Handbook of Clinical Pediatric Endocrinology

SECOND EDITION

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WILEY-BLACKWELL

Contents

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Preface

The first edition of this Handbook appeared four years ago and seems to have been useful, so this update, based on the 6th edition of *Brook's Clinical Pediatric Endocrinology*, follows a very similar format but with some notable additions.

Molecular biology has advanced rapidly in those years and is beginning to have a real clinical impact so considerable attention has been paid to this advance. You will also find clinical pitfalls highlighted and self-assessment challenges in each chapter. Where possible, we have included links to established guidelines and consensus views.

The enrolment of Professor Mehul Dattani as co-editor has been a great comfort to his (literally) senior colleague and it is my hope that you will profit as much from his extraordinary grasp of the science and practice of clinical pediatric endocrinology as I have. As always, we should be very glad to have errors drawn to our attention.

The team at Wiley-Blackwell, Oliver Walters, Jenny Seward, Rob Blundell and Helen Harvey, provides as smooth an operation as an author could wish for; we are very grateful for their help in producing this book. We hope that you will enjoy it.

Charles Brook
Mehul Dattani
2012

List of Abbreviations

1,25(OH)$_2$ D	1,25-dihydroxyvitamin D
11**β-HSDII**	11β-hydroxysteroid dehydrogenase type II
17PGN	17α-hydroxypregnenolone
AAA	Achalasia, Addisonian, Alacrima syndrome
ACE	angiotensin-converting enzyme
ACT	adrenocortical tumor
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
ADHR	autosomal-dominant hypophosphatemic rickets
AES	Androgen Excess Society
AFP	α-fetoprotein
AHO	Albright hereditary osteodystrophy
AI	aromatase inhibitor
AJCC	American Joint Committee on Cancer
ALS	acid-labile subunit
ALT	alanine aminotransferase
AME	apparent mineralocorticoid excess
AMH	anti-müllerian hormone
ANCA	antineutrophil cytoplasmic antibody
ANP	atrial natriuretic peptide
APECED	autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia

APS	autoimmune polyendocrine/glandular syndrome
ARHR	autosomal-recessive hypophosphatemic rickets
ATD	antithyroid drugs
ATP	adenosine triphosphate
AVP	arginine vasopressin
AZF	azoospermia factor
BG	blood glucose
BMD	bone mineral density
BMI	Body Mass Index
BMP	bone morphometric protein
BMT	bone marrow transplant
BMU	bone remodeling unit
BNP	brain natriuretic peptide
BWS	Beckwith–Wiedemann syndrome
CAH	congenital adrenal hyperplasia
CAIS	complete androgen insensitivity syndrome
cAMP	cyclic adenosine monophosphate
CaSR	calcium-sensing receptor
CBG	corticosteroid-binding globulin
CDG	congenital disorders of glycosylation
CDGP	constitutional delay of growth and puberty
CDI	central diabetes insipidus
CEA	chorionic embryonic antigen
CF	cystic fibrosis
CGH	comparative genomic hybridization

CGM	continuous glucose monitoring
CGMS	continuous glucose monitoring sensor
cGvHD	chronic graft versus host disease
CH	congenital hypothyroidism
CHD	chromodomain helicase DNA-binding protein
CHI	congenital hyperinsulinism/congenital hyperinsulinism of infancy
CI	cranial irradiation
CKK	cholecystokinin
CLT	chronic lymphocytic thyroiditis
CMO	corticosterone methyl oxidase
CNP	C-type natriuretic peptide
CNS	central nervous system
CNV	copy number variation
CPHD	combined pituitary hormone deficiency
CPP	central precocious puberty
CRF	chronic renal failure
CRH	corticotropin-releasing hormone
CSI	cranio-spinal irradiation
CSII	continuous subcutaneous insulin infusion
CSW	cerebral salt wasting
CT	computed tomography/calcitonin
CV_a	analytical variance
CV_i	within-subject biological variation
CYP	cytochrome P450

DAZ	deleted in azoospermia
DBD	DNA-binding domain
DBP	vitamin D-binding protein
DDAVP	desamino-D-arginine vasopressin
DECIPHER	Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources
DEXA	dual energy X-ray absorptiometry
DHEAS	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DI	diabetes insipidus/dentinogenesis imperfecta
DIDMOAD	diabetes insipidus, diabetes mellitus, optic atrophy and deafness
DIT	di-iodotyrosine
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DOC	deoxycorticosterone
DQ	developmental quotient
DSD	disorders of sex development
DWBS	diagnostic whole-body scan
ECF	extracellular fluid
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
EGF	epidermal growth factor
ELISA	enzyme-linked immunosorbent assay
FA	follicular adenoma
FBH	familial benign hypercalcemia

FDA	Food and Drug Administration
FGD	familial glucocorticoid deficiency
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FH	final height
FIGO	International Federation of Gynecology and Obstetrics
FIPH	familial isolated primary hyperparathyroidism
FISH	fluorescence *in situ* hybridization
FNA	fine needle aspiration
FSH	follicle-stimulating hormone
FT	free thyroxine
FT-UMP	follicular tumor of uncertain malignant potential
GABA	γ-aminobutyric acid
G-CSF	granulocyte-colony stimulating factor
GDP	guanosine diphosphate
GDPP	gonadotropin-dependent precocious puberty
GFR	glomerular filtration rate
GH	growth hormone
GHBP	growth hormone binding protein
GHD	growth hormone deficiency
GHI	growth hormone insensitivity
GHIS	growth hormone insensitivity syndrome
GHR	growth hormone receptor
GHRH	growth hormone-releasing hormone
GI	gastrointestinal/glycemic index

GIP	glucose-dependent insulinotropic peptide
GIPP	gonadotropin-independent precocious puberty
GLP	glucagon-like peptide
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotropin-releasing hormone analog
GPCR	guanine-protein-coupled receptor
GRA	glucocorticoid-remediable aldosteronism
Gsα	G-protein α
GSD	glycogen storage disease
GTP	guanosine triphosphate
GTT	glucose tolerance test
GWAS	genome-wide association study
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HH	hypogonadotropic hypogonadism
HLA	human leukocyte antigen
HMGCoA	hydroxymethylglutaryl coenzyme A
HOCM	hypertrophic obstructive cardiomyopathy
HPA	hypothalamo-pituitary axis
HPG	hypothalamo-pituitary-gonadal
HPLC	high-performance liquid chromatography
HRE	hormone response element
HSD	hydroxysteroid dehydrogenase
HVDRR	hereditary 1α,25$(OH)_2$D-resistant rickets
IA	immunoassay

ICF	intracellular fluid compartment
ICSI	intracytoplasmic sperm injection
IFA	immunofunctional assay
IFG	impaired fasting glucose
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor binding protein
IGHD	idiopathic isolated GH deficiency
IGT	impaired glucose tolerance
IHH	isolated/idiopathic hypogonadotropic hypogonadism
IJO	idiopathic juvenile osteoporosis
IL	interleukin
IM	intramuscular
IMA	immunometric assay
IP_3	inositol 1,4,5-triphosphate
IPEX	immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
IQ	intellectual quotient
IRS	insulin receptor substrate
ISS	idiopathic short stature
ITT	insulin tolerance test
IUGR	intrauterine growth restriction
IV	intravenous
KL	Klotho
KS	Kallman syndrome
LBD	ligand binding domain

LCAD	long-chain acyl CoA dehydrogenase
LCH	Langerhans cell histiocytosis
LDL	low-density lipoprotein
LH	luteinizing hormone
LHR	luteinizing hormone receptor
LHRH	luteinizing hormone-releasing hormone
lod	logarithm of odds
MAPK	mitogen-activated protein kinase
MAS	McCune–Albright syndrome
MC4R	melanocortin 4 receptor
MCAD	medium-chain acyl CoA dehydrogenase deficiency
MCP	monocyte chemoattractant protein
M-CSF	macrophage-colony stimulating factor
MCT	monocarboxylate transporter
MEN	multiple endocrine neoplasia
MHC	major histocompatibility complex
MIBG	meta-iodobenzylguanidine
miRNA	micro RNA
MIT	mono-iodotyrosine
MMI	methimazole
MODY	maturity-onset of diabetes in the young
MOPD	microcephalic osteodysplastic primordial dwarfism
MPHD	multiple pituitary hormone deficiency
MR	magnetic resonance

MRI	magnetic resonance imaging
mRNA	messenger RNA
MRS	magnetic resonance spectroscopy
MSH	melanocyte-stimulating hormone
MTC	medullary thyroid carcinoma
mtDNA	mitochondrial DNA
MUAC	mid-upper arm circumference
NDI	nephrogenic diabetes insipidus
NF	neurofibromatosis
NGS	next-generation sequencing
NSPHT	neonatal severe primary hyperparathyroidism
OCP	oral contraceptive pill
OGTT	oral glucose tolerance test
OHD	hydroxylase deficiency/hydroxyvitamin D
OHP	hydroxyprogesterone
OI	osteogenesis imperfecta
OMIM	Online Mendelian Inheritance in Man
OPG	osteoporosis-pseudoglioma syndrome
PAI	plasminogen activator inhibitor
PAIS	partial androgen insensitivity syndrome
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PDGF	platelet-derived growth factor
PET	positron emission tomography
PFD	polyostotic fibrous dysplasia

PG	plasma glucose
PHA	pseudohypoaldosteronism
PHHI	persistent hyperinsulinemic hypoglycemia of infancy
PHP	pseudohypoparathyroidism
PLC	phospholipase C
PNDM	permanent neonatal-onset diabetes mellitus
POMC	pro-opiomelanocortin
POR	P450 oxidoreductase
PP	pancreatic polypeptide
PPHP	pseudo-pseudohypoparathyroidism
PPP	pseudo precocious puberty
PRA	plasma renin activity
PRL	prolactin
PROK	prokineticin
PROKR	prokineticin receptor
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTU	propylthiouracil
PWS	Prader–Willi syndrome
QC	quality control
RAI	radioactive iodine
RANKL	RANK-ligand
RBP	retinol binding protein
RCV	reference change value
rhIGF	recombinant human insulin-like growth factor

rhTSH	recombinant human thyroid-stimulating hormone
RRA	radioreceptor assay/radioiodine remnant ablation
rRNA	ribosomal RNA
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
RT-PCR	reverse transcription polymerase chain reaction
SC	subcutaneous
SCAD	short-chain acyl CoA dehydrogenase deficiency
scc	side chain cleavage
SCID	severe combined immunodeficiency
SCST	sex cord stromal cell tumors
SD	standard deviation
SDH	succinate dehydrogenase
SDS	standard deviation (Z) score
SG	specific gravity
SGA	small for gestational age
SHBG	sex hormone-binding globulin
SHH	Sonic Hedgehog
SIADH	syndrome of inappropriate antidiuretic hormone
siRNA	small interfering RNA
SLE	systemic lupus erythematosus
SMBG	self-monitoring of blood glucose
SNP	single nucleotide polymorphism
SOD	septo-optic dysplasia

SS	somatostatin
StAR	steroidogenic acute regulatory protein
STK	serine-threonine kinase
STR	short tandem repeat
T	testosterone
TACE	tumor necrosis factor α converting enzyme
TBG	thyroxine-binding globulin
TBI	total body irradiation
TDF	testis-determining factor
Tg	thyroglobulin
TG	triglyceride
TGCT	testicular germ cell tumor
TNF	tumor necrosis factor
TPO	thyroid peroxidase
TPP	thyrotoxic periodic paralysis
TRH	thyrotropin-releasing hormone
tRNA	transfer RNA
TRP	tubular reabsorption of phosphate
TSH	thyroid-stimulating hormone
UFC	urine free cortisol
UV	ultraviolet
VDDR	vitamin D-dependent rickets
VDR	vitamin D receptor
VDRR	vitamin D-resistant rickets
VHL	Von Hippel–Lindau

VIP	vasoactive intestinal peptide
VLCAD	very long-chain acyl CoA dehydrogenase
VNTR	variable number of tandem repeats
WAGR	Wilms tumor, aniridia, genital anomalies and mental retardation
WDR	WD-repeat containing protein
WDT-UMP	well-differentiated tumor of uncertain malignant potential
XLH	X-linked dominant hypophosphatemic (vitamin D-resistant) rickets

CHAPTER 1

The Relevance of Molecular Biology to Clinical Practice

Key learning points

1. The inheritance of genetic disorders in humans may be mendelian or more complex.
2. The human genome contains around 30,000–40,000 genes, and its complexity is further increased by the use of alternative promoters, epigenetic phenomena and alternative splicing.
3. Further complexity is imparted by disorders of imprinting, mitochondrial disorders, mosaicism, digenic/oligogenic inheritance, sex-influenced phenotypes and variability of penetrance and expressivity.
4. Novel genetic techniques such as array-CGH and next-generation sequencing will revolutionize molecular diagnostics over the next few years.
5. Molecular diagnosis is increasingly important for optimal medical management of a number of human disorders.

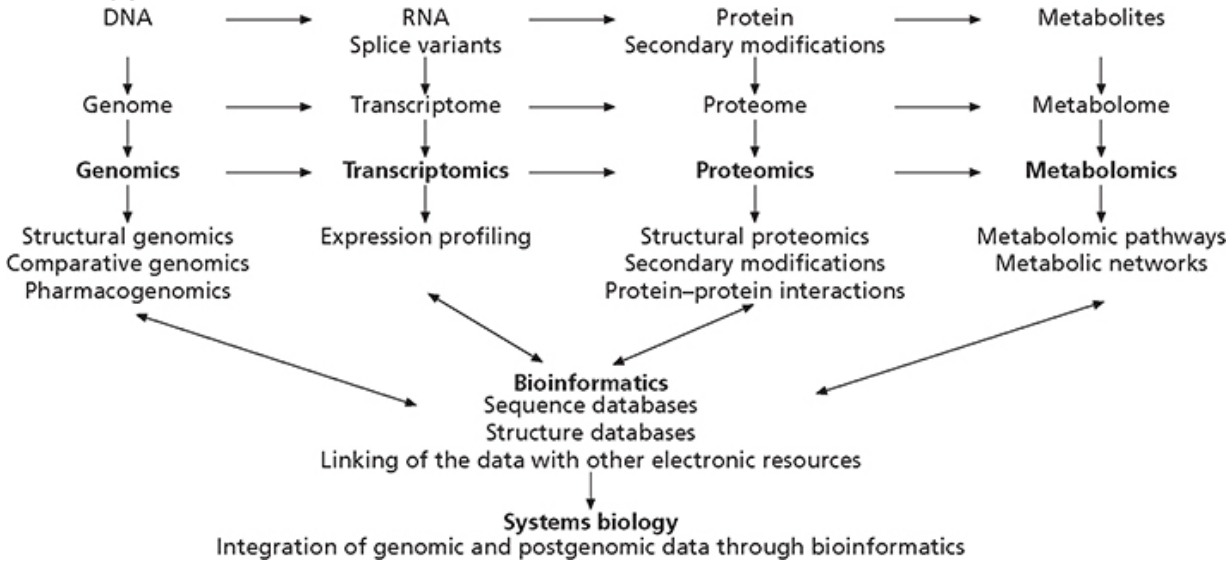
An understanding of and a facility with the molecular basis of many endocrine and non-endocrine disorders is essential to the practice of pediatric endocrinology in the 21st century and knowledge is accumulating rapidly (see Online Mendelian Inheritance in Man [OMIM], a comprehensive catalog of human genes and genetic disorders in order to keep pace with this field: www.ncbi.nlm.nih.gov/sites/entrez?db=omim) (see also Web

links box). With the exception of simple trauma, every disease has a genetic component.

In monogenic disorders, for example, congenital adrenal hyperplasia (CAH), the genetic component is the major etiological factor. Multiple genes operating in conjunction with environmental and lifestyle factors contribute to the pathogenesis of polygenic or multifactorial disorders. Genetic factors also influence the manifestation of disease directly through the genetic defect or indirectly by defining the host's susceptibility and resistance to an environmental disease such as infection.

Genetics (Fig. 1.1) is the science of heredity and variation and has heretofore focused on chromosomal abnormalities and inborn errors of metabolism. Analysis of the transmission of human traits and disease within families has led to understanding many monogenic disorders. Diabetes mellitus type 2, obesity, hypertension, heart disease, asthma and mental illnesses are complex and the genetic susceptibilities to these disorders are influenced by exogenous factors interacting with genetic susceptibilities.

Figure 1.1 Overview of genomics, transcriptomics, proteomics, metabolomics, bioinformatics and systems biology.



Phenotype can also be influenced by genetic and environmental modifiers in monogenic disorders. For example, the expression of the phenotype in monogenic forms of diabetes mellitus due to mutations in the maturity onset of diabetes in the young (MODY) genes is influenced by factors such as diet and physical activity.

The term *genome*, introduced before the recognition that DNA is the genetic material, designates the totality of all genes on all chromosomes in the nucleus of a cell. Genomics refers to the discipline of mapping, sequencing and analyzing genomes. Genome analysis can be divided into structural and functional genomics. The analysis of differences among genomes of individuals of a given species is the focus of comparative genomics. The complement of messenger RNAs (mRNAs) transcribed by the cellular genome is called the transcriptome and the generation of mRNA expression profiles is referred to as transcriptomics. Epigenetic alterations and chemical modifications of DNA or chromatin proteins influence gene transcription. The sum of all epigenetic information defines the epigenome, which, in contrast to the genome, is highly variable between cells and changes within a single cell over time. Epigenetic modifications lead to phenotypic changes without alteration of DNA sequence, and may be heritable.

The term *proteome* describes all the proteins expressed and modified following expression by the entire genome in the lifetime of a cell. Proteomics refers to the study of the proteome using techniques of large-scale protein separation and identification. The field of metabolomics aims at determining the composition and alterations of the metabolome, the complement of low molecular weight molecules. The relevance of these analyses lies in the fact that proteins and metabolites function in modular networks rather than linear pathways. Hence, any physiological or

pathological alteration may have many effects on the proteome and metabolome.

Pharmacogenomics, which involves the analysis of the genetic factors determining the response of an individual to a particular therapeutic agent, is emerging as a major new field. Genetic polymorphisms can not only influence the effects of medications but also result in variable absorption, distribution, metabolism, and excretion of a drug.

The growth of biological information has required computerized databases to store, organize, annotate and index the data which has led to the development of bioinformatics, the application of informatics to (molecular) biology. Computational and mathematical tools are essential for the management of nucleotide and protein sequences, the prediction and modeling of secondary and tertiary structures, the analysis of gene and protein expression and the modeling of molecular pathways, interactions and networks.

The integration of data generated by transcriptomic, proteomic, epigenomic and metabolomic analyses through informatics is an emerging discipline aimed at understanding phenotypic variations and creating comprehensive models of cellular organization and function. These efforts are based on the expectation that an understanding of the complex and dynamic changes in a biological system may provide insights into pathogenic processes and the development of novel therapeutic strategies and compounds.

The human genome

Genes were identified because they conferred specific traits transmitted from one generation to the next. They are functional units regulated by transcription and encode messenger (m)RNA which is subsequently translated into