http://dx.doi.org/10.5665/sleep.1852

Searching for Genetic Clues at the Interface of Sleep and Mood

Commentary on Carskadon et al. Short sleep as an environmental exposure: a preliminary study associating 5-HTTLPR genotype to self-reported sleep duration and depressed mood in first-year university students. SLEEP 2012;35:791-796.

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The link between mood and sleep has long been established. Indeed, in Major Depressive Disorder, sleep duration changes represent an important diagnostic criterion.[1] Similarly, in Bipolar Disorder, decreased sleep is a key clinical feature.[1] Moreover, in terms of causality, sleep deprivation is a successful, rapid chronobiological antidepressant in patients with mood disorders.[2] Searching for genetic markers to elucidate this established relationship is a research area of critical need. Despite this need, the identification of single candidate genes associated with mood disorders such as Major Depressive Disorder and Bipolar Disorder is a substantial challenge, since the likelihood is high that such complex psychiatric illnesses are under polygenic influences and are associated with interactions between the environment and genetic variants.[3] Single candidate gene associations with sleep duration undoubtedly face similar challenges. The article by Carskadon and colleagues[4] in this issue of *SLEEP* tackles this complex search using a highly focused approach.

Carskadon et al.'s preliminary study[4] determined whether the 5-HTTLPR polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*) was associated with depressed mood in first-year university students (N = 135) who show an established pattern of shorter sleep. Phenotypes were based on self-rated depression assessed using the Centers for Epidemiology Studies-Depression (CES-D) scale (median split: high > 12; low < 13) and self-rated nocturnal total sleep time (TST; shorter ≤ 7 h; longer ≥ 7.5 h) determined via diary information obtained for 21-64 days (mean = 51 days ± 11) prior to genotyping. 5-HTTLPR genotypes were composed of three groups: S′S′: participants with two copies of the lower expressing alleles (SS, SL_G, or L_GL_G); S′L′: participants with one copy of a lower expressing allele (SL_A or L_GL_A); and L′L′: participants homozygous for the higher expressing L_A allele (L_AL_A).

Carskadon and colleagues[4] found that S′S′ participants—those with diminished expression of the serotonin transporter—were overrepresented in the shorter TST/high CES-D phenotype group. In addition, the authors found that a high proportion of Asian participants (74%) were in the S′S′ group, highlighting the possibility that ethnic, cultural, or social factors may have led this group to show a combination of lower mood and shorter sleep—this important finding has both treatment and prevention ramifications and should be investigated in future studies.

The findings of Carskadon et al.[4] are intriguing in terms of identifying vulnerability to lower mood as a function of a genetic marker (5-HTTLPR) and a behavioral marker (shorter sleep duration). This manuscript builds upon prior studies of 5HTTLPR indicating its involvement in both sleep and mood regulation. The 5-HTTLPR genotype has been reported to modulate the influence of stress on depression[5,6] and on sleep quality.[7] The 5-HTTLPR genotype also has been shown to alter resting brain function assessed with fMRI in healthy individuals' emotion-related brain regions, including the amygdala and ventromedial prefrontal cortex,[8] and to modulate amygdala activity during mood regulation.[9,10]

Most candidate gene studies in our field have focused on experimental manipulations of sleep loss. These laboratory studies have the benefit of utilizing controlled conditions and objective measures of sleep, but as a tradeoff, only examine sleep loss acutely, rather than over the longer term in more naturalistic environments. Such studies have identified a number of genetic polymorphisms related to differential responses to sleep loss, including total sleep deprivation and chronic partial sleep deprivation (reviewed in[11]). Notably, the latter is similar to the sleep-wake patterns found in mood disorders, whereby patients experience repeatedly curtailed or fragmented sleep rather than loss of an entire night of sleep.[12] Interestingly, as is true for 5-HTTLPR, some of the recently identified candidate genes, such as *PERIOD3 (PER3)*, Circadian Locomotor Output Cycles Kaput (*CLOCK*), and catechol-O-Methyltransferase *(COMT)* also are associated with mood disorders, in terms of treatment responses, or risk factors for symptom development, exacerbation, or recurrence[13-15]; thus, these studies may ultimately provide valuable insight into predicting sleep, alertness, and cognitive responses to sleep loss in patients with mood disorders.

Carskadon et al.'s article[4] adds to the aforementioned collection of phenotype-genotype sleep studies by using 5-HTTLPR as a genetic tool to investigate the gene × environment interaction between depressed mood and sleep duration. It impressively extends our current knowledge of common candidate genes in a number of ways: it goes beyond the laboratory and utilizes a more naturalistic setting; it studies a young adult/late adolescent cohort; and it employs longitudinal collection of chronic exposure to longer or shorter sleep duration via a prospective approach. The findings from this study serve as a basis for a number of future avenues of research, including: extension of this paradigm to objective measures of sleep (actigraphy

Submitted for publication April, 2012
Accepted for publication April, 2012
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or polysomnography) and clinical measures (clinician-rated instruments); extension of this model to other stressful situations that promote shorter sleep; and investigation of the role of 5-HTTLPR in experimental manipulations of sleep restriction using sleep homeostatic, neurobehavioral, and neuroimaging assessments. The scientific fields of sleep and mood disorders share apparent overlap of both phenotypes and genotypes. Future studies should strategically exploit these commonalities to identify genetic markers and potential epigenetic factors that may predict how changes in sleep duration might expose vulnerability to mood changes and vice versa. Such an approach would benefit both fields immensely.

CITATION

Goel N. Searching for genetic clues at the interface of sleep and mood. *SLEEP* 2012;35(6):739-740.

DISCLOSURE STATEMENT

Dr. Goel has indicated no financial conflicts of interest.

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