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Review

Genetic basis of human circadian rhythm disorders

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ABSTRACT

Circadian rhythm disorders constitute a group of phenotypes that usually present as altered sleep–wake schedules. Until a human genetics approach was applied to investigate these traits, the genetic components regulating human circadian rhythm and sleep behaviors remained mysterious. Steady advances in the last decade have dramatically improved our understanding of the genes involved in circadian rhythmicity and sleep regulation. Finding these genes presents new opportunities to use a wide range of approaches, including *in vitro* molecular studies and *in vivo* animal modeling, to elevate our understanding of how sleep and circadian rhythms are regulated and maintained. Ultimately, this knowledge will reveal how circadian and sleep disruption contribute to various ailments and shed light on how best to maintain and recover good health.

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Introduction

Behavioral studies using model organisms are stimulating and relatively approachable since the researchers can, for the most part, control both external and internal variables. These studies have provided us novel insights into the genetic nature of many interesting behaviors. Predictably, gaps remain when trying to translate what scientists learn in model organisms to something applicable or useful for human health conditions. In contrast to model organisms, studying behavior in humans such as sleep requirement and preferred sleep–wake times is a daunting task due to the complexity of confounding co-morbidities, environmental factors, and the polygenic nature of behavioral phenotypes.

Like most organisms, humans exhibit daily behaviors that are regulated in a circadian (24-hour) manner. Early pioneers of circadian

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biology research, such as Jurgen Aschoff, observed that human behaviors under constant conditions exhibited rhythms with an approximately 24-hour periodicity (Aschoff et al., 1971). Aschoff's studies in humans revealed the existence of an endogenous biological time-keeping mechanism. Decades later, studies from model organisms uncovered a molecular clock comprised of many genetic players that governs the circadian oscillation of physiology and behaviors through complex methods of regulation (Dunlap et al., 2004; Hastings et al., 2008). Not surprisingly, there are shared molecular mechanisms for the molecular clock among diverse organisms, including *Neurospora*, *Drosophila*, rodents and humans. However, there are also salient differences. For instance, core clock mechanisms are presumably more widely integrated with other forms of physiological regulation in metazoans compared with unicellular organisms due to the inherent complexity of intercellular interactions. In addition, while molecular differences between vertebrates and invertebrates cannot be overlooked (Hardin, 2011; Lowrey and Takahashi, 2011), differences between closely related species, such as rodents and humans, are also expected. For instance, mice are nocturnal and with circadian period average approximately 23.5 h under constant darkness (Lowrey and Takahashi, 2011), whereas humans are diurnal with an average slightly longer than 24 h (Czeisler et al., 1999). More importantly, the highly polyphasic nature of sleep where dozens to hundreds of sleep–wake transitions occur every hour in mice directly contrasts with the single 5–9 hour block of consolidated sleep in most modern adult humans with only a few sleep to wake transitions.

Identification of the underlying genetic basis of human circadian rhythm behaviors was first advanced with the characterization of the first Mendelian circadian trait, familial advanced sleep phase (FASP), in 1999 (Jones et al., 1999). This study began with meticulous phenotypic characterization of a 69 year old woman who had life-long early sleep–wake onset, which led to the identification of a large family segregating this behavior. This story pioneered the field of human sleep genetics at the molecular level, including the search for rare Mendelian single gene/mutation forms and genome-wide association studies aimed at discovering novel variants in larger populations. Since the initial FASP findings, other human circadian/sleep phenotypes have been attributed to underlying genetic components, such as familial natural short sleep (FNSS) (He et al., 2009; Zhang et al., 2011). Therefore, studies of rare and extreme Mendelian behavioral traits have established a foundation for identifying human genetic components for circadian rhythms and sleep behaviors, which then provide further opportunities for understanding the molecular mechanisms of these behaviors. This review will outline the current understanding of the field of circadian rhythm disorders.

Human circadian rhythm sleep disorders

Human alertness demonstrates a circadian rhythmicity with a seemingly paradoxical nadir of sleepiness at the end of the day (the "Maintenance of Wakefulness Zone") (Strogatz et al., 1987), followed by a peak in difficulty sustaining wakefulness in the second third of the sleep period (approximately 3–5 A.M.) and then a gradual increase in alertness until the next evening. Pineal release of melatonin is stimulated by the suprachiasmatic nucleus of the hypothalamus (SCN) starting about 1–2 h before habitual sleep onset time and continuing through the night, unless such stimulation is masked by light of more than 50–100 lx intensity (Lewy et al., 1980).

The International Classification of Sleep Disorders lists approximately 60 disorders of human sleep (ASDA, 1997) including circadian rhythm sleep disorders (CRSD). CRSD usually present as a social problem in a person's sleep/wake timing. The most common complaints for CRSD are difficulty initiating or ending sleep at appropriate social times.

Circadian rhythm sleep disorders are classified into the following types according to the American Academy of Sleep Medicine (AASM, 2012):

1. Advanced sleep phase disorder (ASPD)

Individuals with ASPD have earlier sleep/wake times than a majority of the population, whereby the entire sleep–wake cycle of ASPD is shifted up to several hours earlier with respect to solar time (Fig. 1) (AASP, 2005). These people are considered "morning larks". People with ASPD fall asleep during the "Maintenance of Wakefulness Zone" for conventional sleepers and tend to wake up alert and energetic in the early morning hours when most people are the sleepiest. ASPD patients usually present with both difficulty in staying awake to satisfy domestic responsibilities in the evening and an obligate early morning awakening before others are active. This can result in significant sleep deprivation if social responsibilities keep the patient awake late and their biological clock wakes them up early. ASPD is more common in the elderly. It is notable that many people have extremely early sleep and wake times and in whom it is *not* considered a disorder. Such individuals may in fact feel virtuous for being the 'early bird' that gets the worm. Thus, perception of waking early may be positive or negative and is really in the eye of the beholder, underscoring the fact that these clinical classifications are truly behavioral phenotypes.

The International Classification of Sleep Disorders criteria for the clinical diagnosis of ASPD are based on the report of a patient who seeks medical attention specifically because of a complaint of a sleep time that is earlier than his/her "desired" sleep schedule (ASDA, 1997). No (solar) clock times of the habitual morning wake up are specified, and no measurements of melatonin, temperature, or other rhythms are required.

2. Delayed sleep phase disorder (DSPD)

DSPD individuals are "night owls" and routinely have later sleep/wake onset compared to the rest of the population (Fig. 1) (AASP, 2005). Their entire sleep–wake cycle is shifted later with respect to solar time, and DSPD patients feel wide awake, energetic and motivated until late in the night. Depending on the severity, sleep onset may be delayed until 01:00 to 06:00 A.M., and the circadian "morning" increase in alertness does not occur until approximately 10:00 A.M. to 2:00 P.M. DSPD individuals are often sleep deprived because sleep onset is delayed by the biological clock and morning waking time is enforced by the alarm clock and social responsibilities. DSPD is common in adolescents and young adults with an estimated prevalence of 7–16%. Again, it is important to point out that there are many night owls who do *not* consider it a disorder.

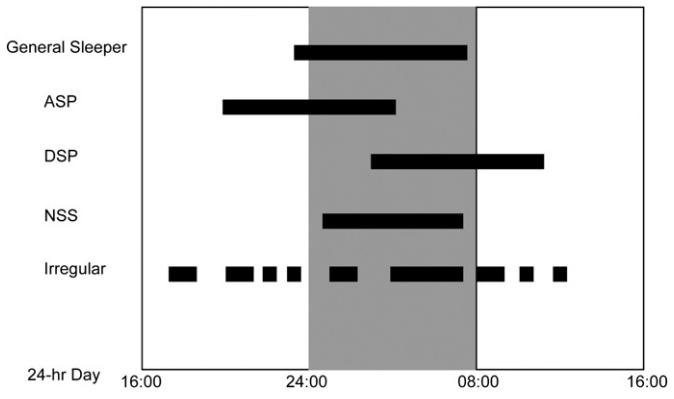

Fig. 1. Schematic sleep schedules for ASP, DSP, NSS, and ISW in comparison to general sleepers during each 24 hour period. Black-filled bars represent time spent in sleep.