The genetics of circadian rhythms, sleep and health

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Abstract
Circadian rhythms are 24-h rhythms in physiology and behaviour generated by molecular clocks, which serve to coordinate internal time with the external world. The circadian system is a master regulator of nearly all physiology and its disruption has major consequences on health. Sleep and circadian rhythm disruption (SCRD) is a ubiquitous feature in today’s 24/7 society, and studies on shift-workers have shown that SCRD can lead not only to cognitive impairment, but also metabolic syndrome and psychiatric illness including depression (1,2). Mouse models of clock mutants recapitulate these deficits, implicating mechanistic and causal links between SCRD and disease pathophysiology (3–5). Importantly, treating clock disruption reverses and attenuates these adverse health states in animal models (6,7), thus establishing the circadian system as a novel therapeutic target. Significantly, circadian and clock-controlled gene mutations have recently been identified by Genome-Wide Association Studies (GWAS) in the aetiology of sleep, mental health and metabolic disorders. This review will focus upon the genetics of circadian rhythms in sleep and health.

Introduction to the Circadian Clock
Life has evolved under a 24-h rhythm where environmental factors such as temperature and light fluctuate with a daily predictable sequence. As a consequence, most organisms have evolved circadian clocks that anticipate these regular environmental changes and establish endogenous 24-h rhythms to get the correct physiology and behaviour to the appropriate time window each day. The mechanisms underlying circadian regulation are cell autonomous transcription-translation feedback loops (TTFLs): In mammals, the transcription factors CLOCK and BMAL1 drive the expression of Period (Per1/2) and Cryptochrome (Cry1/2), whose protein products in turn feed-back to inhibit CLOCK and BMAL1 (8) (Fig. 1). Downstream of these four factors lie thousands of clock-controlled genes that orchestrate the oscillation of tissue-specific metabolic and physiological functions. Most cells in the body possess a molecular clock and are maintained in synchrony by a master pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus (9).

In order for the circadian network to have adaptive value, it must receive and respond to signals that provide temporal cues (zeitgebers). Zeitgebers modulate the temporal expression patterns of clock genes such as Per1/2 (10), to set the phase, amplitude and period of the molecular clockwork. Light, which signals the dawn-dusk cycle, is the best-characterised zeitgeber, and this light input from the photosensitive retinal ganglion cells (pRGCs) of the retina (11) is transmitted directly to the ventral SCN through synaptic connections, where glutamate signaling then drives cAMP response element binding factor (CREB-CRTC)-mediated transcription of Per genes in the SCN (12) (Fig. 2). Peripheral circadian clocks throughout the body receive inputs from the SCN and numerous additional signals, including feeding (13); glucocorticoids (14); temperature (15); and...
Circadian Rhythm Disruption in Mental Illness

There is considerable evidence that patients with neuropsychiatric diseases, such as bipolar disorder, schizophrenia and depression exhibit SCRD and this, alongside the evidence from mouse models has been extensively reviewed previously (2,25). This disruption encompasses a wide range of sleep perturbations, including fragmented sleep, reduced total sleep time and changes in normal sleep architecture (26). Furthermore, these patients show dysregulation of multiple circadian outputs and of the core molecular clock (Fig. 1). Remarkably, fibroblasts isolated from schizophrenic patients show a loss of rhythmicity in CR1 and PER1 expression, and their peripheral blood leukocytes have decreased and/or disrupted diurnal expression of CLOCK, PER1/2, CR1 and a functional CLOCK homologue NPAS2 in comparison to healthy controls (27). Fibroblasts isolated from bipolar patients display a larger variance in period and amplitude and deficits in the entrainment pathways. Lithium is used for the treatment of bipolar disorder, and lithium’s primary therapeutic target is

![Diagram of the mammalian molecular clock](https://academic.oup.com/hmg/article-abstract/26/R2/R128/3965504/26/R2/R128?anchor= Pendulum)
postulated to be Rev-erba (28) (Fig. 1). Additionally, patients with major depressive disorder display a marked disruption in the circadian rhythm and phasing of core clock genes across multiple brain regions (29).

It is becoming increasingly clear that disruption of the molecular clock is not just a consequence of neuropsychiatric illness, but instead forms part of a bidirectional feedback loop with neuropsychiatric disease, whereby perturbations in one exacerbate dysfunction in the other (2,5). In this context, it is worth noting that, many disease relevant processes are under circadian control, such as sleep-wake timing and monoaminergic neurotransmitter synthesis, signalling and degradation (30–32). Furthermore, multiple single nucleotide polymorphisms (SNPs) in the genes encoding the core components of the molecular clock have been demonstrated, albeit weakly, to be associated with schizophrenia, bipolar disorder and depression, suggesting a causal role for clock dysfunction in neuropsychiatric disease (Table 1).

Currently the functional consequence of these SNPs and the strength of their association with disease remains unclear, however, recent work has provided insight into how mutations may impact clock function. Two rare missense mutations in the PERIOD3 gene (PER3-P415A/H417R), found to be associated with seasonal depression, were demonstrated to generate a mutant PER3 protein unable to stabilise PER1/2 and induce their nuclear localisation, resulting in circadian rhythm disruption (63).

A similar relationship has been found in patients with neurodegenerative diseases. Many conditions are associated with the disruption of sleep, circadian outputs and the core molecular clock (64). Patients with Alzheimer’s disease (AD) exhibit neuronal loss in the SCN (65), and a recent study by Lim et al. found that the diurnal and seasonal transcriptional rhythmicity of core clock genes in the dorsolateral prefrontal cortex is disrupted in AD patients (66). In addition, the expression of Bmal1/2 is dampened in peripheral blood leukocytes isolated from Parkinson’s disease (PD) patients (67,68).

As with neuropsychiatric illness, disruption of the core molecular clock is both a consequence of, and a contributor to, neurodegenerative diseases. Many conditions are associated with circadian rhythm disruption (69) (Fig. 1). In animal models it has been shown that sleep deprivation leads to increased Aβ plaque formation and that sleep is required for the clearance of Aβ (70). Additionally, the circadian clock regulates many molecular processes commonly involved in neurodegeneration, such as oxidative stress (71), metabolism (see next section), neuroinflammation (72,73).
Table 1. A list of single nucleotide polymorphisms (SNPs) in core clock genes that are associated with neuropsychiatric or neurodegenerative diseases. Only P values highlighted in bold remain significant after multiple comparisons correction.

| Gene | Disease | Sample size | Total SNPs tested | SNP | P value | Test used | Reference |
|------|---------|-------------|-------------------|-----|---------|-----------|-----------|
| ARNTL | BPD | 180 controls, 234 patients | 44 | rs1481892 | P = 0.018 | Cochran-Armitage trend test | (33) |
| | | | | rs4757142 | P = 0.0009 | | |
| | | | | rs1982350 | P = 0.005 | | |
| | | | | rs7107287 | P = 0.033 | | |
| BPD | | 477 controls, 523 patients | 268 | rs1481892 | P = 0.018 | Cochran-Armitage trend test | (34) |
| | | | | rs712633 | P = 0.04 | | |
| SAD | | 136 controls, 147 patients | 115 | rs2290035 | P = 0.02 | Logistic regression analysis | (35) |
| MD | | 926 controls, 459 patients | | rs2290036 | P = 0.005 | Logistic regression analysis | (36) |
| PS | | 913 controls, 535 patients | 6 | rs2290036 | P = 0.005 | Logistic regression analysis | (37) |
| BPD | | 405 controls, 465 patients | 92 | rs3789327 | P = 0.0212 | Association testing using FBAT | (38) |
| AD | | 423 controls, 476 patients | 1 | rs2278749 | P < 0.0001 | Pearson’s chi-squared test | (39) |
| PD | | 1342 controls, 1394 patients | 125 | rs7950226 | P = 0.0088 | Cochran-Armitage trend test | (40) |
| | | | | rs11605776 | P = 0.0049 | | |
| | | | | rs10832022 | P = 0.0049 | | |
| | | | | rs7941761 | P = 0.0197 | | |
| | | | | rs1562437 | P = 0.0013 | | |
| | | | | rs3816358 | P = 0.0275 | | |
| | | | | rs900147 | P = 0.00423 * | | |
| CLOCK | BPD | 101 patients, 128 controls, 145 patients | 1 | rs180260 | P = 0.026 | One-way ANOVA | (41) |
| | BPD | | 635 controls, 145 patients | 44 | rs180260 | P = 0.0138 | Association determined using the SNPassoc software package | (42) |
| | | | | rs11932595 | P = 0.0319 | | |
| SZ | | 128 controls, 199 patients | 1 | rs180260 | P = 0.026 | Logistic regression analysis | (43) |
| SZ | | | | rs180260 | P < 0.05 | Pearson’s chi-squared test | (44) |
| MD | | 776 controls, 592 patients | 32 | rs180260 | P = 0.028 | Pearson’s chi-squared test | (45) |
| AD | | 423 controls, 296 patients | 1 | rs180260 | P < 0.0001 | Pearson’s chi-squared test | (46) |
| BPD | | 405 controls, 465 patients | 92 | rs17777929 | P = 0.0317 | Association testing using FBAT | (47) |
| BPD | | 614 controls, 518 patients | 62 | rs534654 | P = 0.0097 | Pearson’s chi-squared test | (48) |
| | | | | rs4340844 | P = 0.015 | | |
| | | | | rs6850524 | P = 0.012 | | |
| BPD | 444 BPD families, 130 unrelated BPD families | 197 | | rs6850524 | P = 0.032 | Pearson’s chi-squared test | (49) |
| | | | | rs3805148 | P = 0.009 | | |
| | | | | rs3736544 | P = 0.024 | | |
| | | | | rs12504300 | P = 0.009 | | |
| | | | | rs4864542 | P = 0.01 | | |
| | | | | rs12648271 | P = 0.037 | | |
| BPD | | 440 controls, 199 patients | 209 | rs10462028 | P = 0.02 | Logistic regression analysis | (50) |
| AD | | 188 controls, 130 patients | 1 | rs1554483 | P = 0.009 | Pearson’s chi-squared test | (51) |
| AD | | 423 controls, 296 patients | 1 | rs4580704 | P < 0.0001 | Pearson’s chi-squared test | (52) |
| CRY1 | MD | 654 BPD patients, 335 patients | 7 | rs10861688 | P = 0.0048 * | Covariated linear regression | (53) |
| MD | 440 controls, 105 patients | 209 | rs2287161 | P = 0.007 † | Logistic regression analysis | (54) |
| MD | | 485 controls, 105 patients | 3 | rs2287161 | P = 0.010 | Logistic regression analysis | (55) |
| CRY2 | BPD | 477 controls, 268 | rs1554338 | P = 0.031 | Cochran-Armitage trend test | (56) |

(Continued)
Table 1. (Continued)

| Gene | Disease | Sample size | Total SNPs tested | SNP       | P value     | Test used                             | Reference |
|------|---------|-------------|-------------------|-----------|------------|---------------------------------------|-----------|
| MD   | 523 patients | 118 patients | 4 | rs10838524 | $P = 0.0017$ | Logistic regression analysis           | (54)      |
|      |          |             |                   |           | $P = 0.00074$ |                                       |           |
|      |          |             |                   |           | $P = 0.007$  |                                       |           |
| DT   | 3871 patients | 136 patients | 48 | rs10838524 | $q = 0.04$ | Linear and logistic regression analysis | (55)      |
|      |          |             |                   |           | $q = 0.04$  |                                       |           |
|      |          |             |                   |           | $q = 0.04$  |                                       |           |
|      |          |             |                   |           | $q = 0.04$  |                                       |           |
| DT   | 4154 patients | 166 patients | 48 | rs10838524 | $q = 0.003$ | Logistic regression analysis           | (56)      |
|      |          |             |                   |           | $q = 0.002$ |                                       |           |
|      |          |             |                   |           | $q = 0.002$ |                                       |           |
|      |          |             |                   |           | $q = 0.002$ |                                       |           |
| MD   | 4154 patients | 862 patients | 48 | rs10838524 | $q = 0.05$  | Logistic regression analysis           | (56)      |
|      |          |             |                   |           | $q = 0.05$  |                                       |           |
|      |          |             |                   |           | $q = 0.05$  |                                       |           |
|      |          |             |                   |           | $q = 0.05$  |                                       |           |
| NR1D1| BPD      | 444 BPD families | 197 | rs2071427 | $P = 0.0019$ | Pearson’s chi-squared test             | (48)      |
|      |          | 130 control families | | rs2269457 | $P = 0.0029$ |                                       |           |
|      |          |             |                   |           | $P = 0.0005$ |                                       |           |
| PD   | 1342 patients | 1394 patients | 125 | rs3744805 | $P = 0.00294$ | Cochran-Armitage trend test           | (40)      |
|      |          |             |                   |           | $P = 0.0009$ |                                       |           |
| PER1 | PD       | 1342 patients | 125 | rs2253820 | $P = 0.00067$* | Cochran-Armitage trend test         | (40)      |
| PER2 | SAD      | 173 controls | 13 | rs10870  | $P = 0.03$  | Logistic regression analysis           | (35)      |
| MD   | 459 controls | 926 patients | 115 | rs2304672 | $P = 0.0087$ | Logistic regression analysis           | (57)      |
|      |          |             |                   |           | $P = 0.0033$ |                                       |           |
|      |          |             |                   |           | $P = 0.0036$ |                                       |           |
|      |          |             |                   |           | $P = 0.0018$ |                                       |           |
| SZ   | 477 controls | 527 patients | 268 | rs2304672 | $P = 0.046$ | Cochran-Armitage trend test           | (34)      |
|      |          |             |                   |           | $P = 0.033$  |                                       |           |
| BPD  | 180 controls | 138 patients | 44 | rs2859387 | $P = 0.039$ | Cochran-Armitage trend test           | (33)      |
| PER3 | SZ       | 180 controls | 44 | rs228729 | $P = 0.028$ | Cochran-Armitage trend test           | (33)      |
|      |          | 331 patients |             |           |             |                                       |           |
|      |          |             |                   |           |             |                                       |           |
|      |          |             |                   |           |             |                                       |           |
| SZ   | 477 controls | 527 patients | 268 | rs2304674 | $P = 0.036$ | Cochran-Armitage trend test           | (34)      |
|      |          |             |                   |           | $P = 0.031$  |                                       |           |
| MD   | 2915 controls | 1296 patients | 529 | rs12137927 | $P = 0.00054$ | Logistic regression analysis         | (58)      |
|      |          |             |                   |           | $P = 0.00013$ |                                       |           |
|      |          |             |                   |           | $P = 0.00014$ |                                       |           |
| MD   | 776 controls | 592 patients | 32 | rs17031614 | $P = 0.017$ | Pearson’s chi-squared test           | (45)      |
|      |          |             |                   |           | $P = 0.007$  |                                       |           |
| RORA | MD       | 459 controls | 926 patients | 115 | rs2028122 | $P = 0.044$ | Logistic regression analysis           | (57)      |
|      |          |             |                   |           | $P = 0.0007$ |                                       |           |
|      |          |             |                   |           | $P = 0.0009$ |                                       |           |
| MD   | 4811 participants | Whole genome |             | rs12912233 | $P = 6.3 \times 10^{-7}$ | Weighted z score-based fixed effects meta-analysis | (59)      |
|      |          |             |                   |           | $P = 6.3 \times 10^{-6}$ |                                       |           |
|      |          |             |                   |           | $P = 7.2 \times 10^{-6}$ |                                       |           |
|      |          |             |                   |           | $P = 1.5 \times 10^{-5}$ |                                       |           |
| MD   | 2915 controls | 1296 patients | 529 | rs11632098 | $P = 0.00056$ | Logistic regression analysis         | (58)      |
|      |          |             |                   |           | $P = 6.3 \times 10^{-7}$ |                                       |           |
| BPD  | 1759 controls | 479 patients | 353 | rs782931 | $P = 0.01$* | Pearson’s chi-squared test           | (60)      |
| BPD  | 200 controls | 280 patients | 27 | rs4774388 | $P = 0.024$ | Additive, dominant and recessive genetic models with a maximum test for associations | (61)      |
| BPD  | 1770 controls | 448 patients | 429 | 43 SNPs reached nominal significance | $P = 0.002-0.044$ |                                        |           |
| RORB | SZ       | 477 controls | 268 | rs10491929 | $P = 0.023$ | Cochran-Armitage trend test           | (34)      |

(Continued)
Furthermore, growth and synaptic vesicle assembly within these cells. Variations in the expression of genes involved in survival, proliferation, and inflammation within these cells further exacerbate β-cell dysfunction. The disruption of these components has been reported. Remarkably, being obese alters the expression of both neurodegenerative and neuropsychiatric conditions.

### Metabolic Disorders

The metabolic system is under strong circadian control, and these relationships are summarised in Figure 3. One of the first indications of the strong coupling between circadian clocks and metabolism was suggested by the observation that the majority of cycling transcripts in the liver are implicated in multiple metabolic pathways (19,75). Processes such as glucose, cholesterol, and triglyceride metabolism are a few examples, whose rate-limiting steps were shown to be major sites of circadian regulation.

Clock genes are linked directly to metabolic syndrome (MetS), both in mutant mice and humans. For example, homozygous Clock mutant mice (Clock<sup>−/−</sup>) exhibit significant hypoglycemia, hyperinsulinemia, hepatic steatosis and dyslipidemia (76), all of which are significant markers of MetS. Remarkably, being obese alters the expression of both neurodegenerative and neuropsychiatric conditions.

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**Table 1. (Continued)**

| Gene | Disease | Sample size | Total SNPs tested | SNP | P value | Test used | Reference |
|------|---------|-------------|------------------|-----|---------|-----------|-----------|
| BPD  | 527 patients | 268 | rs17691363 | P = 0.035 | Cochran-Armitage trend test | (34) |
| PD   | 1342 controls | 125 | rs17691363 | P = 0.026 | Cochran-Armitage trend test | (62) |
| BPD  | 200 controls | 27 | rs1327836 | P = 0.003 | Additive, dominant and recessive genetic models with a maximum test for associations | (61) |
| BPD  | 1770 controls | 429 | rs1761135 | P = 0.027 | | |

*denotes a Bonferroni corrected P value, † denotes a permutation corrected P value. All other P values are not adjusted for multiple comparisons. q denotes the false discovery rate q-values, used to correct for multiple comparisons. q < 0.05 was taken to be statistically significant.

**Abbreviations:** AD: Alzheimer’s disease; BPD: Bipolar disorder; DT: dysthymia; MD: major depression; PD: Parkinson’s disease; PS: psychosis; SAD: seasonal affective disorder; SZ: schizophrenia.

and protein dynamics (74). Evidence linking SNPs in core clock genes with neurodegenerative diseases is currently scarce, with only a limited number of studies demonstrating the association of SNPs in CLOCK, BMAL1 and/or PER1 with AD or PD. Collectively, there is currently compelling evidence that disruption of the molecular clock contributes to the progression of both neurodegenerative and neuropsychiatric conditions.

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In humans, like mice, polymorphisms of CLOCK and BMAL1 have been associated with metabolic disorders. For example, CLOCK gene polymorphisms have been linked to a higher susceptibility to obesity (81,82) and two haplotypes of BMAL1 have been associated with hypertension and type 2 diabetes mellitus, replicated both in humans and in rodent models (83). Similar studies have also linked polymorphisms in other core clock genes like PER2 and NPAS2 to fasting hyperglycemia and hypertension respectively (84). In a small population of lean and obese women, a correlation between obesity and core clock components has been reported. Remarkably, being obese alters expression of core clock genes in adipocytes throughout the day and induces notable upregulation of CRY2 and REV-ERβa, two important negative feedback components of circadian clocks (85) (Fig. 1). Furthermore, a rare SNP in visfatin (NAMPT/PBEF1), a gene known to be involved in the negative arm of the clock (86) (not shown in Figures), has been associated with protection from obesity in human populations (87).

It is now evident that circadian clocks do not only regulate metabolism, but metabolic pathways can in turn feedback upon the circadian clockwork (Fig. 3). Restricting feeding to daytime (sleep phase) in mice causes uncoupling of peripheral clocks within the liver, kidney, heart and pancreas from SCN rhythms (13,88). In addition, a high-caloric diet has been shown to disrupt behavioural and molecular circadian rhythms in mice (89). Furthermore, two important regulators of homeostasis and metabolism in Drosophila, FOXO and GSK3β/Shaggy, were shown to be necessary for robust circadian rhythms (90,91), which emphasises the connection between metabolism and circadian clocks across the animal kingdom.
Collectively, the results from humans and animal models highlight the considerable involvement of the circadian machinery in metabolic pathways. A two-way interplay between these two systems is clear and the mechanisms governing their intercommunication are slowly emerging (Fig. 3).

**Disorders of Sleep Timing**

The human population displays a wide spread of circadian phenotypes or chronotypes, with early types (larks) at one end of the spectrum and late types (owls) at the other. Chronotype is influenced by an individual’s genetics, development and exposure to light and dawn and dusk. In terms of the genetics, clock gene mutations can explain some of the differences in chronotype. Two recent large scale genomic studies identified variants in several clock-related loci (92,93), particularly *PER2/3*, underlying morningness in the general population. Different chronotypes can usually alter sleep patterns to accommodate both their social demands and circadian clock; Winston Churchill believed in the importance of good sleep, but was a very late chronotype and compensated with long afternoon naps (94). However, extreme misalignment with the external light-dark cycle leads to severely disrupted sleep-wake cycles, chronic fatigue and exhaustion. The underlying cause could be either deficits in core clock machinery leading to non-24h rhythms or deficits in the input pathways and entrainment systems that result in a misaligned rhythm.

Examples of the first include delayed or advanced sleep phase disorders; Familial Advanced Sleep Phase syndrome is linked to mutations in *Per2* (95) and Familial Delayed Sleep Phase Syndrome to mutations in Casein Kinase 1 Delta (96) (Fig. 1). Recently, mutations in *Cry1* have been linked to Familial Delayed Sleep Phase syndrome, with a remarkably high frequency of 0.6% in the population, thereby affecting sleep in large numbers of individuals (97). In these conditions, due to a faster or slower molecular clock, the time window defined by the clock as optimal to sleep is shifted with respect to the external light-dark cycle, resulting in severe misalignment. In addition, situations where input pathways are deficient are also relatively common. Low levels of light within the nursing home environment result in circadian rhythm disruption (98) and patients with severe eye damage due to either genetic causes or trauma lose light input to the circadian clock resulting in severe misalignment (99). In these situations, behavioural rhythms imposed by care or feeding may help mask this disruption, but desynchronised and drifting peripheral clocks demonstrate the lack of entrainment which is manifest as poor and disrupted sleep.

**Treatment of Sleep and Circadian Rhythm Disruption (SCRD)**

Despite our growing knowledge of the molecular mechanisms underlying the 24h circadian clock and its role in the
development of chronic and debilitating diseases, there are limited therapeutic options available for the treatment of SCRD. As light is the primary zeitgeber for the SCN clock, bright light therapies and cognitive behavioural therapies that strengthen natural zeitgebers such as scheduled outdoor exercise (100, 101) have been shown to have some success. However, potent pharmacological interventions are still lacking. Melatonin has long been characterised as an output of the circadian clock and can be used to modify the phase of the clock, presumably acting via the melatonin receptors that are expressed in the neurons of the SCN and multiple other cell populations across the body. Melatonin has therefore been studied as a possible chronotherapeutic drug and shows promise in certain circadian-related conditions (102, 103). Prolonged release melatonin (tradename Circadin) is used to treat primary insomnia (104) in the aged and the agonist Agomelatine in the treatment of major depressive disorder (105). Most recently, Tasimelteon was approved in the United States in an orphan circadian disorder, non-24h sleep-wake disorder in the totally blind (106). Targeting the melatonin system, however, has limited efficacy; for example, Tasimelteon showed a beneficial effect on stabilising sleep-wake in 20% of the patient population after one month of treatment (106). As a consequence, recent efforts have focussed on developing alternatives, mainly targeting the core clock. Solt et al. reported a novel REV-ERB agonist receptor agonist was effective at regulating both sleep as well as metabolism in mice (6, 107) and Hirota et al. have developed a small molecule Cryptochrome activator (108). An alternative strategy that has yet to be employed is the development of molecules that act on the light input pathway to the clock, providing a pharmacological replacement for light for the treatment of SCRD.

Acknowledgements
The authors are very grateful for valuable input and critical comments from Prof. Andrea Nemeth and Dr. Jing Yu.

Conflict of Interest statement. None declared.

Funding
We would like to acknowledge the following sources of funding: BBSRC ref. BB/N01992X/1 to AJ, Wellcome Trust ref. 106174/Z/14/Z to RGF, BBSRC ref. BB/N001664/1 to SV, and a Said Foundation scholarship to ZW. AJ, SRV and RGF are in receipt of funding from Circadian Therapeutics.

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