Genetics of Sleep Disorders

Philip R. Gehrman, PhD[a,*], Brendan T. Keenan, MS[b], Enda M. Byrne, PhD[b,c], Allan I. Pack, MBChB, PhD, FRCP[d]

KEYWORDS

• Sleep disorder • Genetics • Insomnia • Sleep apnea • Narcolepsy
• Restless legs syndrome

KEY POINTS

- Past genetic studies have been hampered by methodological limitations, in particular small sample sizes.
- Genetic studies of narcolepsy highlight the important role of human leukocyte antigen variants in disease risk.
- Genes that confer risk for sleep apnea may do so through their influence on intermediate traits, such as obesity or craniofacial features.
- For insomnia, early work suggests that genetic factors may overlap with those for psychiatric disorders.
- There is a need to apply modern genetic approaches to the study of sleep disorders.

INTRODUCTION

There is growing evidence that adequate sleep quantity and quality is important for mental health. In psychiatric populations, sleep disorders are highly prevalent, including insomnia, obstructive sleep apnea, and circadian rhythm sleep disorders. The pathophysiology of these sleep disorders is likely complex, having components shared with those for psychiatric disorders as well as elements specific to sleep disturbance. Genetic factors are known to play a role in both psychiatric and sleep disorders, but causal genetic variants are only beginning to be discovered. This article reviews the current understanding of the genetic basis for sleep disorders and suggests possible links with mental health and illness.

Disclosures: None.
[a] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, 3535 Market Street, Suite 670, Philadelphia, PA 19104, USA; [b] Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, 125 South 31st Street, Suite 2100, Philadelphia, PA 19104-3403, USA; [c] Queensland Brain Institute, Brisbane QLD 4072, Australia; [d] Division of Sleep Medicine, Department of Medicine, Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, 125 South 31st Street, Suite 2100, Philadelphia, PA 19104-3403, USA
* Corresponding author.
E-mail address: gehrman@exchange.upenn.edu

Psychiatr Clin N Am 38 (2015) 667–681
http://dx.doi.org/10.1016/j.psc.2015.07.004 **psych.theclinics.com**
0193-953X/15/$ – see front matter Published by Elsevier Inc.

Abbreviations

AHI	Apnea-Hypopnea Index
ARNTL2	Aryl hydrocarbon receptor nuclear translocator–like 2
ASPS	Advanced sleep phase syndrome
BMAL	Brain and muscle aryl hydrocarbon receptor nuclear translocator–like
BTB	BR-C, ttk and bab
BTBD9	BTB/POZ domain-containing protein
CACNA1C	Calcium channel, voltage-dependent, L type, alpha1C subunit
CK	Casein kinase
CLOCK	Circadian locomotor output cycles kaput
CRSD	Circadian rhythm sleep disorder
CRY	Cryptochrome
EEG	Electroencephalogram
GWAS	Genome-wide association study
h^2	Heritability
HLA	Human leukocyte antigen
LOD	Logarithm of the odds
LPAR1	Lysophosphatidic acid receptor I
MAP2K5	Mitogen-activated protein kinase 5
MEIS1	Myeloid ecotropic viral integration site 1 homolog
nNOS	Neuronal nitric oxide synthase
OSA	Obstructive sleep apnea
PER	Period
P2RY11	Purinergic receptor subtype $P2Y_{11}$
POZ	Pox virus and Zinc finger
PTPRD	Protein tyrosine phosphatase receptor type delta
RLS	Restless legs syndrome
SKOR1	SKI family transcriptional corepressor 1
SNP	Single-nucleotide polymorphism
VNTR	Variable number tandem repeat

METHODS FOR IDENTIFYING GENETIC VARIANTS

The goals of research on the genetic basis for sleep disorders are to identify genetic variants that confer risk for disease and to understand how these variants affect the function of biological systems. Like psychiatric phenotypes, sleep disorders are complex traits that are likely to be influenced by a large number of gene variants, including regulatory portions of DNA. The proportion of variation in risk for a disease or trait in the population that can be attributed to genetic variation is known as the heritability. There are now a large number of studies showing that sleep disorders are heritable; that is, genetic factors play a substantial role in their pathophysiology. This statement is also true for normal variation in sleep/wake traits. Despite the established genetic heritability, only a small number of validated genetic risk variants have been discovered for sleep-related traits. There are several reasons for this lack of discovery, including low statistical power caused by inadequate sample sizes, phenotypes that are assessed with considerable variability, and the heterogeneous nature of many disorders and disease pathways.

Heritability analyses represent the first step in understanding the genetic basis for sleep disorders. These analyses determine the extent to which genetic factors explain the variance in a given trait. Heritability is usually established using twin or family