutagenic agents was initially ascribed to chemical changes in either the incoming or template nucleotide, resulting in altered pairing properties, mainly involving hydrogen bonding. Benzer and Freese[3] and Brenner et al.[4] defined mutation in terms of substitutions, additions, and deletions of nucleotides. DNA in eukaryotes is organized into discrete chromosomes. Changes in the structure (rearrangements and translocations) and numerical distribution of these chromosomes that leave a viable organism are also mutation, but it is only recently, with the availability of extensive DNA sequence information, that these changes can even be partially accounted for biochemically.

Advances in our understanding of the complex biochemistry of DNA replication and its interaction with the various DNA repair and recombination pathways has led to a more mechanistic approach to understanding mutation (Fig. 1.1). The discovery in the late 1990s of a series of DNA polymerases with altered fidelity and ability to replicate past damaged sites in DNA[5] advanced a view of mutation as an event involving both initial changes in the DNA and the interaction of these changes with the protein complement of the cell. Most recently, the advent of rapid and relatively inexpensive DNA sequencing technology has permitted a direct measurement of normal human mutation rates and the recognition that *de novo* mutation plays a role in human disease. The identification of thousands of mutational changes in individual tumors, only a small minority of which are involved as "drivers" in the etiology of the tumors, has permitted recognition of a set of mutational "signatures" that implicate particular repair processes in the generation of the mutations. The observation of numerous closely linked mutations in tumor cells suggests the operation of unique mutagenic mechanisms whose operation in normal cells remains an open question.

THE TYPES OF MUTATION

Mutations are defined in this chapter as changes in the parental sequence of the DNA (Table 1.1). This definition is not without problems, since it is sometimes difficult to distinguish such changes from the normal process of recombination. Mutations include single

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TABLE 1.1 Special Abbreviations and Definitions

Term/Abbreviations	Definition
Abasic (apurinic/apyrimidinic) site	Site in DNA missing a base attached to the 1′-position of the sugar
APOBEC/AID	Apolipoprotein B mRNA editing enzyme (APOBEC) and activation-induced deaminase (AID). A family of cytidine deaminases
Aneuploidy	Eucaryotic cells with the normal diploid ($2n$) number of chromosomes are "euploid." "Haploid" cells are n. "Polyploid" cells are $3n$, $4n$, etc. "Aneuploid" cells are $2n \pm$ a number other than n
Base excision repair (BER)	A repair mechanism in which single nucleotide bases are removed and replaced by a patch of one or, at most, a few nucleotides
Chromothripsis	Multiple localized chromosome rearrangements occurring in a single event and in one or a few chromosomes
Copy number variation (CNV)	Altered number of copies of a gene or extended DNA sequence present in the genome
Double-strand break repair (DSBR)	Joining together of two DNA fragments to make a single molecule
Epigenetic	Heritable changes in gene expression that cannot be tied to DNA sequence variation and involving the active perpetuation of local chromatin states
Fidelity	A measure of the relative ability of DNA polymerases to insert the "correct" complementary base
Frameshift mutation	The insertion or deletion of a number of nucleotides not divisible by 3, properly speaking in a coding region of a gene. Largely replaced by the term "indel."
Genome	(1) The complete set of genetic material present in an organism. (2) The complete sequence of the DNA in an organism
Genotype	The genetic constitution of an organism
Holliday junction	A mobile junction formed in recombination between four strands of DNA. It is "resolved" by specific enzymes to regenerate two double-stranded molecules
Homologous recombination (HR)	A DSBR process involving the use of an allelic DNA sequence as a source of information
Indel	Insertion or deletion of a small number of nucleotides in the DNA structure
Insertional mutagenesis	Mutation by insertion of one or more nucleotides. Often used to denote inactivation of the genes by insertion of large transposable elements
Inversion	A rearrangement of the chromosome so that the order of the nucleotide pairs is reversed: if the normal order is ABCDEF, the order AEDCBF would constitute an inversion
Kataegis	Multiple, localized mutations, mostly C→T
L1 element	A common retrotransposon found in the human genome
Microhomology-mediated end joining (MMEJ)	An end joining DSBR mechanism utilizing the homology of a relatively few bases to orient the broken strands
Mismatch repair (MMR)	An excision repair process mainly devoted to correcting errors in replication
Missense mutation	A change in a gene, which results in a change in the meaning of a codon, e.g., the change from GAA (glutamic acid) to GUA (valine)
Mobile element insertion (MEI)	See transposon below. Mutational event in which a mobile element is inserted at a new position in the genome
Mutator	A mutation, often of a repair gene, that has the effect of increasing the spontaneous mutation rate
Nucleotide excision repair (NER)	The paradigm of an excision repair pathway. NER recognizes a wide range of damage and proceeds by cutting out and replacing an extensive series of nucleotides
Nonallelic homologous recombination (NAHR)	HR in which the complement is a homologous sequence other than the normal allele and which can lead to chromosome aberrations
Nonsense mutation	A mutation that results in one of the termination codons UAA, UAG, or UGA
Phenotype	The observable traits of an organism
Point mutation	A mutation involving one or a few nucleotides as distinguished from insertions, deletions, and duplications involving hundreds, thousands, or more nucleotides

TABLE 1.1 Special Abbreviations and Definitions (*cont.*)

Term/Abbreviations	Definition
Proofreading	In DNA synthesis, the process where an exonuclease checks a newly-inserted nucleotide for goodness of fit. Sometimes referred to as editing
Pseudogene	A copy of a gene made inactive by the accumulation of mutations and often devoid of introns
Retrotransposon	A transposable element that can shift its position in DNA via an RNA intermediate
Reactive oxygen species (ROS)	Chemically reactive radicals containing oxygen formed in metabolism and produced in clusters by ionizing radiation
Somatic hypermutation (SHM)	Process producing multiple mutations in mature B cells, mostly but not exclusively in the immunoglobulin gene during antibody maturation
Single nucleotide variation (SNV)	A point mutation involving a single nucleotide pair
Syn/*anti* base configuration	In the *anti* configuration, the bulky part of the base of a nucleoside or nucleotide rotates away from the sugar. In the *syn* configuration the bulky part rotates over the sugar
Synonymous/silent mutation	A nucleotide change that does not change the meaning of a codon, e.g., the change from GGU (glycine) to GGA (glycine). Not all synonymous mutations are silent, that is, without phenotypic effect
Translocation	Attachment of a segment of one chromosome to a different (nonhomologous) chromosome
Transposition	The movement of a transposable element from one position in the genome to another
Transition	The mutational change from a purine to another purine or a pyrimidine to another pyrimidine. G↔A and C↔T are the possible transitions
Transposon, mobile element (ME)	A DNA sequence able to move from one position to another within the genome. Movements are generally rare and are catalyzed by special enzymes coded for by the transposon
Transversion	The mutational change from a purine to a pyrimidine or a pyrimidine to a purine. A↔T, G↔T, C↔G, C↔A are possible transversions
Translesion synthesis (TLS)	Synthesis of DNA by specialized polymerases utilizing a damaged template
Transcription coupled nucleotide excision repair (TC-NER)	Specialized NER mechanism targeted to genes in the process of transcription
Ubiquitin	A conserved small (76 amino acids in humans) protein, which when covalently added to proteins in single or multiple copies serves as a signal for processes such as degradation and/or changes in conformation

nucleotide variation (SNV), insertion or deletion of small numbers of nucleotides (indels, frameshifts), rearrangements of the DNA sequence, change in the number of copies of larger stretches of DNA (copy number variation, CNV), and changes in the structure (inversions and translocations) or number of chromosomes (aneuploidy). The insertion or movement of transposable elements may affect phenotype and be obviously mutagenic. Nucleotide changes may occur outside the exome, the protein coding region of the genome, and these may or may not have an observable effect on phenotype. This view of mutation as a sequence change anywhere in the genome[6] is a product of the sequencing revolution, since the recognition of mutation in the pre-sequencing era required some observable change in the phenotype. The definition of mutation as any change in DNA sequence results in classifying sequence changes that have no obvious phenotypic effect as mutations. There are about 20,000–25,000 human genes, and the exome comprises somewhere about 2% of the total number of nucleotides.[7] Much of the remainder of the DNA is transcribed into RNA,[8] and some of this plays an important regulatory role in gene function, but as yet there is no automatic way to predict whether or what a change in DNA sequence will mean for physiology.

The possible single base changes were first cataloged by Ernst Freese and Seymour Benzer.[3,9] Freese coined the term "transition" to denote the change from one purine to another, or of one pyrimidine to another. The four possible transitions are cytosine (C) to thymine (T) and its reverse, and adenine (A) to guanine (G) and its reverse. Freese defined "transversions" as changes from a purine to a pyrimidine or the reverse. Change from an A or a G to a C or a T, and the reverse C or T to A or G was defined