

Cambridge University Press
978-1-107-04125-7 - The Genetic Basis of Sleep and Sleep Disorders
Paul Shaw, Mehdi Tafti and Michael Thorpy
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The Genetic Basis of Sleep and Sleep Disorders

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University Printing House, Cambridge CB2 8BS, United Kingdom

Published in the United States of America by Cambridge University Press, New York

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning and research at the highest international levels of excellence.

www.cambridge.org

Information on this title: www.cambridge.org/9781107041257

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First published 2013

Printing in the United Kingdom by TJ International Ltd, Padstow Cornwall

A catalogue record for this publication is available from the British Library

Library of Congress Cataloguing in Publication data

The genetic basis of sleep and sleep disorders / [edited by] Paul Shaw, Mehdi Tafti, Michael Thorpy.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-1-107-04125-7 (Hardback)

I. Shaw, Paul, 1963– II. Tafti, Mehdi. III. Thorpy, Michael J.

[DNLM: 1. Sleep–genetics. 2. Sleep Disorders–genetics.WL 108] RC547

616.8'498042–dc23 2013014823

ISBN 978-1-107-04125-7 Hardback

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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.

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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, astroglial 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

Preface

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

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Abbreviations

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

List of abbreviations

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

List of abbreviations

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