The Genetic Basis of Sleep and Sleep Disorders

EDITED BY

Paul Shaw, Mehdi Tafti
and **Michael Thorpy**

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The Genetic Basis of Sleep and Sleep Disorders

Paul Shaw
Department of Anatomy and Neurobiology, Washington University in St. Louis, St. Louis, MO, USA

Mehdi Tafti
Center for Integrative Genomics at the University of Lausanne, Lausanne, Switzerland

Michael Thorpy
Albert Einstein College of Medicine, New York, NY, USA and the Sleep–Wake Disorders Center in the Department of Neurology at Montefiore Medical Center, New York, NY, USA

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Foreword

This is a beautiful and useful book for the numerous world's sleep and dream clinicians and researchers (hypnologists and oneirologists) and sleep researchers and we should thank the editors, Paul Shaw, Mehdi Tafti, and Michael Thorpy. Although I am not a specialist in genetics, I have been introduced to this discipline by one of my best students and coworkers, Jean Louis Vataltx, who pioneered this field in 1972, by reporting in *Nature* a study in inbred mice. Certainly, genetic studies of the sleep–wake cycle help the physiologist and I was interested to read the paper from the University of Missouri reporting the role of metabolic genes in sleep regulation. I was wondering which relationships between sleep deprivation and cognitive deficits (paper No. 17), and sleep and long-term memory storage (paper No. 20) have been demonstrated. In this field, may I suggest that results obtained in animal models should not be applied to humans.

Some 30 years ago, I had the rare opportunity to study a man, continuously recorded by EEG, who suffered from Morvan's disease and did not sleep for 5 months. He was not sleepy and did not show any memory disturbances nor cognitive deficits and was able to complete several difficult cognitive tests. At the end of our report (Fischer-Perroudon C, Mouret J, Jouvet M. *Electroencephalogr Clin Neurophysiol.* 1974;**36**(1):1–18. French), we had the following question: what was the function of sleep?

However, it was only later that I recognized the very important role of genetics. In studying the patterns of rapid eye movements during dreaming in man, we found that these patterns were genetically controlled since they were identical in monozygotic twins, reared together or apart. This result opened the hypothesis that dreaming (REM sleep) might be an iterative genetic programming of the psychological individuation in man. Thus, long life to the future of genetic studies of dreaming.

Michel Jouvet
Emeritus Professor of Experimental Medicine
University of Lyon, France

Preface

The genetics of sleep and sleep disorders is still largely unknown and not well understood; however, new studies show the importance not only for understanding brain physiology but for sleep disorders and the circadian regulation that influences most body systems. In order to understand the physiology and pathophysiology of sleep, genetic studies are being developed that include new genetic techniques to tell us not only about brain regions that are activated or deactivated by sleep and alertness but also help us understand the pathophysiological mechanisms involved. This book, *Genetics of Sleep and Sleep Disorders*, details the important advances in the genetics of sleep disorders that hold promise to help us understand the underlying physiology and pathophysiology of sleep that will also aid in the diagnosis of sleep disorders.

There has been a major increase during the last decades in knowledge of the genetics of sleep and sleep disorders. Genetic epidemiologic studies have contributed considerably; however, there are marked differences in the level of knowledge between different aspects of sleep and individual disorders. Linkage, genome-wide association, and sequencing are yielding new insights into the basis of sleep traits. Mutations in the clock genes have been associated with Mendelian alterations of circadian rhythms and candidate gene association studies have been reported for a variety of sleep disorders. Most sleep disorders are considered to be complex genetic disorders. Recent progress has been made in identifying the genetic basis of narcolepsy and RLS and genome-wide association studies have demonstrated several genetic loci associated with their pathogenesis. The genetic basis remains to be determined for the more prevalent sleep disorders, insomnia and obstructive sleep apnea. Epigenetic mechanisms are being recognized as playing a major part in gene regulation of sleep. In the future whole-genome sequencing may clarify the genetic basis of complex traits including those associated with circadian sleep–wake regulation and help discover new gene networks involved in the regulation of sleep and the pathogenesis of sleep disorders.

This book represents the first major overview of the accumulated scientific developments in genetics to the study of sleep and sleep disorders.

No previous book has been published which comprehensively focuses on genetics of sleep and its disorders. This book accumulates the most recently available information on genetics and epigenetics and is written by top specialists in the field, geneticists, sleep disorders physicians and sleep researchers, from the Americas, Europe, and Asia. The chapters are arranged in five major sections: an introductory section on principles of genetics and genomics, genetics of sleep and circadian rhythms, sleep physiology and homeostasis, genetics of the sleep disorders including, insomnia, sleep-related breathing disorders, circadian rhythm disorders, parasomnias and sleep-related movement disorders, psychiatric and medical disorders associated with sleep and finally therapeutics. The introductory section comprises chapters on linkage and associations, complex trait analysis, and genome-wide association studies, including the fundamentals and methodology of genetic methods. The second section addresses genetics of normal sleep and circadian sleep–wake rhythms and includes epidemiology, and presentations on *Drosophila*, *C. elegans* and zebrafish genetic models, new techniques such as optogenetic photostimulation, astrogial regulation, metabolic genes, circadian pacemaker control and epigenetic mechanisms. Section three presents the genetics of the electrocephalographic basis of normal sleep, homeostasis and circadian entrainment, sleep deprivation and effects on memory and synaptic plasticity. Section four discusses the role of genetics in the understanding of the sleep disorders including, insomnia, narcolepsy and the hypersomnias, sleep-related breathing

disorders, circadian rhythm sleep disorders, restless legs syndrome, relevant psychiatric disorders and nocturnal epilepsy, and finally the future role of gene therapy.

This volume is intended primarily for sleep disorder specialists, sleep researchers, and geneticists; however, it is suitable for neurologists, psychiatrists, and any professional and researcher interested in the interdisciplinary field of sleep medicine. It will be of use for neurology, psychiatry and genetics residents and fellows, clinical psychologists, advanced graduate medical students, neuropsychologists, house officers, and other mental health and social workers who want to get an understanding the genetic basis of the physiology of sleep and pathophysiological and diagnostic features of sleep disorders.

We are greatly indebted to all the authors who have contributed to this book and are appreciative of the help of the staff of the Cambridge University Press in getting this book in print so quickly so that the contents are up-to-date and current. As findings in this area are rapidly advancing it is anticipated that future editions of this volume *Genetics of Sleep and Sleep Disorders* will take these developments into account.

Paul, Mehdi and Michael

Contributors

Ted Abel
Department of Biology, School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA, USA

Antoine Adamantidis
Department of Psychiatry, McGill University, Douglas Mental Health University Institute, Montreal, Quebec, Canada

Karla V. Allebrandt
Institute for Medical Psychology, Centre for Chronobiology, Medical Faculty, Ludwig-Maximilians-University, Munich, Germany

Simon N. Archer
Surrey Sleep Research Centre, Faculty of Health & Medical Sciences, University of Surrey, Guildford, UK

Amelie Baud
Wellcome Trust Centre for Human Genetics, Oxford, UK

Michel Billiard
Department of Neurology, Gui de Chauliac Hospital, Montpellier, France

Carlos Blanco-Centurion
Ralph H. Johnson VA and Medical University of South Carolina, Charleston, SC, USA

Diane B. Boivin
Centre for Study and Treatment of Circadian Rhythms, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Ethan Buhr
Department of Neuroscience, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA

Matthew E. Carter
Department of Biochemistry, University of Washington, Seattle, WA, USA

Nicolas Cermakian
Laboratory of Molecular Chronobiology, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Jennifer H.K. Choi
Department of Biology, School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA, USA

S.Y. Christin Chong
Department of Neurology, University of California San Francisco, San Francisco, CA, USA

Chiara Cirelli
Department of Psychiatry, University of Wisconsin/ Madison, Madison, WI, USA

Marc Cuesta
Centre for Study and Treatment of Circadian Rhythms and Laboratory of Molecular Chronobiology, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Thomas Curie
Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland

Yves Dauvilliers
National Reference Network for Narcolepsy, Sleep-Disorders Center, Department of Neurology, Hôpital Gui de Chauliac, Montpellier, France

Luis de Lecea
Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA

Derk-Jan Dijk
Surrey Sleep Research Centre, Faculty of Health & Medical Sciences, University of Surrey, Guildford, UK

Stephane Dissel
Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Annette C. Fedson
Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, PA, USA

Jonathan Flint
Wellcome Trust Centre for Human Genetics, Oxford, UK

Marcos G. Frank
University of Pennsylvania School of Medicine, Department of Neuroscience, Philadelphia, PA, USA

Paul Franken
Center for Integrative Genomics, University of Lausanne, Switzerland

Ying-Hui Fu
Department of Neurology, University of California San Francisco, San Francisco, CA, USA

Thorarinn Gislason
Department of Respiratory Medicine and Sleep, Landspitali University Hospital and Faculty of Medicine, University of Iceland, Reykjavik, Iceland

David Gozal
Sections of Pediatric Sleep Medicine and Pediatric Pulmonology, Department of Pediatrics, Comer Children's Hospital, Pritzker School of Medicine, The University of Chicago, Chicago, IL, USA

Devon A. Grant
Sleep and Performance Research Center, Washington State University, Spokane, WA, USA

Hakon Hakonarson
The Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Makoto Honda
Sleep Research Project, Department of Psychiatry and Behavioral Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

Hyun Hor
Center for Genomic Regulation (CRG), Centre for Genomic Regulation (CRG) and Universitat Pompeu Fabra (UPF), Barcelona, Spain

Christer Hublin
Finnish Institute of Occupational Health, Helsinki, Finland

Peng Jiang
Center for Sleep and Circadian Biology, Northwestern University, Evanston, IL, USA

Takashi Kanbayashi
Department of Neuropsychiatry, Akita University School of Medicine, Akita, Japan

Jaakko Kaprio
Dept. of Public Health, University of Helsinki, Finland

Andrew Kasarskis
Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, NY, USA

Leila Kheirandish-Gozal
Pediatric Sleep Medicine and Pediatric Pulmonology, Department of Pediatrics, Comer Children's Hospital, Pritzker School of Medicine, The University of Chicago, Chicago, IL, USA

RodaRani Konadhode
Ralph H. Johnson VA and Medical University of South Carolina, Charleston, SC, USA

Michael Lazarus
International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, Japan

Meng Liu
Ralph H. Johnson VA and Medical University of South Carolina, Charleston, SC, USA

Michael March
The Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Mark F. Mehler
Director, Institute for Brain Disorders and Neural Regeneration and Chair, The Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA

Keivan Kaveh Moghadam
DIBINEM, Alma Mater University of Bologna – IRCCS Insituto delle Scienze Neurologiche, Bologna, Italy

Valérie Mongrain
Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal; Department of Psychiatry, Université de Montréal, Canada

Charles M. Morin
Ecole de Psychologie, Université Laval, Quebec City, Quebec, Canada

Benjamin M. Neale
Analytical and Translational Genetics Unit, Massachusetts General Hospital, The Broad Institute, Boston, MA, USA

Seiji Nishino
Sleep & Circadian Neurobiology Laboratory, Stanford University School of Medicine, Palo Alto, CA, USA

Allan I. Pack
Center for Sleep and Circadian Neurobiology, University of Pennsylvania and Division of Sleep Medicine, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Dheeraj Pelluru
Ralph H. Johnson VA and Medical University of South Carolina, Charleston, SC, USA

Rosa Peraita-Adrados
Sleep Disorders and Epilepsy Unit – Clinical Neurophysiology Service, University General Hospital Gregorio Maranon, Madrid, Spain

Giuseppe Plazzi
DIBINEM, Alma Mater University of Bologna – IRCCS Insituto delle Scienze Neurologiche, Bologna, Italy

David A. Prober
Division of Biology, California Institute of Technology, Pasadena, CA, USA

Louis J. Ptáček
Department of Neurology, University of California San Francisco and Howard Hughes Medical Institute, San Francisco, CA, USA

Irfan A. Qureshi
Assistant Professor, The Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA

David M. Raizen
Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

John J. Renger
Neuroscience Department, Merck Research Laboratories, West Point, PA, USA

Till Roenneberg
Institute for Medical Psychology, Centre for Chronobiology, Medical Faculty, Ludwig-Maximilians-University, Munich, Germany

Elizabeth J. Rossin
Analytical and Translational Genetics Unit, Massachusetts General Hospital, The Broad Institute, Boston, MA, USA

Takeshi Sakurai
Department of Molecular Neuroscience and Integrative Physiology, Faculty of Medicine, Kanazawa University, Kanazawa, Ishikawa, Japan

Paul Salin
Team SLEEP, Centre de Recherche en Neuroscience de Lyon, Université Claude Bernard, Lyon, France

Karen D. Schilli
Missouri University of Science and Technology, Department of Biological Sciences, Rolla, MO, USA

Eva C. Schulte
Neurologische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München and Institut für Humangenetik, Helmholtz Zentrum München, Munich, Germany

Laurent Seugnet
Team Integrated Physiology of Brain Arousal Systems, Centre de Recherche en Neuroscience de Lyon, Université Claude Bernard, Lyon, France

Paul J. Shaw
Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Priyattam J. Shiromani
Ralph H. Johnson VA and Medical University of South Carolina, Charleston, SC, USA

Patrick Sleiman
The Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Mehdi Tafti
Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland

Joseph S. Takahashi
Department of Neuroscience, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA

Matthew S. Thimgan
Missouri University of Science and Technology, Department of Biological Sciences, Rolla, MO, USA

Katsushi Tokunaga
Department of Human Genetics, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Giulio Tononi
Department of Psychiatry, University of Wisconsin/Madison, Madison, WI, USA

Fred W. Turek
Center for Sleep and Circadian Biology, Northwestern University, Evanston, IL, USA

Yoshihiro Urade
International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, Japan

Hans P.A. Van Dongen
Sleep and Performance Research Center, Washington State University, Spokane, WA, USA

Juliane Winkelmann
Neurologische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Institut für Humangenetik, Helmholtz Zentrum München, and Institut für Humangenetik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Christopher J. Winrow
Neuroscience Department, Merck Research Laboratories, West Point, PA, USA

Abbreviations

5hmC	5-hydroxymethylated cytosine
5-HT	serotonin
5mC	5-methylcytosine
AAV	adeno-associated viral
aCGH	array comparative genomic hybridization
Ach	acetylcholine
AD	Alzheimer's disease
ADAR	adenosine deaminase acting on RNA
ADCA-DN	autosomal dominant cerebellar ataxia, deafness and narcolepsy
ADHD	attention deficit hyperactivity disorder
ADNFLE	autosomal dominant NFLE
AgRP	agouti-related protein
AHI	apnea hypoxia index
AID	activation-induced deaminase
AIL	advanced intercrossed line
AMP	adenosine monophosphate
AMPK	AMP kinase
ANOVA	analysis of variance
APOBEC	apolipoprotein B editing catalytic subunit (enzymes)
ApoE	apolipoprotein E
APS	aversive phototaxic suppression
ARAS	ascending reticular activating system
AS	Angelman syndrome
ASM	anterior superior medial
ASO	alpha-synuclein overexpressing
ATP	adenosine triphosphate
AVP	arginine vasopressin
BAC	bacterial artificial chromosome
BDNF	brain-derived neurotrophic factor
BF	basal forebrain
bHLH	basic helix–loop–helix
BLPD	borderline-personality disorder
BMI	body mass index
BNST	bed nucleus of the stria terminalis
BPD	bipolar affective disorder
cAMP	cyclic adenosine monophosphate
CBT	core body temperature
CC	collaborative cross
CCSGs	candidate causal sleep genes
cGMP	cyclic guanosine monophosphate
CiRC	circadian integrated response characteristic
CLS	Coffin Lowry syndrome
cM	centiMorgan
CNS	central nervous system
CNV	copy number variant
COX	Cyclooxygenase
CPA	cyclopentyladenosine
CPAP	continuous positive airway pressure
CR	constant routine
CRB	CREB-binding protein
CREB	cAMP response element-binding protein
CRSD	circadian rhythm sleep disorder
CSF	cerebrospinal fluid
DA	dopamine
DAG	diacylglycerol
DAT	Dopamine Active Transporter
DLMO	dim-light melatonin onset
DNMTs	DNA methyltransferases
DO	Diversity Outbred
DORA	dual orexin receptor antagonist
Dox	doxycycline
DREADDs	Designer Receptors Exclusively Activated by Designer Drugs
DRN	dorsal raphe nuclei
DSIP	delta sleep inducing peptide
DSPD	delayed sleep phase disorder
DSPS	delayed sleep phase syndrome
DZ	dizygotic
EDS	excessive daytime sleepiness
EEG	electroencephalogram/graphic
EGF	epidermal growth factor
EGFP	epidermal growth factor protein
EGFR	epidermal growth factor receptor
EHS	essential hypersomnia
EMG	electromyography
EMS	ethyl methane sulfonate
endo-siRNAs	endogenous short-interfering RNAs
ENW	episodic nocturnal wanderings
EPAC	exchange proteins activated by cAMP
eQTL	expression QTL
ERG	ether-a-go-go related
ERK	extracellular signal-regulated kinase
FABP	fatty acid binding proteins
FASPD	familial advanced sleep phase disorder
FASPS	familial advanced sleep phase syndrome
FB	fan-shaped body
FDR	false discovery rate
FFA	free fatty acid
FFI	fatal familial insomnia
FFT	fast Fourier transform
FNSS	familial natural short sleep
GA	GFP-Aequorin
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
GDGF	glial-derived growth factor

GFAP	Glial Fibrillary Acidic Protein
GFP	green fluorescent protein
GH	growth hormone
GHRH	growth hormone releasing hormone
GPI	glycosylphosphatidylinositol
GRE	glucocorticoid responsive element
GWAS	genome-wide association study
HAT	histone acetyltransferase
Hcrt	hypocretin
Hcrt/ox	hypocretin/orexin
HD	Huntington's disease
HDAC	histone deacetylase
HDC	Histidine decarboxylase
HLA	Human Leukocyte Antigen System
HMDP	hybrid mouse diversity panel
H-PGDS	hematopoietic PGDS
HPLC-MS/MS	high-performance liquid chromatography-coupled tandem mass spectrometry
HS	heterogeneous stocks
HSF	heat shock factor
i.c.v.	intracerebroventricular
i.p.	intraperitoneal
IBD	identical by descent
IBS	identity by state
ICV	intracerebroventricular
IEG	immediate early genes
IMM	intermediate and medium mesopallium
IP3	inositol trisphosphate
IRLSSG	International RLS Study Group
ISAC	Icelandic Sleep Apnea Cohort
KLS	Kleine–Levin syndrome
KO	knockout
LC	locus coeruleus
LD	linkage disequilibrium
LDT	laterodorsal tegmental
LFP	local field potential
LHA	lateral hypothalamus
LNvs	ventral lateral neurons
LOD	logarithm of odds
L-PGDS	lipocalin-type PGDS
LTM	long-term memories
LTP	long-term potentiation
MB	mushroom body
MBD	methyl-CpG-binding domain
MBT	malignant brain tumor
MCH	Melanin-Concentrating Hormone
MCTQ	Munich ChronoType Questionnaire
MD1	myotonic dystrophy type 1
MDD	major depressive disorder
mEPSCs	miniature excitatory postsynaptic currents
MEQ	morningness–eveningness questionnaire
MeS	metabolic syndrome
mGluR	metabotropic glutamate 5 receptors
MHC	Major Histocompatibility Complex
miRNAs	microRNAs
MOG	myelin oligodendrocyte glycoprotein
MRH	menstrual-related hypersomnia
MSLT	multiple sleep latency test
MZ	monozygotic
NA	noradrenergic
NAc	nucleus accumbens
NADPH	nicotinamide adenine dinucleotide phosphate
NAT	natural antisense transcript
ncRNA	non-coding RNA
ND	Norrie disease
NE	norepinephrine
NFLE	nocturnal frontal lobe epilepsy
NMDA	*N*-Methyl-D-aspartic acid
NMO	neuromyelitis optica
NPC	Niemann–Pick disease, type C
NPD	nocturnal paroxysmal dystonia
NPS	neuropeptide S
NPY	neuropeptide Y
NREM	non-rapid eye movement
NSAID	non-steroidal anti-inflammatory drugs
NSS	natural short sleeper
OCD	obsessive–compulsive disorder
OMIM	Online Mendelian Inheritance in Man
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
PA	paroxysmal arousals
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus*
PAS	PER–ARNT–SIM
PBMC	peripheral blood mononuclear cell
PCA	principle components analysis
PCR	polymerase chain reaction
PD	Parkinson's disease
PDF	pigment dispersing factor
PG	prostaglandin
PGDS	PGD synthase
PH	posterior hypothalamus
PHD	plant homeodomain
PI	pars intercerebralis
piRNAs	PIWI-interacting RNAs
PKA	protein kinase A
PKG	protein kinase G
PLM	periodic limb movement
PLMS	periodic limb movements in sleep
POA	preoptic area
PPARs	peroxisome proliferator-activated receptors
PPT	pedunculopontine tegmental (nucleus)
PRC	phase response curve
PSG	polysomnography
PTM	post-translational modification
PTSD	post-traumatic stress disorder
PWS	Prader–Willi syndrome
QC	quality control
QTL	quantitative trait locus
RA	Robust nucleus of the Arcopallium
RBP	RNA binding protein
RDI	respiratory disturbance index
RDL	Resistance to Dieldrin
REM	rapid eye movement
RI	recombinant inbred
RISC	RNA-induced silencing complex
RLS	restless leg syndrome

RNAi	RNA interference
RORE	Retinoic-acid-related Orphan receptor Response Element
RSD	REM sleep deprivation
SAD	seasonal affective disorder
SAGIC	Sleep Apnea Genetics International Consortium
SAM	*S*-adenosyl methionine
SCF	Skp1–Cullin–F-box
SCN	suprachiasmatic nucleus
SDB	sleep-disordered breathing
SDP	strain distribution pattern
sfo	step-function-opsin
SHY	synaptic homeostasis hypothesis
SMS	Smith–Magenis syndrome
SNARE	soluble *N*-ethylmaleimide-sensitive fusion protein attachment protein receptor
snoRNAs	small nucleolar RNAs
SNP	single nucleotide polymorphism
SNRIs	serotonin/noradrenaline reuptake inhibitors
SNV	single nucleotide variant
SOD2	superoxide dismutase 2
SORA	single orexin receptor antagonist
SOREMP	sleep onset REM period
SRIF	Somatostatin
SSRIs	serotonin-specific reuptake inhibitors
SWA	slow-wave activity
SWR	sharp-wave ripple
SWS	slow-wave sleep
TALEN	TAL-effector nuclease
TCRα	T-cell receptor alpha
TDT	transmission disequilibrium test
TET	Ten–Eleven Translocation
tet.O	tet-operator
TH	tyrosine hydroxylase
TIB	time in bed
TLR4	toll-like receptor 4
TMN	tuberomammilary nucleus
TRP	transient receptor potential
TSD	total sleep deprivation
tTA	tetracycline transactivator
UAS	Upstream Activation Sequence
UTR	untranslated region
VLPO	ventrolateral preoptic area
VNTR	variable-number tandem repeats
VTA	ventral tegmental area
WT	wild-type
XCI	X chromosome inactivation
ZFN	zinc finger nuclease

Contents

Chapter 1

Linkage and associations

Elizabeth J. Rossin and Benjamin M. Neale

Introduction

Human genetics is one of the most promising approaches to identifying the cellular underpinnings of human diseases and traits. For diseases whose etiology is largely unknown, identifying genes that contribute risk can lead to novel biological insights and potentially reveal proteins and pathways to target with therapeutics. Historically, the search for such genetic variation that influences phenotype has been particularly successful in rare genetic disorders, termed Mendelian disease, that are caused by severe mutations in DNA: classic examples of such diseases include hemochromatosis, cystic fibrosis and phenylketonuria [1]. For these diseases, DNA changes in particular genes lead to deficient or altered protein that in turn results in a cascade of physiological outcomes, ultimately culminating in the medical sequelae that define the disease. Not only have these findings helped elucidate the biological pathways important to these phenotypes, but also understanding the damaged cellular processes has been proven to be relevant to patients' medical treatment. A primary goal of human genetics is to understand disease biology and ultimately aid in the identification of novel therapeutic design.

The application of genetics to severe rare diseases that follow clear inheritance patterns in families has led to the successful identification of the root cause in many instances. These Mendelian diseases are almost completely caused by genetic factors, which explains the success of genetics to unequivocally determine the cause. In contrast, complex traits are characterized by the combination of many genetic and environmental factors that together create the phenotype. An additional consequence of this complex trait architecture is that the familial clustering of the trait does not follow a clear and predictable inheritance pattern. For most complex phenotypes, we do not understand the bulk of the underlying pathophysiology, in spite of the fact that many of these traits are clearly heritable. Since the nineteenth century, scientists and physicians have studied twins and families for complex phenotypes and identified clear evidence of heritability. The fact that traits tend to run in families and that more genetically similar family members tend to be more phenotypically similar provides empirical support of the genetic hypothesis. Consequently, the identification of genetic variants is possible and provides the opportunity to gain insight into the biological processes relevant to human disease. Twin and family studies in sleep phenotypes have revealed significant heritability; the earliest observation of sleep phenotypes being heritable was made in 1937 when Geyer reported higher sleep profile concordance in monozygotic twins than dizogotic twins [2].

As with many traits, the majority of sleep disorders and sleep-related traits are complex phenotypes. However, there are some examples of familial diseases that present with disordered sleep as either a primary or secondary finding. Phenotypes in both these categories include diseases such as restless leg syndrome (RLS) and narcolepsy–cataplexy as well as quantitative traits in normal individuals including duration and quality of sleep. A number of instances of sleep disorders segregating in a Mendelian fashion within large families have been documented, but there are also well-established studies of heritability of sleep and sleep disorders as complex traits as discussed later in this chapter [3–9].

Identifying genes for heritable Mendelian and complex traits alike requires genetic mapping, i.e. the identification and localization of genes that underlie heritable phenotypes. Genetic mapping is accomplished by correlating DNA variation with phenotype.

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