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CLINICAL REVIEW

The genetics of insomnia – Evidence for epigenetic mechanisms?

Laura Palagini [a,*], Knut Biber [b], Dieter Riemann [b]

[a] Department of Neuroscience, University of Pisa, School of Medicine, Via Roma 67, 56100 Pisa, Italy
[b] Department of Psychiatry & Psychotherapy, University of Freiburg Medical Center, Hauptstrasse 5, 79104 Freiburg, Germany

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SUMMARY

Sleep is a complex physiological process and still remains one of the great mysteries of science. Over the past 10 y, genetic research has provided a new avenue to address the regulation and function of sleep. Gene loci that contribute quantitatively to sleep characteristics and variability have already been identified. However, up to now, a genetic basis has been established only for a few sleep disorders. Little is yet known about the genetic background of insomnia, one of the most common sleep disorders. According to the conceptualisation of the 3P model of insomnia, predisposing, precipitating and perpetuating factors contribute to the development and maintenance of insomnia. Growing evidence from studies of predisposing factors suggests a certain degree of heritability for insomnia and for a reactivity of sleep patterns to stressful events, explaining the emergence of insomnia in response to stressful life events. While a genetic susceptibility may modulate the impact of stress on the brain, this finding does not provide us with a complete understanding of the capacity of stress to produce long-lasting perturbations of brain and behaviour. Epigenetic gene–environment interactions have been identified just recently and may provide a more complex understanding of the genetic control of sleep and its disorders. It was recently hypothesised that stress-response-related brain plasticity might be epigenetically controlled and, moreover, several epigenetic mechanisms have been assumed to be involved in the regulation of sleep. Hence, it might be postulated that insomnia may be influenced by an epigenetic control process of both sleep mechanisms and stress-response-related gene–environment interactions having an impact on brain plasticity. This paper reviews the evidence for the genetic basis of insomnia and recent theories about epigenetic mechanisms involved in both sleep regulation and brain-stress response, leading to the hypothesis of an involvement of epigenetic mechanisms in the development and maintenance of insomnia.

Introduction

Sleep is a complex physiological process and still remains one of the great mysteries of science [1,2]. Hypotheses for the function of sleep include somatic, metabolic and cellular theories, as well as brain-specific alterations affecting synaptic plasticity and leading to synaptic downscaling [3–10]. Over the past 10 y, genetic research has provided a new avenue to address the regulation and function of sleep [11–14]. Major findings include the identification of gene loci that contribute quantitatively to sleep characteristics and variability. From *Drosophila*, zebrafish and worms to mammalian model organisms, some genes implicated in sleep homeostatic regulation have been identified. Circadian genes (Clock, PER1,2,3, Bmal1 and Timeless), neurotransmitters and their receptors, cytokines/immune or stress-response genes (nuclear factor-kappa B (NF-κB), tumour necrosis factor (TNF), interleukin-1β (IL-1β), IL-6 and IL-10), synaptic transmission genes (Homer, c-Fos and Gria3), ion channels (K^+ channels and Ca^{++} channels) and signal metabolic/cellular growth genes (Ghrelin Rho, Leptin epidermal growth factor (EGF), Dwarf and growth hormone releasing hormone (GHRH)) have been identified in mammalians to be important in sleep regulation (for overview see: [12,14,15]). Moreover, genetic determinants underlying variability in sleep phenotypes have started to be revealed: a wide inter-individual variability in sleep behaviour such as sleep stage organisation, sleep timing, sleep quality and sleep–wake regulation has been confirmed [16–19]. In addition, research of the last decade has focussed on understanding factors contributing to sleep disturbances too: well-documented familial and twin sleep disorder studies suggest an important influence of genetic factors [11–14,16–19]. However, up to now, only for a few sleep disorders has a genetic basis been established. These include mainly rare diseases (that may result

* Corresponding author. Tel.: +39 050 993165; fax: +39 050 992656.
E-mail address: lpalagini@tiscali.it (L. Palagini).

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from a single gene mutation) such as fatal familial insomnia (mutation of prion protein gene PRNP), familial advanced sleep-phase syndrome (mutations in human Period2 (hPER2)), delayed sleep phase syndrome (polymorphism in Per3), narcolepsy with cataplexy (orexin/hypocretin genes) and also the more common restless legs syndrome [15,20–22]. Most sleep disorders are complex in terms of a variable expressivity of the phenotype. Therefore, the contribution of genes and interindividual genetic polymorphisms alone cannot provide a complete understanding of both the majority of the more common sleep disorders (i.e., insomnia) and of their long-lasting perturbations of brain and behaviour. In addition, it seems reasonable to assume that environmental factors influence gene function. The assumption that environmental influences cause persisting alterations of gene function through an 'epigenetic' process adds a new and fruitful perspective in studying health/disease and sleep disorders. The term 'epigenetics' encompasses a number of mechanisms by which gene expression is affected beyond the level of the genetic code in response to environmental stimuli, including stressors. Changes in gene expression based on epigenetic mechanisms, unlike those of the relatively static genome, are dynamic, and most important, from the perspective of diseases/disorders and their treatment, potentially reversible. In mature, differentiated neurons in the central nervous system (CNS), epigenetic mechanisms – including deoxyribonucleic acid (DNA) methylation, histone modification (often leading to chromatin remodelling), and regulatory non-coding ribonucleic acid (RNA)s – play critical roles in encoding experience and environmental stimuli into stable, behaviourally meaningful changes of gene expression (for an overview see [23]). It is postulated that epigenetic mechanisms mediate the effects of behavioural and environmental exposures early in life, as well as lifelong environmental exposures and the susceptibility to disease later in life. Epigenetic processes are active in the brain and have been linked to an increasing number of brain disorders including sleep disorders [24,25]. In addition, epigenetic mechanisms have long been thought to be involved in learning and memory [26] and in stress response [27,28]. Several epigenetic mechanisms seem to be involved in the regulation of sleep: histone modifications have been identified in an animal model to contribute to chromatin remodelling and thereby to the epigenetic control of circadian gene expression [29,30]. Recently, sleep has also been linked to activity-dependent epigenetic brain plasticity [31].

Knowledge is still very scarce about the genetic and epigenetic background of insomnia, one of the most common sleep disorders, which affects 10–15% of the adult population [32]. Insomnia is characterised by difficulty initiating or maintaining sleep, early-morning awakening or the feeling of non-restorative or unrefreshing sleep [32]. Fatigue, cognitive impairments and poor motivation are commonly reported as daytime consequences of insomnia with a negative impact on personal, professional and social functioning. Insomnia may moreover contribute to the development of several co-morbidities [33,34], including major depression [35–37]. One of the most influential heuristic models of the evolution of insomnia is the 3P model developed by Spielman and colleagues [38]. This model provides a useful framework, including predisposing, precipitating and perpetuating factors that are proposed to play important roles in the initiation and maintenance of the disorder. It has been suggested that predisposing factors are present before insomnia is manifested and are hypothesised to interact with stressful life events which act as precipitating factors over time to increase the risk of insomnia in vulnerable individuals. Consequences of insomnia on functional and structural brain alterations have been found [39,40], though not unequivocal [41]. While genetic predisposition may influence the impact of stressful events on the brain, it does not provide us with a complete understanding of the capacity of stress to produce long-lasting perturbations of brain and behaviour. The growing discipline of epigenetics bears great promise of deepening our understanding of the persistent impacts of stress on health and disease and its contribution to develop and perpetuate insomnia. Recently, it has been hypothesised that the brain plasticity-related stress response might be epigenetically controlled [27,28,42,43]. Hence, we might hypothesise that insomnia may both develop and be maintained due to an epigenetic stress-response-related gene–environment interaction with even long-lasting effects on brain plasticity.

This paper reviews the evidence for the genetic basis of insomnia and recent theories about epigenetic mechanisms involved in both sleep regulation and brain-stress response, hypothesising an epigenetic brain stress-response-related mechanism which might account for the development and maintenance of insomnia.

Genes and insomnia: predisposing factors

Given the conceptualisation of insomnia in the context of the 3P model, it suggests the importance of predisposing, precipitating and perpetuating factors [38]. Predisposing factors are present before insomnia is manifested and are hypothesised to interact with precipitating factors over time to increase the risk of insomnia in vulnerable individuals. Both family and twin studies are helpful in shedding light on an important component within this framework. The twin studies method allows us to determine causes of variance between phenotypes (i.e., genetic, shared environmental and non-shared environmental). This method enables one not only to assess whether insomnia is heritable, but also to determine to what extent its genetic and environmental influences overlap, which is a crucial step for hypothesis development. In addition, the study of specific genotypes that account for some of the phenotypic variance in insomnia might contribute to identify the genetic underpinnings of subjects predisposed to insomnia. A so-called 'sleep reactivity', moreover, has been investigated as a predisposing factor for insomnia. The next chapters will review all the available evidence related to these concepts.

Family studies

A number of family studies have provided evidence for an assumed genetic basis of insomnia. Studies of insomnia in population-based and clinical samples have demonstrated an increased risk of self-reported insomnia symptoms in individuals with a positive family history of insomnia, reflecting possible genetic and/or shared environmental effects [44–49] (see Table 1).

Hauri and Olmstead [44] found that 55% of their patients with childhood-onset insomnia could identify at least one family member with sleep difficulties, compared to 39% of patients with an onset of insomnia in adulthood.

Bastien et al. [45] evaluated the familial incidence of sleep disturbances among individuals with insomnia complaints. Their findings indicate that 35% of patients consulting for insomnia had a positive family history of sleep disturbances. The mother was the most frequently afflicted family member. A positive family history was found more frequent when the insomnia complaint involved only sleep-onset difficulties relative to sleep-maintenance difficulties or a mixed symptom insomnia.

Dauvilliers et al. [46] interviewed 256 chronic insomniacs. Of those with primary insomnia, 73% reported familial insomnia. Among the psychiatric insomniacs, 43% reported familial insomnia. The mother was the relative most frequently affected. A tendency to a younger age at onset was observed in familial and primary insomnia.

Beaulieu-Bonneau et al. [47] found that in a sample of 953 adults, 35% reported at least one first-degree relative with past or current insomnia. The mother was the most frequently afflicted