Commentary

From genes to chronotypes: the influence of circadian clock genes on our daily patterns of sleep and wakefulness

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The functions of circadian clocks and oscillators depend on a small number of genes. This collection of circadian clock genes forms an autoregulatory feedback loop, and provides the mechanism that underlies the operation of circadian clocks and oscillators in the brain and body (1). The resulting endogenous clocks and oscillators go on to drive diverse rhythms in behavior and physiology. Therefore, it was with some foresight that Hu *et al.* [2016] surveyed "23andMe" clients on their daily sleep-wake preferences, and performed an extensive genome-wide association study (GWAS) on 89,283 individuals (2). Even with a relatively coarse self-reported measure of "morningness", the authors were able to identify 15 loci that were associated with preferred wake times, and notably, many of these loci related back to known circadian clock genes. Taken together, this study provides important new evidence that single nucleotide polymorphisms (SNPs) located close to certain clock genes, are associated with meaningful changes in our innate circadian preferences to wake early or to sleep late.

About a third of our lives are spent sleeping, and even though we are volitional creatures in many of our actions, when and how much we sleep is strongly influenced by an interaction of homeostatic and circadian processes (3). Homeostatic pressures maintain a set point, aiming for a certain amount of sleep within each 24-hour cycle, and this set point can vary from individual to individual. Homeostatic regulation of sleep is also somewhat flexible, whereby sleep debts can accumulate and then be repaid in the future. In contrast, circadian mechanisms influence the times of day when we are predisposed to sleep or wake, despite homeostatic needs. For instance, night-shift workers are often very tired during the night shift, even when they have had adequate sleep in the last 24 h. Likewise, night-shift workers may also find it very difficult to fall asleep, or to stay asleep, during the day, even if their need for sleep is high. These observations reflect fundamental circadian drives that keep us asleep at night, and keep us alert during the day, and these drives are nearly impossible to overcome without fundamental adjustments of the circadian clocks that drive them. Thus, homeostatic pressures interact with circadian pressures, and typically produce a consistent and predictable daily routine that can vary across individuals and broadly translate to "morningness".

Hu *et al.* [2016] suggest that these effects on morningness are being mediated by the suprachiasmatic nucleus (SCN), which is the "master" circadian clock that drives many rhythms in behavior and physiology (4). Consistent with this idea, clock gene expression in the SCN oscillates over the course of 24 h (1), and these cycles are putatively linked with the clock-function(s) of this nucleus. However, the genomic changes observed by Hu *et al.* [2016] are present throughout the body, and daily oscillations in clock gene expression are observed in many other structures outside of the SCN (5-9). For instance, oscillations in clock gene expression are observed in the limbic forebrain, hippocampus, olfactory bulbs, adrenal glands, lungs, and heart. These extra-SCN oscillations are only beginning to be linked with functional consequences, but seem to reflect

unique function(s) that are somewhat more limited to the tissue of interest (10-12). Therefore, in addition to the potential importance of the SCN, we would suggest that the expression of clock genes outside of the SCN could also be another major force that determines chronotype.

The endogenous circadian period is not precisely 24 h, and it needs small adjustments each day to remain in synchrony with the precise 24 h environmental cycle. The SCN is adjusted primarily by light, which can either advance or delay the clock depending on the time of day and amount of light (13). In the case of some blind individuals, the circadian system does not receive adequate light stimulation and the circadian system is never synchronized to the environment. In the case of familial advanced sleep phase syndrome, extreme circadian periods require large circadian adjustments each day, which could account for the extreme morningness observed in this population (14). Finally, within a single time-zone, slightly different sunrise times are experienced depending on the east-west longitude. In line with these systematically different environments, consistent differences are also observed in the timing of the sleep-wake cycles of individuals at each longitude (15). Collectively, these findings illustrate the intimate links between circadian clocks, the daily and predictable adjustments of these clocks, and morningness.

Morningness is also strongly affected by age, whereby older people tend to get up earlier, and this effect presumably occurs through mechanism(s) that are independent from genetics. Many extra-SCN rhythms of clock gene expression are also known to respond to a variety of metabolic, temperature, and hormonal cues (7,16,17). Therefore, even though no causal relationships were observed (2), it remains quite feasible that other factors such as depression and Body Mass Index might have been able to produce disruptions in extra-SCN expression of clock genes, regardless of which SNPs were or were not present. Moreover, any factor that disrupts sleep, such as sleep apnea, might reasonably be thought to act through a homeostatic mechanism rather than a circadian mechanism, per se. If sleep is generally disrupted, then individuals will need to stay in bed longer to sleep long enough, and it might follow that they would generally be less likely to be a morning person. Therefore, it is again the interaction between circadian and homeostatic drives that either permit or prevent "morningness", and both the SCN and extra-SCN oscillators may contribute to this chronotype.

Ultimately, our innate daily routines can be forced to conform to regular business hours, and can also respond to the challenges of shift work or jet-lag. Despite the obvious plasticity of this system, our "morningness" and endogenous circadian drives remain. By utilizing the "23andMe" data, Hu *et al.* [2016] have begun to demonstrate the immense potential of these ventures into "big data", and have successfully highlighted the important contributions of circadian clocks and oscillators to our daily routine. In the last decade, clear health consequences have been observed when circadian rhythms are disrupted by chronic jet-lag in humans, or abnormal circadian periods in rodents (18,19). The links between circadian timing and mental health have also recently implicated in extra-SCN clock gene expression (20). We are excited to see the potential that will be unlocked as these genomic databases continue to expand, with more people and more heterogeneous sampling. As activity monitors and sleep loggers become more widespread and reliable, we also look forward to the potential synergy between merging these enormous genetic data sets with better and more objective behavioral and lifestyle data.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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