Genetic Markers of Sleep and Sleepiness

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KEYWORDS

• Candidate gene • GWAS • Sleepiness • Sleep • Individual differences • Chronotype
• Circadian clock genes • Heritability

KEY POINTS

- The circadian clock interacts with the sleep homeostatic drive in humans.
- Chronotype and sleep parameters show substantial heritability, underscoring their genetic component.
- Candidate gene and genome-wide association (GWA) studies indicate circadian clock genes and noncircadian genes are related to individual differences in chronotype.
- Similarly, candidate gene and GWA studies show circadian clock genes and noncircadian genes are associated with variation in sleep parameters.

Both sleep and wakefulness are modulated by an endogenous biological clock located in the suprachiasmatic nuclei of the anterior hypothalamus. Beyond driving the timing of wake and sleep, the clock modulates waking behavior, as reflected in sleepiness.[1] The daily sleep and wakefulness modulations have been instantiated in the 2-process mathematical model of sleep regulation and its variants.[2–4]

This 2-process model has been applied to the temporal profiles of sleep[3,5] and wakefulness.[6] The model consists of a sleep homeostatic process and a circadian process that interact to determine sleep onset and offset timing.[1,7] The homeostatic process, represented by the drive for sleep, increases during wakefulness (observed when wakefulness is maintained beyond habitual bedtime into the night and subsequent day) and decreases during sleep (represented by recuperation obtained from sleep). When this homeostatic drive increases above a certain threshold, sleep is triggered; when it decreases below a different threshold, wakefulness is invoked.

The circadian process represents daily oscillatory modulation of these threshold levels. The circadian system actively promotes wakefulness more than sleep.[8] The circadian drive for wakefulness can be experienced as spontaneously enhanced alertness in the early evening after a sleepless night. Notably, there are robust individual differences in the sleep homeostatic and circadian processes, underscoring genetic underpinnings.

This article, which focuses on healthy adult sleepers, begins with a discussion of the heritability (h^2) and genetic basis of chronotype, drawing on candidate gene and genome-wide association (GWA) studies. The h^2 of sleep is discussed and candidate gene studies using circadian clock genes to investigate variation in sleep parameters are described. GWA studies of sleep are then reviewed. The article concludes with a discussion of future research areas.

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GENETICS OF INDIVIDUAL DIFFERENCES IN CIRCADIAN RHYTHMS AND CHRONOTYPE

Healthy adults show interindividual differences in free-running circadian period (tau),[9–15] which shows robust stability within individuals.[12] They also demonstrate interindividual differences in circadian amplitude[16,17] and circadian phase,[10,16–18] partly due to genetic influences.[17]

Chronotype (Morningness-Eveningness)

Chronotype or morningness-eveningness (ie, the tendency to be an early lark or a late owl) is the most frequently measured interindividual variation in circadian rhythmicity. Morning-type and evening-type individuals differ endogenously in the circadian phase of their biological clocks.[16,18]

Self-report questionnaires, such as the Horne-Östberg Morningness-Eveningness Questionnaire[19] and its variants,[20] and the Munich ChronoType Questionnaire,[21,22] are the most commonly used measures of circadian phase preference. Chronotype is a phenotypic aspect of circadian rhythmicity in humans.[1] As predicted from the 2-process model, chronotypes show differences in homeostatic sleep regulation[23–25] and responses to sleep fragmentation in laboratory studies.[26]

Heritability of Chronotype

The fraction of variance in a trait or phenotype explained by genetic influence is the h^2. Twin studies, which allow for assessment of the relative contributions of genetics and environment, demonstrate chronotype has substantial h^2 (.40–.54) across diverse populations.[27–36] Family studies also demonstrate substantial h^2 (.23–.48).[37–39]

Candidate Gene Studies of Chronotype

Most candidate gene studies investigating the genetic basis of chronotype have targeted circadian clock genes. The 3111C allele (single nucleotide polymorphism [SNP] rs1801260) in the *Circadian Locomotor Output Cycles Kaput* (*CLOCK*) gene 5′-UTR region has been associated with eveningness and delayed sleep timing[40–42] (but see[13,43–48]) and *CLOCK* rs11824092[49] has also been linked to chronotype. The variable number tandem repeat (VNTR) polymorphism in the *PERIOD3* (*PER3*) gene (rs57875989) has been linked to chronotype (albeit not consistently[44,50–64]), as have *PER3* SNPs rs228697,[65] rs10462020,[66] and rs2640909.[67] The bp2114 G/A G3853 A and 111G polymorphisms of *PERIOD2* (*PER2*)[68–70] have also been associated with chronotype (but see[43]); however, rs6753456 does not show an association.[71]

Similarly, the *PERIOD1* (*PER1*) T2434C polymorphism has been associated with morning preference.[72] Moreover, rs7221412 near *PER1* has been related to activity rhythm timing in 2 independent cohorts: activity timing was delayed by 67 minutes in *GG* versus *AA* homozygotes and *GG* individuals died about 7 hours later than *AA/AG* individuals.[73]

SNPs rs922270, rs11824092, and rs1481892 of the *Aryl Hydrocarbon Receptor Nuclear Translocator-like 2* (*ARNTL2*) gene[49,66] and the *Nuclear Receptor Subfamily 1 Group D Member 1* (*NR1D1*) gene encoding for nuclear receptor REV-ERBα[74] have been associated with chronotype, whereas the *G-protein B3 subunit* (*GNβ3*) gene 825 C/T SNP,[48] the *Timeless* (*TIM*) gene A2634G SNP,[75] and the *Melanopsin* (*OPN4*) gene Ile394Thr SNP[76] all failed to show such an association.

Genome-Wide Association Studies of Chronotype

Both h^2 and candidate gene studies of chronotype successfully laid the groundwork for GWA studies, which are comprehensive and unbiased approaches to identify genes and genomic variants associated with a phenotype, trait, or disease, using population samples. Different alleles (risk variants) are characterized by the frequency of their occurrence, spanning from rare (frequency <1%) to common (frequency >5%). These are associated with a range of effects, from small (increased risk by a factor of 0.1) to large (increased risk by a factor of >100) on a given phenotype, trait, or disease.

The first GWAS of chronotype capitalized on personalized genetic platforms, using 89,283 individuals from the 23andMe database.[77] This study found 15 genetic variants associated with morningness, including 7 near well-established circadian genes: *PER2*, *PER3*, *Regulator of G-Protein Signaling 16* (*RGS16*), *Vasoactive Intestinal Peptide* (*VIP*), *Hypocretin Receptor 2* (*HCRTR2*), *Ras Related Dexamethasone Induced 1* (*RASD1*), and *F-Box and Leucine-Rich Repeat Protein 3* (*FBXL3*) (**Table 1**).

Using 100,420 individuals from the UK Biobank cohort, Lane and colleagues[78] identified 12 significant and 1 suggestive genetic loci associated with chronotype, including variants near 4 circadian genes: *PER2*, *RGS16*, *F-Box and Leucine-Rich Repeat Protein 13* (*FBXL13*), and *Aph-1 Homolog A, Gamma Secretase Subunit* (*APH1A*). Notably, 8 of the 15 previously reported gene loci[77] were replicated, and all 15 showed a consistent directional effect (see **Table 1**).