

# Nutrigenomics



Carsten Carlberg • Stine Marie Ulven  
Ferdinand Molnár

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Carsten Carlberg  
Institute of Biomedicine  
University of Eastern Finland  
Kuopio, Finland

Stine Marie Ulven  
Department of Nutrition  
University of Oslo  
Oslo, Norway

Ferdinand Molnár  
School of Pharmacy  
University of Eastern Finland  
Kuopio, Finland

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# Preface

Our daily diet is more than a collection of carbohydrates, lipids and proteins that provide energy and serve as building blocks of our life; our diet is also the most dominant environmental signal to which we are exposed from womb to death. The fascinating area of *nutrigenomics* analyses this daily communication between diet, food and nutrients, their metabolites and our genome. This book describes how nutrition shapes human evolution and demonstrates its consequences for our susceptibility to diseases, such as diabetes and atherosclerosis. Inappropriate diet can yield stress for our cells, tissues and organs and then it is often associated with low-grade chronic inflammation. Overnutrition paired with physical inactivity leads to overweight and obesity and results in increased burden for a body that originally was adapted for a life in the savannas of East Africa. Therefore, this textbook does not discuss a theoretical topic in science, but it talks about real life and our life-long “chat” with diet. We are all food consumers, thus each of us is concerned by the topic of this book and should be aware of its mechanisms.

The availability of the sequence of the complete human genome and the consequent development of next-generation sequencing technologies have significantly affected nearly all areas of bioscience. This new knowledge was the starting point for new disciplines, such as genomics and its sub-discipline nutrigenomics. The latter comprises not only the variation of the human genome, such as single nucleotide polymorphisms (SNPs), but also the dynamic packaging of the genome into chromatin including all information stored in this epigenome. Moreover, this book describes the proteins that are involved in the signal transduction between dietary molecules and the genome, such as nuclear receptors, chromatin modifiers and energy status-sensing kinases, and their mechanism of action.

The purpose of this book is to provide an overview on the principles of nutrigenomics and their relation to health or disease. We are not aiming to compete with more comprehensive textbooks on molecular nutrition, evolutionary biology, genomics, gene regulation or metabolic diseases, but rather will focus on the essentials and will combine, in a compact form, elements from different disciplines. In order to facilitate the latter, we favour a high figure-to-text ratio following the rule “a picture tells more than thousand words”.

The content of this book is based on the lecture course “Nutrigenomics”, which is held since 2003 once per year by one of us (C. Carlberg) at the University of Eastern Finland in Kuopio. The book is subdivided into 3 sections and 12 chapters. Following the “Introduction”, there are sections on the “Molecular genetic basis” and the “Links to disease”, which take a view on nutrigenomics from the perspective of molecular mechanisms or from the causes of metabolic diseases, respectively.

This book is primarily designed for master level students of biosciences, but may also be used by students of other biomedical disciplines and by PhD students. The book has five major learning objectives. Students should:

- (i) Get an overview on human variation on the level of the genome and epigenome, in response to dietary molecules and the regulatory proteins involved in the respective signal transduction processes
- (ii) Have an understanding of the diseases that are strongly associated with dietary intake and physical inactivity, such as obesity, type 2 diabetes, atherosclerosis and the metabolic syndrome
- (iii) Recognize the key components and mechanisms in nutrigenomics and the multiple layers of its regulatory complexity
- (iv) Show the ability to analyze the human genome and epigenome and its variation in nutrition sensing and information processing processes, i.e. to judge their impact for on the complex etiology of metabolic diseases
- (v) Apply knowledge in nutrigenomics in designing, performing and analyzing respective experiments, such as quantitative PCR, RNA-seq or ChIP-seq

We hope the readers will enjoy this demonstrative book and get as enthusiastic about the topic of nutrigenomics as the authors do.

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Carsten Carlberg  
Stine Marie Ulven  
Ferdinand Molnár

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# Abbreviations

1,25(OH) <sub>2</sub> D <sub>3</sub>	1,25-dihydroxyvitamin D <sub>3</sub>
25(OH)D <sub>3</sub>	25-hydroxyvitamin D <sub>3</sub>
5,10-MTHF	5,10-methylene THF
α-MSH	α-melanocyte-stimulating hormone
ABC	ATP-binding cassette
ABL	abetalipoproteinemia
AC	adenylate cyclase
ACAT1	acetyl-CoA acetyltransferase 1
ACC	acetyl-CoA carboxylase
ACL	ATP citrate lyase
ADRB3	adrenoceptor beta 3
AGRP	agouti-related peptide
AKT	Akt murine thymoma viral oncogene homolog
ALA	α-linolenic acid
ALOX5	arachidonate 5-lipoxygenase
ALOX15	arachidonate 15-lipoxygenase
AMPK	adenosine monophosphate-activated protein kinase
AMY1	amylase
ANGPTL2	angiopoietin-like protein 2
APEH	N-acylaminoacyl-peptide hydrolase
AP-1	activating protein 1
APO	apolipoprotein
AR	androgen receptor
ARL4C	ADP-ribosylation factor-like
ARNTL	aryl hydrocarbon receptor nuclear translocator-like
ASC	apoptosis-associated speck
ASIP	agouti signaling protein
ATF6	activating transcription factor 6
ATM	ataxia telangiectasia mutated
atRA	all- <i>trans</i> retinoic acid
β-OHB	β-hydroxybutyrate

BAAT	bile acid-CoA-amino acid N-acetyltransferase
BAT	brown adipose tissue
BDNF	brain-derived neurotrophic factor
BLK	B lymphoid tyrosine kinase
BMD	bone mineral density
BMI	body mass index
BMP	bone morphogenetic protein
bp	base pair
CAMKK	Ca <sup>2+</sup> /calmodulin-dependent protein kinase kinase
CAMP	cathelicidin anti-microbial peptide
CAR	constitutively androstane receptor
CASP	caspase
CBL	Cbl proto-oncogene, E3 ubiquitin protein ligase
CBP	CREB-binding protein
CCL	chemokine (C-C motif) ligand
CCR	C-C chemokine receptor
CD36	CD36 molecule
CDC42	cell-division cycle 42
CDKAL1	CDK5 regulatory subunit associated protein 1-like 1
CDKN	cyclin-dependent kinase inhibitor
CDP	common dendritic cell progenitor
CEBP	CCAAT-binding protein
CEL	carboxyl ester lipase
CETP	cholesterol ester transfer protein
CHD	coronary heart disease
ChIP	chromatin immunoprecipitation
CITED1	CBP/p300-interacting transactivator 1
CLOCK	clock circadian regulator
CNR	cannabinoid receptor 1
CNS	central nervous system
CNV	copy number variant
CPT1A	carnitine palmitoyltransferase 1A
CREB3L3	cAMP responsive element binding protein 3-like 3
CRP	C-reactive protein
CRTC2	CREB-regulated transcription co-activator 2
CRY1	cryptochrome circadian clock 1
CSF2	colony stimulating factor 2
CVD	cardiovascular disease
CXCL5	chemokine (C-X-C motif) ligand 5
CXCR2	CXC-chemokine receptor 2
CYP	cytochrome P450
D2HGDH	D-2-hydroxyglutarate dehydrogenase
DAG	diacylglycerol
DALY	disability-adjusted life-year
DAMP	damage-associated molecular pattern

DGAT1	diacylglycerol O-acyltransferase 1
DHA	docosahexaenoic acid
DHF	dihydrofolate
DEFB4	defensin, beta 4A
DNMT	DNA methyltransferase
EHMT1	euchromatic histone-lysine N-methyltransferase 1
EGIR	European Group for the study of Insulin Resistance
EIF2A	eukaryotic translation initiation factor 2A
EIF2AK3	eukaryotic translation initiation factor 2-alpha kinase 3
ENCODE	encyclopedia of DNA elements
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
eQTL	expression quantitative trait locus
ER	endoplasmatic reticulum
ERN1	endoplasmic reticulum to nucleus signaling 1
ES cell	embryonic stem cell
E%	percent of total energy
FABP6	ileal fatty acid-binding protein 6
FAD	flavin adenine dinucleotide
FAIRE	formaldehyde-assisted isolation of regulatory elements
FAO	Food and Agriculture Organization
FAS	Fas cell surface death receptor
FASN	fatty acid synthase
FFA	free fatty acid
FGF	fibroblast growth factor
FGFR4	FGF receptor 4
FH	fumarate hydratase
FOX	forkhead box
FTO	fat mass and obesity associated
FXR	farnesoid X receptor
G6PC	glucose-6-phosphatase
GAB1	GRB2-associated binder 1
GCK	glucokinase
GC-MS	gas chromatography-mass spectrometry
GDH	glutamate dehydrogenase
GH	growth hormone
GLP1	glucagon-like peptide 1
GO	gene ontology
GPAT	glycerol phosphate acyl transferase
GPR	G-protein-coupled receptor
GR	glucocorticoid receptor
GRB	growth factor receptor-bound protein
GS	glycogen synthase
GSK3	glycogen synthesis kinase 3

GWAS	genome-wide association study
HAT	histone acetyltransferase
HDAC	histone deacetylase
HDM	histone demethylase
HDL	high-density lipoprotein
HHEX	hematopoietically expressed homeobox
HIF1 $\alpha$	hypoxia-inducible factor 1 $\alpha$
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2
HMT	histone methyltransferase
HNF	hepatocyte nuclear factor
HPT	hypothalamic-pituitary-thyroid
HSF1	shock transcription factor 1
HSP	heat-shock protein
HTG	hypertriglycerolemia
IAP	intracisternal A particle
ICAM1	intercellular adhesion molecule 1
IDF	International Diabetes Federation
IDH	isocitrate dehydrogenase
IDOL	inducible degrader of LDLR
IFG	impaired fasting glucose
IFN $\gamma$	interferon gamma
IGF	insulin-like growth factor
IGF1R	IGF1 receptor
IGF2BP2	insulin-like growth factor 2 mRNA binding protein 2
IGT	impaired glucose tolerance
IKBK	inhibitor of kappa light polypeptide gene enhancer in B cells, kinase
IL	interleukin
IL1R	IL1 receptor
IL1RN	IL1 receptor antagonist
indel	insertion-deletion variant
IR	insulin receptor
IRF3	interferon-regulatory factor 3
IRS	insulin receptor substrate
IRX3	iroquois homeobox 3
ITGA4	integrin, alpha 4
ITGB2	integrin, beta 2
IVF	<i>in vitro</i> fertilization
JAK	Janus kinase
K <sup>ATP</sup>	ATP-sensitive K <sup>+</sup>
kb	kilobase
KEAP1	kelch-like ECH-associated protein 1
KLF	Krüppel-like factor



KCNJ11	potassium inwardly rectifying channel, subfamily J, member 11
LA	linolenic acid
LBD	ligand-binding domain
LCAD	long-chain acyl-CoA dehydrogenase
LCAT	lecithin cholesterol acyltransferase
LCT	lactase
LDL	low-density lipoprotein
LDLR	LDL receptor
LDLRAP1	LDLR accessory protein 1
LEP	leptin
LEPR	leptin receptor
LIPC	hepatic lipase
LIPE	hormone sensitive lipase
LIPG	endothelial lipase
LINE	long interspersed element
LPCAT3	lysophospholipid acyltransferase 3
LPL	lipoprotein lipase
LRH-1	liver receptor homolog 1
LRP1	LDLR-related protein 1
LXR	liver X receptor
MAF	minor allele frequency
MAFA	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A
MAN2A1	mannosidase, alpha, class 2A, member 1
MAP	mitogen-activated protein
MAPK8	mitogen-activated protein kinase 8 (also called JNK)
MC4R	melanocortin 4 receptor
M-CFU	myeloid stem cells
MCM6	minichromosome maintenance type 6
MDH	malate dehydrogenase
MDP	macrophage and dendritic cell progenitor
MECP2	methyl-CpG-binding protein 2
MED	mediator
MHC	major histocompatibility complex
miRNA	micro RNA
MLXIPL	MLX interacting protein-like
mmHg	millimeters of mercury
MODY	maturity onset diabetes of the young
MPO	myeloperoxidase
MR	mineralocorticoid receptor
mRNA	messenger RNA
MSR1	macrophage scavenger receptor 1
MTHFR	methylenetetrahydrofolate reductase
MTNR1B	melatonin receptor 1B
mTORC	mammalian target of rapamycin complex
MTTP	microsomal triglycerole transfer protein

MYCL	v-myc avian myelocytomatosis viral oncogene lung carcinoma derived homolog
MYD88	myeloid differentiation primary response protein 88
MYF5	myogenic factor 5
NAD	nicotinamide adenine dinucleotide
NAFLD	non-alcoholic fatty liver disease
NAMPT	nicotinamide mononucleotide phosphoribosyltransferase (also called visfatin)
NANOG	NANOG homeobox
NCEH1	neutral cholesterol ester hydrolase 1
NCOA	nuclear receptor coactivator
NCEP	National Cholesterol Education Program
ncRNA	non-coding RNA
NEUROD1	neuronal differentiation 1
NF- $\kappa$ B	nuclear factor $\kappa$ B
NLRP	NLR protein
NLR	NOD-like receptor
NO	nitric oxide
NOS2	inducible nitric oxide synthase 2
NPC1L1	Niemann-Pick C1-like protein 1
NPY	neuropeptide Y
NR1P1	nuclear receptor interacting protein 1
NSAID	non-steroidal anti-inflammatory drug
NTS	nucleus tractus solitarius
OAADR	O-acetyl ADP-ribose
O-GlcNAc	O-linked N-acetylglucosamine
OGA	O-GlcNAcase
OGT	O-GlcNAc transferase
OGTT	oral glucose tolerance test
PAMP	pathogen-associated molecular pattern
PAX	paired box
PC	pyruvate carboxylase
PCK	phosphoenolpyruvate carboxykinase
PCSK1	POMC proprotein convertase subtilisin/kexin type 1
PDH	pyruvate dehydrogenase
PDPK	3-phosphoinositide dependent protein kinase
PDX1	pancreatic and duodenal homeobox 1
PER1	period circadian clock 1
PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2
PGE2	prostaglandin E2
PH	pleckstrin-homology
PI3K	phosphoinositide 3-kinase
PIP3	phosphatidylinositol-3,4,5-triphosphate
PKA	protein kinase A
PLAU	plasminogen activator, urokinase

PLTP	phospholipid transfer protein
PNPLA	patatin-like phospholipase domain containing
Pol II	RNA polymerase II
POMC	pro-opiomelanocortin
POU5F1	POU class 5 homeobox 1
PPAR	peroxisome proliferator-activated receptor
PPARGC1A	PPAR gamma, coactivator 1 alpha
PPP2	protein phosphatase 2
PRDM16	PR domain containing 16
PRR	pattern recognition receptor
PUFA	polyunsaturated fatty acid
PTB	phosphotyrosine-binding
PTEN	phosphatase and tensin homologue
PTGS2	prostaglandin-endoperoxide synthase 2 (also known as COX2)
PTPN1	protein tyrosine phosphatase, non-receptor type 1
PVN	paraventricular nuclei
PXR	pregnane X receptor
qPCR	quantitative PCR
RAPTOR	regulatory associated protein of TOR
RAR	retinoic acid receptor
RBP4	retinol binding protein 4
RE	response element
REV-ERB	Reverse-Erb
RHEB	Ras homolog enriched in brain
RHOQ	Ras homolog family, member Q
RIG1	retinoic acid-inducible gene 1
RLR	RIG1-like helicase receptors
RNAi	RNA interference
ROR	RAR-related orphan receptor
ROS	reactive oxygen species
RRAG	Ras-related GTP binding
RPS6K	ribosomal protein S6 kinase
RXR	retinoid X receptor
S6K	S6 kinase
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
SCAP	SREBF chaperone
SCD1	steroyl-CoA desaturase 1
SCN	suprachiasmatic nucleus
SCNN1	sodium channel, non-voltage-gated 1
SDH	succinate dehydrogenase
SEC16B	SEC16 homolog B
SERPINE1	serpin peptidase inhibitor, clade E (also called PAI-1)
SF-1	steroidogenic factor 1
SFA	saturated fatty acids

SFRP5	frizzled-related protein 5
SHC	Src homology 2 domain containing
SI	sucrase-isomaltase
SIM1	single-minded family bHLH transcription factor 1
SINE	short interspersed element
siRNA	small interfering RNA
Sir2	silent information regulator 2
SIRT	sirtuin
SLC	solute carrier
SLCO	solute organic anion transporter
SLK	STE20-like kinase
SNP	single nucleotide polymorphism
SNS	sympathetic nervous system
SOCS3	suppressor of cytokine signaling 3
SOD2	superoxide dismutase 2
SORBS1	sorbin and SH3 domain containing 1
SOS	son of sevenless
SPI1	spleen focus forming virus proviral integration oncogene (also called PU.1)
SREBF1	sterol regulatory element-binding transcription factor 1
STAT	signal transducer and activator of transcription
SULT2A1	sulfotransferase family 2A, member 1
T1D	type 1 diabetes
T2D	type 2 diabetes
TAS1R2	taste receptor, type 1, member 2
TBC1D	TBC1 domain family, member 1
TBP	TATA-box binding protein
TCA	tricarboxylic acid
TD	Tangier disease
TET	ten-eleven translocation
TGFB1	transforming growth factor beta 1
T <sub>H</sub>	T helper
THF	tetrahydrofolate
THRSP	thyroid hormone responsive
TIFIA	transcription initiation factor IA
TLR	Toll-like receptor
TMEM18	transmembrane protein 18
TNF	tumor necrosis factor
TNFR	TNF receptor
TOR	target of rapamycin
TRAF2	TNF receptor-associated factor 2
T <sub>REG</sub>	regulatory T
TSC2	tuberous sclerosis 2
TSS	transcription start site
UBR1	ubiquitin protein ligase E3 component n-recogin 1

UDP	uridine diphosphate
UCP	uncoupling protein
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4
UNC5B	unc-5 homolog B
UTR	untranslated region
UV	ultraviolet
VCAM1	vascular cell adhesion molecule 1
VDR	vitamin D receptor
VLDL	very low-density lipoprotein
VNN1	vanin 1
WAT	white adipose tissue
WHO	World Health Organization
WHR	waist-hip ratio
YWHA	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (also called 14-3-3)
XBP1	X-box binding protein 1