Does our DNA determine when we sleep?

The discovery and study of three kindreds with advanced sleep phase disorder shed light on how we can inherit tendencies to be early morning or late night kinds of people (pages 1062–1065).

CLIFFORD M. SINGER & ALFRED J. LEWY

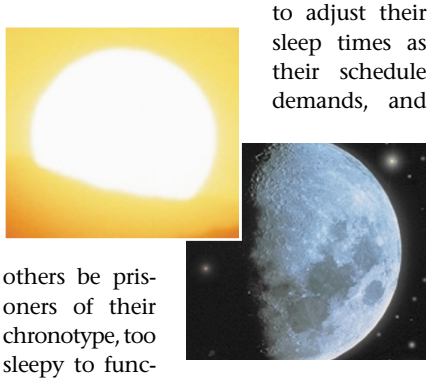
OF THE MANY mysteries that enshroud sleep, the process that controls its timing is perhaps the least understood. This situation is changing, as a study by Jones *et al.* on page 1062 of this issue makes an essential contribution to our understanding of sleep's chronobiology. Jones *et al.* provide compelling evidence that a little understood sleep disorder, advanced sleep phase syndrome (ASPS), is an inheritable condition characterized by an intrinsically short circadian period.

The daily cycle of sleepiness and alertness is a circadian rhythm long considered to be under voluntary control. Since the discovery in 1980 that bright light could suppress the production of melatonin[1] and could shift the setting of the human circadian pacemaker[2,3] we have made rapid advances in our understanding of the processes controlling sleep timing. Molecular biologists and geneticists have recently joined the effort, and we are gaining better insight into the cellular mechanisms by which circadian rhythmicity is generated.

Genetic mutations alter circadian physiology in many species, including mammals. In a search for genes that regulate circadian rhythm in mammals, a semi-dominant mutation was discovered to lengthen circadian period and abolish rhythmicity in mice.[4] The mutated gene became known as 'CLOCK'. In a random sample of normal adults, a single nucleotide polymorphism located in the 3' flanking region of the human CLOCK gene was correlated with morningness–eveningness preferences.[5] It is remarkable that a phenotypic trait as complex as sleep-time preference (chronotype) could be influenced by polymorphisms of a single gene.

CLOCK gene mutations have also been shown to affect specific circadian properties, such as the period of the circadian rhythm under free-running conditions, in which there are no external time cues.[6] The intrinsic circadian period unmasked by these experimental conditions is called τ by chronobiologists. In free-running conditions, physiologic processes will assume the periodicity of τ, which varies from person to person, and is close to but not exactly 24 hours, hence the term circadian or, literally, "about a day." A wide range in τ (23.8 to 27.1 h) was shown to exist in humans[7] although a more recent study reported a smaller range of human variation.[8] It is this genetic variation in τ, studies such as the one by Jones *et al.* suggest, that make some of us 'morning larks' and others 'night owls'.

In spite of the revelation that circadian variation in sleep propensity is due to genetic factors, we still do not understand the detailed mechanisms behind ASPS and its mirror image, delayed sleep phase syndrome (DSPS). People with DSPS are in a perpetual 'night owl' state, unable to sleep before midnight or wake before noon. Why would most people be able to adjust their sleep times as their schedule demands, and



others be prisoners of their chronotype, too sleepy to function in the evening (ASPS) or the morning (DSPS)? Although genetic determinants may be sufficient to lock some individuals into a ASPS, other non-genetic factors may also be involved. Several potential mechanisms have been suggested, including an altered sensitivity to light.[9] Relative insensitivity to light could reduce the body's ability to remain in synch with the earth's light–dark cycle and maintain normal sleep and activity hours. This proposed insensitivity to light could occur at either the retinal or hypothalamic level. Another mechanism that may interrupt the sleep cycle and social clock is the habitual absence of the light exposure, such as with daytime sleep or a dimly-lit environment. There may also be individual differences in the strength of the connection between circadian clock and actual sleeping times, which may explain, for example, why some people are affected by jet lag whereas others are not. We clearly have much more work to do, but the knowledge that τ and chronotype are genetically determined has cleared some smoke.

Insight into the genetics of chronotype has been matched by rapid advances in our ability to treat chronobiological sleep disorders such as jet lag, shift-work maladaptation and sleep disorders in blind individuals. For example, strategically timed exposure to bright light to produces rapid changes in circadian phase position. Bright light exposure has been successfully employed to treat ASPS (refs.10,11), DSPS(ref. 12), jet lag, shift-work maladaptation and non-24-hour sleep–wake syndrome.[13] Some cases of ASPS can also be treated with melatonin.[14]

Advances in our understanding of mechanisms and treatments of chronobiological sleep disorders may restore an element of control in daily schedules of those with ASPS. Although those of us without sleep disorders may have freedom to go to sleep when we choose, it seems that our parents—through their DNA—continue to influence our bedtimes.

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Sleep and Mood Disorders Laboratory,
Dept. of Psychiatry, OHSU,
Portland, Oregon 97201 USA
Email: singerc@ohsu.edu