Editorial

When our body clocks run late: does it make us depressed?

Daniel F. Kripke

University of California, San Diego, La Jolla, California 92037-2226, USA

Correspondence to: Daniel F. Kripke, M.D. University of California, San Diego, 8437 Sugarman Drive, La Jolla, California 92037-2226, USA. Email: dkripke1@san.rr.com.

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A sudden rush of newly-published research has given us much more understanding of what it means to be an "evening person" or "night owl". An evening person feels more alert as evening arrives, may have trouble getting to sleep at a normal bedtime, and may have trouble getting up in the morning. The contrast is a "morning person" who wakes up early rather easily, is energetic in the morning, and becomes more fatigued as the day goes on, perhaps having trouble staying awake to read or to watch television before bedtime. Extreme morning-person hours seemed typical and healthy a century and more ago. Before artificial light became convenient, it seemed natural for people to fall asleep within a few hours after sunset and to arise about dawn, as their farm animals do (1). Today, people at either extreme of the morningness-eveningness spectrum may complain of sleep disorders and seek medical help.

Studies with morningness-eveningness questionnaire scales that encompass both sleep times and daytime behaviors have revealed that the trait is heritable (2). Morningness-eveningness is well-correlated with the circadian rhythm phases of biological markers of the suprachiasmatic nucleus circadian pacemaker such as melatonin, cortisol, and body temperature. Morningness-eveningness is moderately well-correlated with actual sleep timing. Together, the phase-timings of behavioral, psychological, and physiologic markers determine a person's circadian phenotype, known as the chronotype. Up to this year, there had been little well-replicated information on the genetic determinates of the morningness-eveningness trait in the general population.

Using the large GWAS data bank of the 23andMe company, Hu *et al.* were able to examine questionnaire "self-reporting of being a morning person" among 89,283 participants who had volunteered for research analyses of their data (3). Participants answered forced-choice questions asking them to report dichotomously being either a "night person" or "morning person", in response to which 43.6% said they were morning persons. Fifteen genetic loci were inferred to be significantly associated with morningness, several of which were within or near genes already thought to influence the endogenous circadian system (3).

These 15 loci were largely replicated in an independent study from the UK Biobank (4), and some additional loci were reported. The UK Biobank studies were able to use results from a semi-parametric 4-choice question of whether a participant was "definitely a morning person", "definitely an evening person", "more a morning than evening person", or "more an evening than a morning person". Lane *et al.* reported 27% definite morning, 36% more morning, 28% more evening, and 9% definite evening (4). Apparently while both studies were in preparation, these results were already being replicated by a separate independent study of the UK Biobank (5). It is not clear how much the two samples from the UK Biobank may have overlapped, but the statistical approaches certainly had many differences, as did outcomes that only partly replicated.

In these three GWAS, largely consistent with each other, the associations of the almost two dozen candidate loci with chronotype were largely novel and not particularly consistent with previous much-smaller studies. For many of the candidate loci in the three studies, further replications will be needed. Moreover, some of the linkage peaks were so broad that functional studies will be needed for satisfactory designation and verification of the genes functionally influenced by each locus of linked polymorphisms.

It appears that the identified loci may explain as much as 21% of the chronotype variability in these samples

of European ancestry (3), and perhaps more when contrasting the extreme phenotypes (4), but the key marker polymorphisms have rather different frequencies in groups from other ancestries, so the important loci in diverse parts of the world will need more study. As the GWAS approach is expanded and refined, it will provide increasing understanding of the heritable component of the morningness-eveningness trait. As the phrasing of the different morningness-eveningness questions for the 23andMe and UK Biobank samples are compared and the resultant sample percentages contrasted, we are reminded that different phenotype questionnaire phraseologies may lead to different outcomes. One might find stronger gene-phenotype associations when contrasting the extreme phenotypes and even perhaps when contrasting each extreme phenotype with the large middle group. Also, a multi-question morningness-eveningness scale that integrates self-descriptions of sleep times and daytime activation variations may correlate better than a single-item phenotype. Various forms of objective data such as wrist activity monitors could be used.

The phenotype data from these studies by themselves provided important findings. According to Hu *et al.*, the odds ratio for insomnia was 0.66 (95% CI: 0.63–0.69), among morning persons contrasted to evening persons (3). Perhaps this indicates that being an evening person accounts for much insomnia, at least that insomnia defined as, "Do you routinely have trouble getting to sleep at night". Of evening persons, 39.7% reported this symptom (more than one quarter of the total sample). Nevertheless, the insomnia associations with genetic markers for morningness were not strong. Correlations of eveningness with other types of insomnia may be weaker: with midsleep or early awakening, for example. To treat trouble getting to sleep at night, resetting the circadian clock with morning bright light, behavioral habit modifications, or melatonin given a few hours before bedtime might prove to be superior alternatives to the use of sedatives.

In current American society, morningness is generally associated with health and successful performance. The main complaints of excessive morningness (sometimes called advanced sleep phase disorder) are related to early awakening and are most common among people of retirement age. On the other hand, extreme eveningness (sometimes called delayed sleep phase disorder) is commonly encountered as a partly-disabling disorder in all late-adolescent and adult age groups, often making customary school work and employment difficult. Delayed sleep phase seems to be increasing, especially among teen-age students and young adults, and seems partly due to increasing use of television, computers, cell phones and tablets late in the evening. It is thought that the strong blue-light radiation of many display screens used in the evening exacerbates delays of circadian rhythms (6,7).

Since its initial descriptions, an association of delayed sleep phase syndrome with depression has been noted (8,9). Perhaps the most interesting epidemiologic findings of the GWAS studies were the negative associations of morningness with depression (3,4), consistent with a number of much smaller previous studies relating eveningness and explicit delayed sleep phase syndromes to depression, both unipolar and bipolar. Hu *et al.* reported a marginal association of depression with morning-person genetic risks (P=0.10, NS in a two-tailed test) (3). Lane *et al.* reported no association of depression with the genetic risk score for morningness (4). Nevertheless, two recent family studies have supported the heritability of circadian rhythm phase-delay phenotypes, the heritability of depression, and an apparent causal association of both circadian and mood phenotypes with the same polymorphisms (10,11). Another recent report explained molecular mechanisms by which specific polymorphisms in the circadian genes *CLOCK* and *PER3* produce circadian phase delays, and showed that these polymorphisms are likewise associated with major depressive disorders (12). It seems uncertain how much depression and the rs228697 polymorphism causing phase delay in *PER3* (12) are linked to that polymorphism in the *PER3* promoter that has been identified with eveningness and depression in the GWAS studies (3,4).

An intriguing interpretation derived from partial sequencing of Neandertal genomes suggested that Neandertal haplotypes linked to depression were also related to circadian clock genes (13). The authors of this report suggested that the Neandertal haplotypes retained in modern humans were somehow adaptive to the patterns of seasonal sun exposures at higher latitudes. The photoperiod or daylength changes more seasonally at high latitudes, triggering seasonal responses in many species, including variations in sleep timing (1). A specific neuroendocrine and molecular theory has been proposed that explains how circadian phase delays might influence photoperiodic mechanisms, resulting in depression (14). This photoperiodic theory is based on the observation that the nocturnal elevation of the hormone

melatonin has its offset about dawn, but this offset is delayed in the long nights of winter at high latitudes, in some conditions of delayed sleep phase or long sleep, and specifically in depression. Late melatonin offset suppresses expression of TSHB in pars tuberalis, resulting in less T3 synthesis in the hypothalamic third ventricle region and disturbed secretion of several pituitary hormones (15,16). Early morning bright light treatment, by suppressing melatonin and by correcting phase delays, makes the melatonin offset earlier.

What is the clinical implication? If early morning bright light resolves a melatonin offset phase delay and counteracts extreme eveningness, might it also thus resolve depression, even nonseasonal major depression? Growing proof of the antidepressant power of early morning bright light is now available. Most recently, Lam *et al.* compared randomized early morning bright light treatment with a dummy treatment, with fluoxetine (a standard antidepressant), and with all-placebo treatment (17). Effects of early morning bright light alone over 8 weeks produced several times as much benefit as the antidepressant drug. This large antidepressant effect supports the theory of a causal role of phase delays in depression and more specifically, delayed melatonin offset. Combined, bright light and antidepressant provided even more benefit than either antidepressant or bright light alone (17). Indeed, the two treatments appeared possibly synergistic.

Thus, the convergence of new genetic studies helps explain a novel clinical treatment for one of mankind's most disabling disorders. With expanded replications, bright light may prove much better than standard pharmacologic treatments for depressed outpatients. The new studies are going far to document the association of eveningness with depression, to explain the underlying heritable genetic abnormalities, and to begin unlocking the whole chain of molecular, intracellular, endocrine, and organismic mechanisms of depression and its treatment.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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