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Review

Circadian clock gene polymorphisms implicated in human pathologies

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Circadian rhythms, ~24 h cycles of physiological and behavioral processes, can be synchronized by external signals (e.g., light) and persist even in their absence. Consequently, dysregulation of circadian rhythms adversely affects the well-being of the organism. This timekeeping system is generated and sustained by a genetically encoded endogenous mechanism composed of interlocking transcriptional/translational feedback loops that generate rhythmic expression of core clock genes. Genome-wide association studies (GWAS) and forward genetic studies show that SNPs in clock genes influence gene regulation and correlate with the risk of developing various conditions. We discuss genetic variations in core clock genes that are associated with various phenotypes, their implications for human health, and stress the need for thorough studies in this domain of circadian regulation.

Highlights

In addition to circadian rhythms, circadian genes play pivotal roles in myriad signaling pathways. Consequently, their dysregulation contributes to the onset and progression of various diseases.

Identifying SNPs in clock genes offers an exciting avenue to predict the predisposition of an individual to different pathologies/variations in phenotype.

Experimental models and human trials have confirmed that SNPs in core circadian genes are associated with pathologies.

Given the inherent complexity of diseases, that are often polygenic traits influenced by gene–environment interactions, robust statistical approaches utilizing large and diverse sample sizes is crucial when identifying disease-linked SNPs. Furthermore, recognizing the key role of population stratification in minimizing confounding effects ensures the reliability of associations between SNPs and diseases.

Molecular organization of the mammalian circadian clock

Circadian rhythms enable organisms to synchronize their body physiology and behavior to environmental changes via an endogenous, hierarchical network of oscillators (reviewed in [1]). At the molecular level, circadian oscillations are maintained by self-sustaining, interlocked, positive and negative transcriptional/translational feedback loops (reviewed in [2]). In mammals, the positive regulators of the loop, the brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) and the circadian locomotor output cycles kaput (CLOCK, and its paralog the neuronal Per-ARNT-Sim domain protein 2, NPAS2) proteins form a heterodimer, bind to E-box enhancer elements located in the regulatory region of target genes, and initiate transcription of the negative regulator period (*PER1*, *PER2*, and *PER3*) and cryptochrome (*CRY1* and *CRY2*) genes at the beginning of the cycle (Figure 1). Later, PER and CRY proteins accumulate, dimerize, and associate with the casein kinase I isoforms delta (CK1δ) and epsilon (CK1ε) in the cytosol before the trimeric complex (PER:CRY:CK1δ/ε) translocates to the nucleus (Figure 1). As core components, the primary roles of CK1δ and CK1ε include regulating the subcellular localization of PER proteins and, via phosphorylation, their turnover by a process involving recognition by E3 ligases, ubiquitination, and proteasome-mediated degradation. The stability and subcellular localization of CRY is regulated by the competing E3 ligases and F-box and leucine-rich proteins 3 and 21 (FBXL3 and FBXL21) which have antagonistic effects. FBXL21 stabilizes CRYs in the cytosol during the day, whereas FBXL3 ubiquitinates CRYs at night, leading to their proteasomal degradation in the nucleus. Once in the nucleus, the PER:CRY:CK1δ/ε complex interacts with CLOCK:BMAL1 to repress *PER* and *CRY* transcription until nuclear PER and CRY degradation occurs, enabling renewed CLOCK:BMAL1-mediated *de novo* transcription and a new circadian cycle (Figure 1). Auxiliary loops provide stability to the clock. Accordingly, the CLOCK:BMAL1 complex activates the expression of the nuclear receptor subfamily 1 group D members 1 and 2 genes (*NR1D1/2*, encoding REV-ERBα/β), both of which rhythmically repress the transcription of *BMAL1* and nuclear factor interleukin 3 (*NFIL3*) (Figure 1). Conversely, binding of the retinoic acid-related orphan receptors RORα and RORβ to ROR-binding elements (ROREs) activates *BMAL1* and *NFIL3* expression (Figure 1). A third transcriptional loop mediated by NFIL3 and

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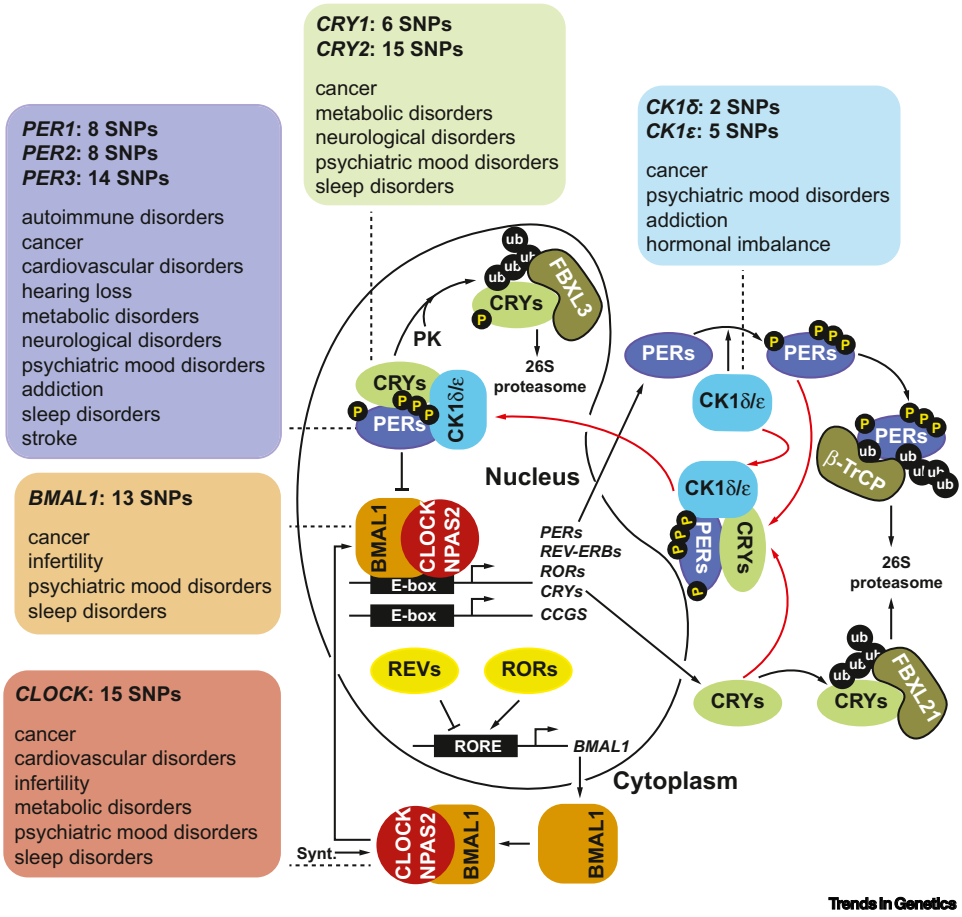

Figure 1. SNPs in genes that sustain the primary circadian feedback loop are associated with various phenotypes in humans. A schematic representation delineating the most salient regulatory processes governing the circadian clock in mammalian cells. The core transcriptional/translational feedback loop involves the transcriptional activators BMAL1 and CLOCK/NPAS2 along with the transcriptional repressors of the CRY and PER families. Casein kinase I isoforms δ and ε play a crucial role in maintaining properly timed expression and degradation of components in the negative arm of the clock, ensuring rhythmicity. The REV-ERB and ROR auxiliary loop provides robustness to the clock. The number of SNPs listed for each gene reflects statistically significant SNPs associated with phenotypes described in the literature and included in this text. In this figure, phenotypes are broadly categorized and summarized for each gene. Red arrows indicate assembly and translocation of the PER:CRY:CK1δ/ε complex from the cytoplasm to the nucleus. Abbreviations: BMAL1, muscle aryl hydrocarbon receptor nuclear translocator-like 1; CCGs, clock-controlled genes; CK1δ/CK1ε, casein kinase I delta/epsilon; CLOCK, circadian locomotor output cycles kaput; CRY1/2, cryptochromes 1 and 2; E-box, enhancer elements; FBXL3 and FBXL21, F-box and leucine-rich proteins 3 and 21; FBXW1A or β-TrCP, F-box/WD repeat-containing protein 1A; NPAS2, neuronal Per-ARNT-Sim domain protein 2; P, phosphorylation; PER1/2/3, period 1–3; PK, protein kinase; REV-ERBs, nuclear receptor subfamily 1 group D members 1 and 2; RORE, ROR-binding element; ROR, retinoic acid-related orphan receptors; Synt., synthesis; ub, ubiquitin; PK, protein kinase; P, phosphorylation.

the D-box binding protein (DBP) is linked to that of the REV-ERB–ROR loop. Thus, all three transcriptional loops are interlocked by sharing crucial *cis*-regulatory elements that modulate clock gene expression in a timely manner [2].

Human diseases and disorders associated with polymorphisms in circadian genes

The rise of high-quality, large-scale genomic sequencing platforms, particularly over the past 10 years, together with advanced analysis pipelines and software tools, has enabled researchers to conduct rapid and low-cost analyses of clinically relevant genomic alterations. A case in point is

the genomic effort to identify SNPs (Figure 2) in core clock genes that are associated with diseases and/or their pathogenesis.

The case for polymorphisms associated with sleep disorders

Initially, SNPs identified in clock components included those linked to circadian sleep disorders that result in irregular sleep rhythms known as familial advanced sleep phase disorder (FASP [3]) and delayed sleep phase disorder (DSPD [4]). The term FASP was coined during a study of three families exhibiting unusually early sleep (between 6 and 9 pm) and wake times (between 2 and 5 am), and whose melatonin and temperature rhythms were shifted forward by ~4 h, but their sleep quality remained comparable to the normal group average [5]. This initial study revealed that FASP is an autosomal dominant trait that shortens the endogenous circadian period to ~23.3 h compared to 24.2 h in unaffected relatives [5]. Most carriers developed the FASP phenotype by 30 years of age, and the earliest onset was observed at age 8 years, indicating high penetrance of the mutation [5].

A quarter of a decade later, evidence from *in vitro* and animal model studies, as well as from patient lineage records, established that rs121908635 causes a $Ser^{662}Gly$ missense mutation in PER2, a position that is a priming phosphorylation site necessary for sequential phosphorylation within the CK1 motif. When mutated, this results in PER2 destabilization. The FASP-like phenotype can also be recapitulated by polymorphisms in other core clock genes. The autosomal dominant mutation rs104894561 results in a $Thr^{44}Ala$ substitution that reduces CK1δ enzymatic activity *in vitro*. In transgenic mice, this mutation results in a shorter circadian period; in humans, it leads to an early onset of FASP that persists until the mid-teen years [6]. A third SNP (rs201220841), $Ala^{260}Thr$ in *CRY2*, prevents FAD binding and stabilization of CRY2, thus favoring CRY2–FBXL3 interaction and ubiquitin-mediated degradation [7]. Lastly, the rs150812083 and rs139315125 SNPs in the coding region of *PER3* result in $Pro^{415}Ala$ and $His^{417}Arg$ substitutions, respectively [8]. In addition to FASP, carriers of either SNP show clinical characteristics of seasonal affective disorder (SAD) and depression-like symptoms, suggesting that circadian rhythms, through *PER3*, cosegregate with the regulatory processes involved in mood [8]. Together, these genetic studies suggest that post-translational modifications and ligand interactions play a crucial role in mediating the stability and turnover of core circadian clock proteins, and thus influence the resulting circadian chronotype.

By contrast, some individuals experience DSPD, a condition characterized by a 2–6 h delay in sleep onset and difficulty in awakening, albeit the quality of sleep is satisfactory and its duration is within the normal range if sleep is uninterrupted [9]. Remarkably, despite being the most diagnosed circadian sleep disorder, with ~3% penetrance in the general population and up to 16% penetrance in adolescents and young adults experiencing insomnia, the etiology of DSPD remained elusive for decades [10]. A hereditable basis for DSPD was only recently uncovered and was mostly attributed to polymorphisms in the *PER3* and *CRY1* genes [4,11] (Tables 1 and 2). Patke *et al.* reported a gain-of-function mutation in *CRY1* which is responsible for a hereditary, autosomal dominant form of DSPD [4]. The rs184039278 mutation is an adenine to cytosine transversion within the 5′ splice site of exon 11, which leads to exon 11 (72 bp) skipping [4] (Table 2). The resulting mutant, CRY1Δ11, has an in-frame deletion of 24 amino acids, preferentially localizes to the nucleus, and shows an increased affinity for CLOCK:BMAL1, leading to increased transcriptional repression resulting in a lengthened circadian period in humans [4]. Interestingly, the frequency of rs184039278 is up to 0.6%, suggesting that this mutation is well represented in the human population experiencing sleep disorders [4]. Although FASP and hereditary DSPD have both been attributed to causative mutations with mostly defined molecular mechanisms, other clock gene variants have been associated with a wide array of phenotypes in human through unknown or unconfirmed mechanisms. However, a note of caution should be added to studies where SNPs have been identified based on a limited number of families

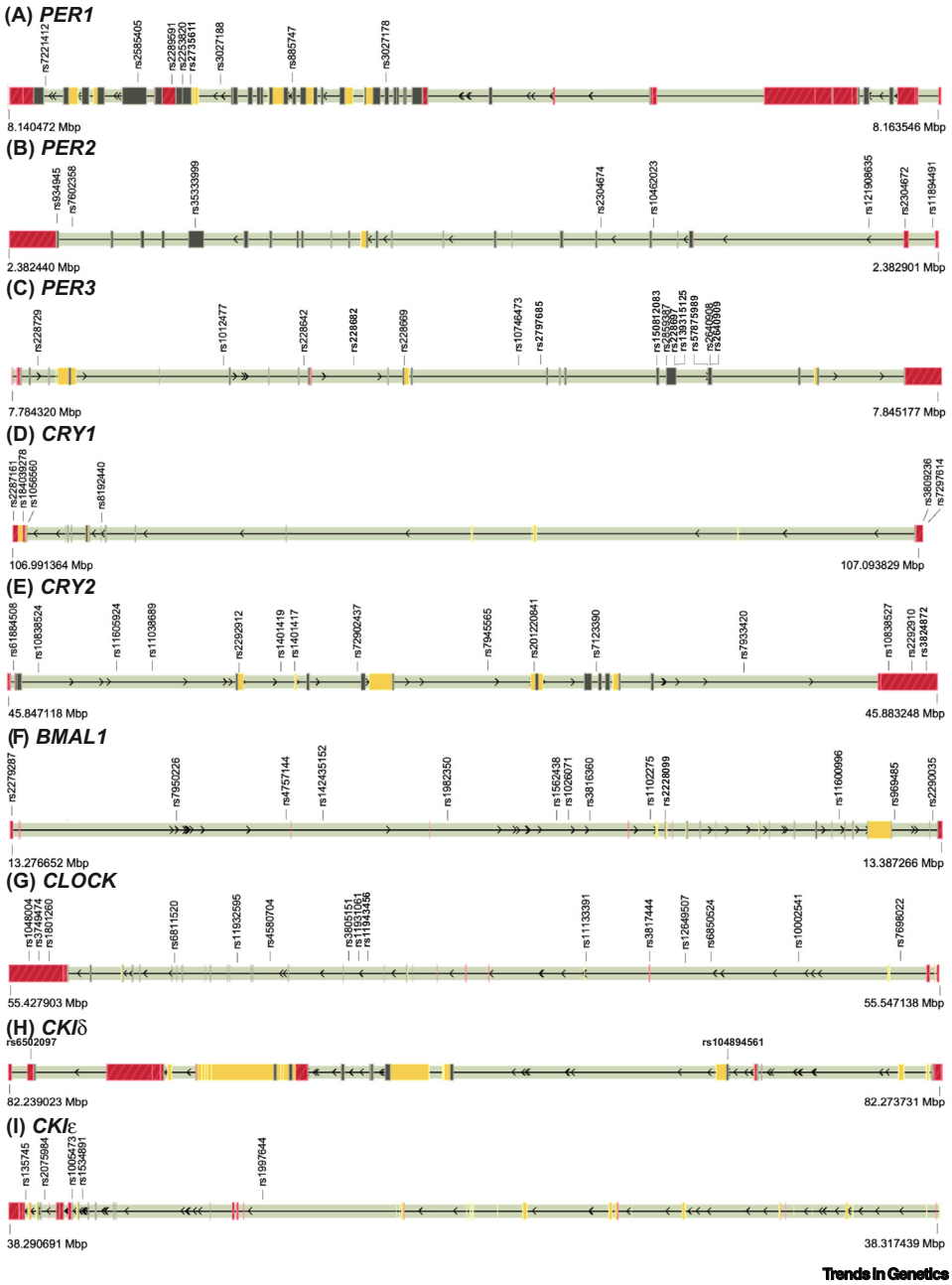

Figure 2. Schematic representation of SNPs in the mammalian core clock genes. Gene assemblies of (A) *PER1* (ENSG00000179094.16, chromosome 17), (B) *PER2* (ENSG00000132326.13, chromosome 2), (C) *PER3* (ENSG00000049246.15, chromosome 1), (D) *CRY1* (ENSG00000008405.12, chromosome 12), (E) *CRY2* (ENSG00000121671.12, chromosome 11), (F) *BMAL1* (ENSG00000133794.20, chromosome 11), (G) *CLOCK* (ENSG00000134852.15, chromosome 4), (H) *CK1δ* (ENSG00000141551.15, chromosome 17), and (I) *CK1ε* (ENSG00000213923.13, chromosome 22), were generated using the Encyclopedia of DNA Elements (ENCODE) Genome Browser tool according to GENCODE V29 genome annotation. SNPs shown are located within the respective human gene assembly and are identified by reference SNP cluster (rs) identification number and relative genomic location based on Genome Reference Consortium Human Build 38 (GRCh38). Colors indicate genomic regions: transcript (light green), protein coding (dark green), non-protein coding (yellow), and untranslated regions (UTRs, red). Non-protein coding regions contain regulatory and structural roles within the genome while UTRs are primarily involved in mRNA translation and stability.

Table 1. Polymorphisms in *PER1*, *PER2*, and *PER3* associated with human phenotypes[a]

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
PER1 (Chr. 17)	rs2253820	38 231/96 756	0.89 [0.82–1] (0.004)	Various studies	T>C	CDS(S)	Breast cancer	[75]
	rs2289591	461/459	1.19 [0.94–1.51] (0.040)	Caucasian	C>A,G,T	INT	Prostate cancer	[71]
		622/628	0.80 [0.66–0.97] (0.027)	Caucasian			Glioma	[85]
	rs2585405	432/837	1.41 [1.01–1.96] (0.03)	Chinese	C>G	CDS(NS)	Hearing loss	[86]
	rs2735611	1590	2.18 [1.20–3.95] (0.0132)	Not defined	G>A	CDS(S)	Extreme DP	[36]
	rs3027178	704/326	1.71 [1.25–2.34] (<0.001)	Chinese	T>G	CDS	Gastric cancer	[41]
		528/388	0.80 [0.65–1] (0.046)	Italian			Alzheimer's disease	[39]
		38 231/96 756	0.68 [0.47–0.98] (0.04)	Various studies			Liposarcoma	[88]
	rs3027188	172/85	0.43 [0.19–0.96] (0.043)	Japanese	G>C	INT	Shift work disorder	[38]
	rs7221412	344/1408	NR (6.0E–07)	European	A>G	INT	Depression	[37]
	rs885747	238/257	0.71 [0.51–0.99] (0.05)	Caucasian	G>A,C,T	INT	Prostate cancer	[71]
PER2 (Chr. 2)	rs10462023	69/457	3.11 [2.81–3.44] (0.033)	Swedish	G>A,T	INT	Depression	[49]
		474/303	1.27 [1.02–1.59] (0.033)	Chinese			Ischemic stroke	[50]
	rs11894491	492/493	NR (0.030)	Not defined	A>G	INT	Systemic lupus	[121]
	rs121908635				T>C	CDS	FASP	[3]
		29/46		Not defined				[5]
	rs2304672	210/210	5.07 (0.031)	Not defined	G>C	5′-UTR	DP	[42]
		13/55	NR (0.049)	Italian			Cognitive function	[46]
		9/36	NR (0.027)	Italian			Cognitive function	[47]
	rs2304674	256/499	2.02 [1.55–2.63] (<0.001)	Korean	A>G	INT	Rheumatoid arthritis	[120]
	rs35333999	200/200	0.49 [0.26–0.91] (0.024)	European	C>T	CDS(NS)	Myocardial infarction	[114]
		26 056/80 065	1.16 [1.10–1.22] (1.5×10^{-9})	European			Evening chronotype	[115]
	rs7602358	8190/9358	1.08 [1.02–1.10] (0.005)	Various studies	G>C,A,T	INT	Prostate and breast cancer	[88]
	rs934945	1538/1605	2.28 [1.22–4.26]	Chinese	C>T	CDS(NS)	Breast cancer	[78]
		488	NR (0.018)	Korean			DP	[45]
		321/364	2.28 [1.22–4.26] (<0.05)	Caucasian			Breast cancer	[87]
		299	NR (0.004)	Korean			DP	[43]

Table 1. (continued)

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
PER3 (Chr. 1)	rs1012477	290/331	1.28 [1.04–1.56] (0.02)	Caucasian	G>C	INT	Prostate cancer	[71]
	rs10746473	138/76	0.36 [0.14–0.96] (0.042)	Chinese	A>G,T	INT	Dizziness and tachycardia	[52]
	rs228642	436/417	1.56 [1.07–2.27] (0.043)	Poland	C>T	INT	Depression, bipolar disorder	[51]
	rs228669	178/489	1.41 [1.04–1.91] (0.03)	Chinese	T>C	CDS(S)	Increased survival to HCC	[80]
	rs228697	925	2.48 [1.34–4.60] (0.012)	Japanese	C>G	CDS(NS)	Diurnal sleep preference	[53]
		380	0.52 [0.28–0.98] (0.042)	Not defined			Anxiety, DP	[54]
		24/253	NR (0.046)	Chinese			Akathisia, agitation	[52]
	rs228729	122/137	2.20 [1.04–4.58] (0.03)	Brazilian	T>C	INT	Obesity	[116]
		93/22	4.91 [1.39–17.37] (0.014)	Chinese			Akathisia, agitation	[52]
		704/326	1.79 [1.29–2.93] (0.003)	Chinese			survival in gastric cancer	[41]
		78/74	0.66 [0.26-1.69] (0.02)	Brazilian			Risk of non-small lung cancer	[117]
	rs2640908	149/98	0.71 [0.53–0.90] (0.027)	Chinese	C>T	CDS(S)	Increased HCC survival	[89]
		83/122	0.46 [0.24–0.88] (0.02)	Japanese			Lower prostate cancer risk	[90]
	rs2797685	125/115	1.9 [1.0–3.61] (0.05)	Caucasian	C>G,T	INT	Grave's disease	[118]
	rs2859387	276/523	NR (0.039)	Caucasian	G>A/C	CDS(S)	Bipolar disorder	[16]
	rs57875989	32/210	3.35 (0.0224)	Not defined	Deletion/insertion	5′ end	DSP and DP	[11]
		99	3.2 (0.041)	Various			Depression	[56]
		302/330	1.95 [1.21–3.15] (0.006)	Indians			Type 2 diabetes	[119]
		242/282	0.52 [0.28–0.98] (0.042)	Various studies			DP, anxiety	[54]
	rs150812083	3/60	NR	European	C>G	CDS(NS)	Seasonal affective disorder in FASP individuals, depression	[8]
	rs139315125	3/60	NR	European	A>G	CDS(NS)		[8]
	rs228682	23/143	0.18 [0.53–2.96] (0.043)	Poland	T>A,C	INT	Alcohol abuse, psychiatric disorders	[51]
	rs2640909	24/8	0.48 [0.22–1.06] (0.029)	Poland	T>C	CDS(NS)		

[a]Abbreviations: CDS(NS), coding sequence non-synonymous; CDS(S), coding sequence synonymous; CI, confidence interval; DP, diurnal preference; DSP, delayed sleep phase; DSPD, delayed sleep phase disorder; INT, intron; NR, not reported; OR, odds ratio.

Table 2. Polymorphisms in *CRY1* and *CRY2* associated with human phenotypes[a]

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
CRY1 (Chr. 12)	rs1056560	1538/1605	0.84 [0.71–0.99] (<0.05)	Chinese	C>A	3′-UTR	Lower risk of breast cancer	[78]
		704/326	0.72 [0.58–0.88] (0.021)	Chinese			Overall survival in gastric cancer	[41]
	rs184039278	39/31	1928 [76–48 904] (<0.0001)	Turkish	T>C,G	INT	Familial DSPD	[4]
		53/48	281 (1.99×10^{-21})	Turkish			ADHD, anxiety	[27]
	rs2287161	105/485	1.75 [1.12–2.71] (0.012)	Chinese	C>G,A,T	5′-UTR	Depression	[28]
		377	NR (0.003)	Iranian			Obesity	[113]
	rs3809236	215/365	1.24 [1.02–1.51] (0.03)	Chinese	G>A,C	5′-UTR	Higher survival in hepatocellular carcinoma	[80]
	rs7297614	24/40	1.75 [1.07– 2.85] (0.02)	Icelandic	C> A,G,T	5′-UTR	Risk of prostate cancer	[79]
	rs8192440	16499	–0.04 [–0.08 to –0.01] (0.02)	Swedish	A>G,T	CDS(S)	Glucose tolerance	[108]
		628/681	0.80 [0.68–0.94] (0.006)	Not defined			Cluster headache	[107]
CRY2 (Chr. 11)	rs10838524	113/906	1.65 [1.21–2.25] (0.0017)	Swedish	A>G	INT	Seasonal depression	[29]
		1715/2500	NR (2.6×10^{-5})	German			risk of elevated fasting glycemia and reduced liver fat content	[111]
		136/3871	1.75 [1.35–2.27] (2×10^{-5})	Finnish			Dysthymia	[31]
	rs10838527	76/1039	1.73 [1.15–2.61] (0.010)	Swedish	A>G	3′-UTR	Seasonal depression	[29]
		4317	1.56 [1.25–1.95] (0.00009)	Finnish				[30]
	rs11038689	44/58	0.71 [0.51–0.99] (0.028)	American	A>G	INT	Breast cancer	[81]
		563/619	0.42 [0.17–1.01] (0.05)	Norwegian				[73]
		455/527	2.34 [1.28–4.27] (0.006)	American			Non-Hodgkin lymphoma	[82]
	rs11605924	9605	0.04 [0.002–0.07] (0.04)	Swedish	A>C	INT	Glucose tolerance	[108]
		1715/2500	NR (<0.0005)	German			Liver fat content, prediabetes	[111]
	rs1401417	187/242	1.7 [1.10–2.70] (0.03)	Chinese	C>G	INT	Prostate cancer	[92]
		563/619	0.31 [0.10–0.94] (0.04)	Norwegian			Breast cancer	[73]
		44/58	0.44 [0.21–0.92] (0.017)	American				[81]

Table 2. (continued)

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
		455/527	2.97 [1.57–5.63] (0.001)	American			Non-Hodgkin lymphoma	[82]
	rs1401419	4306/5910	1.59 [1.27–1.98] (0.00004)	Finnish	T>C	INT	Dysthymia, Depression	[32]
	rs201220841	3/6	NR	Caucasian	G>A	CDS(NS)	FASP	[7]
	rs2292910	4630/5910	0.79 [0.68–0.92] (0.002)	Finnish	A>C	3′-UTR	Depression	[32]
	rs2292912	892/471	1.05 [1.01–1.08] (0.008)	South Asian	C>G,T,A	INT	Diabetes	[112]
	rs3824872	118/1011	1.76 [1.27–2.43] (0.00070)	Swedish	A>C	3′-UTR	Depression	[71]
		1715/2500	NR (0.0205)	German			Liver fat content, prediabetes	[29]
		4630/5910	0.61 [0.46–0.82] (0.001)	Finnish			Depression	[111]
	rs61884508	2552/5910	0.52 [0.33–0.82] (0.004)	Finnish	T>G,C	Intergenic	Seasonal mood variation	[32]
	rs7121611	4318/5910	1.59 [1.28–1.99] (0.00004)	Finnish	T>A	5′-UTR	Dysthythmia	[32]
	rs7123390	4535/5910	0.77 [0.65–0.92] (0.004)	Finnish	G>A	INT	Seasonal depression	[32]
		78/1066	0.60 [0.40–0.91] (0.015)	Finnish			Depression	[29]
		455/527	2.40 [1.39–4.13] (0.002)	American			Non-Hodgkin lymphoma	[82]
		441/479	0.44 [0.22–0.86] (0.028)	American			Breast cancer	[81]
	rs72902437	4746/5910	1.45 [1.08–0.33] (0.01)	Finnish	T>C	INT	Seasonal mood variation	[30]
	rs7933420	1715/2500	NR (2.6×10^{-5})	German	T>A	INT	Liver fat content, prediabetes	[111]
	rs7945565	4619/5910	1.25 [1.09–1.43] (0.001)	Finnish	A>G	INT	Dysthythmia	[32]

[a]Abbreviations: CDS(NS), coding sequence non-synonymous; CDS(S), coding sequence synonymous; CI, confidence interval; INT, intron; NR, not reported; OR, odds ratio; UTR, untranslated region.

selected for a specific sleep trait. Accordingly, the likelihood of rare Mendelian disease variants exhibiting full penetrance when estimated from population-based cohorts tends to be lower, a common occurrence observed with the majority of reported circadian SNPs. Therefore, the use of large repositories such as the UK Biobank to explore the allele frequency of the variants will provide a more accurate estimate of the penetrance in the general population. Importantly, it will also reduce the risk of misdiagnosing or incorrectly treating a condition [127–129]. The purpose of this review is to highlight the diversity of genotypic variants of core circadian clock genes encompassing the primary loop across both healthy and afflicted populations.

Unraveling circadian polymorphisms in psychiatric conditions

Polymorphisms in core clock components in humans have been implicated in various psychiatric disorders, including major depressive disorder (MDD), SAD, bipolar disorder, attention-deficit hyperactivity disorder (ADHD), and anxiety, that have been linked to sleep disturbances

[12–14] (Figure 2 and Tables 1–3). Notably, patients with bipolar disorder show cyclic changes in sleep, activity, eating, and hormone secretion during periods of relapse, emphasizing potential circadian control.

A heritable *BMAL1* SNP with high allelic frequency, rs2279287, is associated with SAD upon exposure to environmental triggers such as disrupted sleep–wake cycles and inappropriate light exposure [15]. Others, such as intronic SNPs rs1026071 and rs1562438, have been linked to sleep disturbances and SAD, whereas rs4757144, rs1481892, rs1982350, rs11600996, and exonic rs2228099 are strongly linked to bipolar disorder, alcohol abuse/dependence (AAD), and even male infertility [13,14,16,17] (Table 3).

Remarkably, the SNP rs1801260, located in the *CLOCK* 3′ untranslated region (3′-UTR), enhances *CLOCK* expression in response to glucocorticoids [18]. Given that glucocorticoids mediate the stress response and vary in endogenous levels between males and females, this may account for the sex-specific effect observed in individuals diagnosed with MDD [19,20]. Accordingly, gene association analyses using data from the National Institute of Mental Health Center for Collaborative Genetic Studies, stratified by sex to explore possible associations between *CLOCK* polymorphisms and MDD, a sexually dimorphic disorder, revealed that rs1801260 is protective only in males [18,20] (Table 3). Variants in *CLOCK* were also associated with sleep duration, sleep quality (as determined by the Pittsburgh sleep quality index, PSQI), and age-related sleep disturbances linked to mood disorders, ADHD symptoms, and neurodegenerative diseases [21–26] (Table 3).

The *CRY1* variants *Δ11* and Δ6, which impact on the affinity of CRY1 for BMAL1:CLOCK, have been associated not only with DSPD but also with ADHD, MDD, and anxiety [27]. In addition, rs2287161 was linked to depression [28] (Figure 2 and Table 2). Population-based and longitudinal studies found a significant association between *CRY2* rs10838524, rs10838527, rs3824872, rs61884508, and rs7123390 polymorphisms and an increased risk of mood and behavior variations, and rs10838524 was linked to dysthymia, poor seasonal outcomes, and MDD [29–32] (Table 2). At the molecular level, the rs61884508 variant of CRY2, that is located in a regulatory region, is predicted to form triplexes, while rs10838527 is predicted to modulate the binding of nuclear receptor subfamily 3 group C member 1 (NR3C1), a glucocorticoid receptor that is associated with affective disorders [30,32–35].

The silent SNP rs2735611 in *PER1* is associated with extreme diurnal preference, possibly owing to linkage disequilibrium with an unidentified second polymorphism within the gene [36]. In a candidate gene association study, *PER1* rs7221412 was found to correlate with delayed human behavioral rhythms, as indicated by actigraphic records [37]. Interestingly, it did not significantly alter internal markers, suggesting a change in the entrained phase rather than in the intrinsic period [37]. In a study of nightshift workers, *PER1* rs3027188 was identified as a risk factor for shift work disorder insomnia [38]. Interestingly, rs3027188 is located in the CK1ε/δ-binding domain of PER1, suggesting an impact on binding and subsequent PER1 phosphorylation [38]. Recently, rs3027178 was associated with susceptibility to Alzheimer's disease (AD) and longevity in a two-phase study, including validation in patients diagnosed with AD [39]. *In silico* analysis indicates that rs3027178 lies within an exonic splicer enhancer region and may influence *PER1* mRNA splicing patterns, potentially altering protein function [40,41].

Multiple studies link *PER2* variants to diurnal preferences and activity patterns in humans [42–45]. Specifically, rs2304672, located 12 bp from the translation start codon, is strongly associated with extreme morning preference and is implicated in lower cognitive function affecting memory,

Table 3. Polymorphisms in *BMAL1*, *CLOCK*, *CK1δ/ε*, associated with human phenotypes[a]

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
BMAL1 (Chr. 11)	rs1026071	231/1151	1.55 [1.00–2.51] (0.048)	Japanese	A>G	INT	Insomnia, sleep onset	[13]
	rs11022775	48/48	1.54 [1.22–1.97] (0.002)	European	C>A,T	INT	Type 2 diabetes, hypertension	[94]
	rs11600996	436/417	1.56 [1.07–2.27] (0.038)	Poland	T>A,C	INT	Bipolar disorder	[51]
	rs142435152	14 760/12 724	NR (0.0002)	Various studies	G>A	INT	Prostate cancer risk	[70]
	rs1562438	234/388	NR (0.018)	American	G>C	INT	Bipolar Disorder	[16]
	rs1562438	231/1151	1.60 [1.06–2.41] (0.026)	Japanese	C>T	INT	Insomnia, sleep onset	[13]
	rs1982350	234/388	NR (0.005)	American	A>G	INT	Bipolar disorder	[16]
	rs2228099	639	0.62 [0.41–0.95]	American	C>G	CDS (S)	Insomnia, early awakening	[14]
	rs2279287	30/30	NR (0.019)	Indian	T>A,C,G	5′ UTR	Seasonal affective disorder	[15]
	rs2290035	563/619	1.91 [1.08–3.37] (0.03)	Norwegian	T>A,C	INT	Breast cancer risk	[73]
		409/417	1.92 [1.21–3.02] (0.006)	Chinese			Lung cancer risk	[74]
	rs3816360	409/417	2.16 [1.41–3.31] (0.004)	Chinese	T>A,C	INT	Lung cancer risk	[74]
	rs4757144	234/388	NR (0.00086)	American	G>A	INT	Bipolar disorder	[16]
	rs7950226	48/48	NR (0.002)	European	G>A	INT	Type 2 diabetes	[94]
		1308/1266	1.22 [1.02–1.46]	Caucasian			Prostate cancer risk	[71] [72]
	rs969485	563/619	1.64 [1.03–2.61] (0.04)	Norwegian	G>A,C	INT	Breast cancer risk	[73]
CLOCK (Chr. 4)	rs10002541	260/260	0.45 [0.23–0.86] (0.016)	Chinese	T>C	INT	Obesity	[100]
		2221	NR (1.58×10^{-5})	Korean			Poor sleep	[21]
	rs1048004	51/265	1.34 [1.02–1.76]	Various	C>A	3′ UTR	Breast cancer	[81]
	rs11133391	655/658	2.41 [1.31–4.42] (0.005)	Not defined	T>C	INT	Glioma	[85]
	rs11931061	75/146	1.56 [1.05–2.33] (0.029)	Brazilian	G>A,T	INT	Inattention	[25]
	rs11932595	517/444	1.9 [1.4–2.7] ($6 \times 10–^{5}$)	European	A>G,T	INT	Male infertility	[17]
		744/635	1.37 [1.03–1.84] (0.0319)	European			Bipolar disorder	[24]
		77000	NR (0.0015)	Caucasian			Longer sleep	[114]
	rs12649507	444	0.68 [0.24–1.35] (<0.05)	Chinese	G>A,T	INT	Depression	[22]
		77 000	NR (0.0051)	Caucasian			Sleep duration	[23]

(continued on next page)

Table 3. (continued)

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
	rs1801260	143	NR (<0.001)	Caucasian	T>C	3′-UTR	ADHD	[26]
		365	NR (<0.05)	Japanese	A>G		Dyslipidemia	[103]
		2485	1.5 [1.1–2.1] (0.036)	Japanese			Type 2 diabetes	[104]
		60/61	0.88 [0.09–1.66] (0.029)	Not defined			Childhood obesity	[102]
		592/776	0.66 (0.036)	Various studies			Depression	[18]
		35/394	NR (<0.05)	Japanese			Low sperm count	[124]
	rs3749474	179	0.04 [0.01–0.07] (0.008)	European	C>T	3′-UTR	Food consumption	[105]
		537	NR	Not defined			Obesity	[98]
		1100	NR (0.021)	European			Higher fat intake	[95] [99]
		375/230	2.25 [1.39–3.66] (0.0006)	European			Obesity	[101]
		2221	NR (0.001)	Korean			Abnormal sleep duration	[21]
		35/394	NR (0.001)	Japanese			Male infertility	[124]
		38231/ 96756	0.86 [0.76–1] (0.02)	Various studies			Decreased cancer risk	[75]
		42 068/47 646	NR	Various studies			Breast cancer	[70]
	rs3805151	1538/1605	1.35 [1.12–1.63]	Chinese	T>A,C	INT	Increased breast cancer risk	[78]
		2221	NR	Korean			Abnormal sleep duration	[21]
	rs3817444	75/419	1.60 [1.06–2.42] (0.026)	Brazilian	A>C,G	INT	Inattention	[25]
		478/194	2.60 [1.31–5.15] (0.005)	Chinese			Male infertility	[125]
		193/216	NR (<0.05)	Japanese			Male infertility	[124]
	rs4580704	3671/7098	0.69 [0.54–0.87] (0.002)	European	G>C,A	INT	Reduced type 2 diabetes	[96]
		1100	1.31 [1.00– 1.70]	European			Decreased hyperglycemia	[95]
		897	NR (<0.001)	European			Decreased cardiovascular disease	[97]
		2221	NR (2.02×10^{-5})	Korean			Sleep duration	[21]
	rs6811520	517/444	1.7 [1.2–2.2] (0.002)	European	T>C	INT	Infertility	[17]
	rs6850524	517/444	1.4 [1.1–1.9] (0.01)	European	C>A,G,T	INT	Infertility	[17]
		2221	NR (1.59×10^{-5})	Korean			Abnormal sleep duration	[21]

Table 3. (continued)

Gene symbol (chromosome)	SNP	Sample size (cases/controls)	OR [95% CI] (*P* value if given)	Population	Risk factor (genotype)	Type	Associated phenotype	Refs
	rs7698022	44/58	2.87 [1.25–6.59]	American	G>A,C,T	INT	Breast cancer	[77]
	rs11943456	38 231/96 756	1.11 [1–1.2] (0.05)	Various studies	T>C	INT	Breast cancer (shiftwork)	[75]
CK1δ (Chr. 17)	rs104894561	5/9	NR	Not defined	T>C	CDS (NS)	FASP	[6]
	rs6502097	1004/1712	1.19 (0.03)	Japanese	C>A,G	INT	Bipolar disorder	[60]
CK1ε (Chr. 22)	rs12315175	1308/1266	3.09 [1.32–7.21]	Caucasian	A>C	INT	Prostate cancer	[71]
	rs135745	101	NR (0.001)	Multiethnic	G>C	3′ UTR	Amphetamine sensitivity	[59]
		741/462	1.41 [1.03–1.92]	Chinese			Oral cancer	[91]
	rs1534891	412/184	0.6 [0.4–0.8] (0.002)	Caucasian	T>A,C	INT	Less risk of heroin addiction	[58]
		416	NR (1.72×10^{-6})	Not defined			Bipolar disorder	[57]
		1306/1266	2.65 [1.16–5.95]	Caucasian			Prostate cancer	[71]
	rs1997644	527/477	NR (0.024)	Not defined	G>A	INT	Bipolar disorder	[61]
		NR	NR	NR			Prostate cancer	[71]
	rs2075984	1004/1712	0.85 (0.0091)	Japanese	C>A,G,T	INT	Schizophrenia	[60]
		215/773	NR (0.006)	Korean			Bipolar disorder	[62]
	rs1005473	187/242	2.7 [1.2–5.9] (0.04)	Chinese	A>C	INT	Prostate cancer	[92]

[a]Abbreviations: CDS(NS), coding sequence non-synonymous; CDS(S), coding sequence synonymous; CI, confidence interval; INT, intron; UTR, untranslated region, NR, not reported.

language comprehension, depression, and reward circuitry activity [42,46–48]. A population-based study also concluded that *PER2* rs10462023 is a risk factor for depression, schizophrenia, and ischemic stroke [49,50] (Figure 2 and Table 1).

A case–control study assessing circadian gene polymorphisms in bipolar disorder with comorbid alcohol abuse/dependence found that *PER3* rs228642 increased the risk of bipolar disorder, whereas rs2640909 and rs228682 were significantly associated with alcohol abuse/dependence and a family history of psychiatric disorders [51]. Another study involving MDD patients unveiled significant associations between *PER3* SNPs and diverse adverse responses to selective serotonin reuptake inhibitor (SSRI) treatment [52]. Specific *PER3* variants (rs228697, rs228729, rs10746473) were correlated with increased sleep duration, diurnal sleep preference, excitement/agitation, akathisia (psychomotor restlessness), weight loss, dizziness, and tachycardia [52–54]. These findings suggest a potential role for *PER3* in the etiology of various psychiatric disorders, possibly via disrupted sleep–wake cycles, and some SNPs are predictors of adverse effects to SSRIs. Finally, a study in young adults revealed that four of four homozygotes for the *PER3* rs57875989, a variable number tandem repeat (VNTR) of an 18 amino acid motif repeated either four or five times, were significantly more prone to depression or bipolar disorder [55,56].

In a family-based study, *CK1ε* rs1534891 was significantly associated with bipolar disorder and correlated with an increased risk of drug addiction [57–59]. Another polymorphism, rs1997644,

showed a nominal association with bipolar disorder in an analysis of 'tag' SNPs, and a larger case–control study identified an association between rs2075984 and schizophrenia [60,61]. A recent study reinforced this, finding a significant association between rs2075984 and bipolar disorder at both the allelic and genotypic levels [62]. The focus on *CK1* polymorphisms, particularly in psychiatric disorders, stems from the role of CK1 in regulating the dopamine- and cAMP-regulated neuronal phosphoprotein, 32 kDa (DARPP32), a key integrator of neurotransmission [63,64]. DARPP32, a regulatory node for multiple signals in the brain, inhibits opposing enzymes such as phosphatase 1 (PP-1) and protein kinase A (PKA) [65]. When DARPP32 becomes abundant in dopaminergic neurons and is phosphorylated by protein kinases A or G at Ser^{34}, it transforms into a high-affinity inhibitor of PP-1 [66,67]. Interestingly, phosphorylation of DARPP32 at Ser^{34} depends on priming at Ser^{102} and Ser^{137} by CK2 and CK1, respectively. However, when DARPP32 is phosphorylated at Thr^{75} by cyclin-dependent kinase 5, it becomes a PKA inhibitor [65]. As a result, PP-1 suppression triggers a PKA signaling cascade that amplifies dopamine receptor 1 signaling [68,69]. Collectively, polymorphisms in CK1δ/ε that alter this interaction are being explored as possible risk factors for psychiatric conditions involving disordered dopaminergic signaling and disrupted clock signals.

Genetic variations in core clock genes and cancer susceptibility

In a large association study (polymorphism and pathway analysis), Mocellin *et al.* investigated whether germline genetic variations in circadian pathways are associated with the risk of developing breast, lung, or prostate carcinomas [70]. Combined, these cancers account for up to 52% of new cases in the USA as of 2022 (American Cancer Society). SNPs in 15 of 17 circadian genes (no SNPs for *TIMELESS* and *CK1δ*) were associated with various cancer subgroups, including estrogen receptor-negative breast cancer, aggressive prostate cancer, lung adenocarcinoma, and squamous lung carcinoma [70]. Some SNPs in *BMAL1*, such as intronic rs142435152 and rs7950226, have a highly statistically significant association with prostate cancer, whereas other SNPs in *BMAL1*, as well as in *CLOCK*, *RORA*, and *RORB*, were found to be shared across various malignancies [70–72]. Similarly, *BMAL1* rs2290035 and rs969485 had significant associations with breast cancer when combined with a work history of 5 years of four night-shifts per week [73]. Furthermore, rs2290035 and rs3816360 were linked to an elevated risk of lung cancer [74] (Table 3).

A meta-analysis involving 96 756 subjects investigated the relationship between genetic variation in clock genes and the risk of developing breast cancer [75]. This work stratified *CLOCK* polymorphisms based on factors such as shiftwork exposure, menopausal status, and hormone receptor status [75] (Table 3). Two *CLOCK* variants, rs11943456 and rs3749474, were significantly associated with increased and decreased breast cancer risk, respectively [75]. Interestingly, the former SNP is located in the first intron of transmembrane protein 165 (*TMEM165*), a gene whose sequence partially overlaps with *CLOCK* [75]. Although TMEM165 is primarily recognized for its role in Golgi glycosylation and its involvement in congenital glycosylation disorders, recent research has indicated a role in breast cancer growth and invasion [76]. Genetic and epigenetic association studies, alongside transcriptional profiling and pathway-based network analyses, led to the identification of additional *CLOCK* SNPs in *cis*-regulatory regions that were linked to increased susceptibility to breast cancer [77,78] (Table 3).

CRY1 rs1056560 is associated with a reduced risk of breast cancer in pre-menopausal women and enhanced response to adjuvant chemotherapy in gastric cancer patients, indicating an overall protective effect against cancer [41,78] (Table 2). In this case, the protective effect of rs1056560, that is located near to predicted microRNA binding sites (has-miR-300 and has-miR-381), was associated with a higher *CRY1* mRNA level [41]. By contrast, the 5′-UTR *CRY1* SNP rs7297614 was linked to increased risk of prostate cancer in the Icelandic population

[79]. In another study assessing clinical outcomes of hepatocellular carcinoma (HCC) following radical surgical resection, the *CRY1* variant rs3809236 was linked to improved survival and decreased recurrence [80] (Table 2). Bioinformatic analyses of rs3809236 suggest that it is located within a transcription factor binding region that could potentially influence *CRY1* expression [80]. These collective findings suggest that SNPs in the *CRY1* regulatory region, which positively modulate its expression, provide a high level of protection against cancer risk.

Zienolddiny *et al.* and Hoffman *et al.* established a protective effect of *CRY2* rs11038689 and rs1401417 polymorphisms against the development of estrogen and progesterone receptor-negative breast cancer in women working night shifts [73,81]. However, rs1401417, rs11038689, and rs7123390 were significantly associated with an increased risk of non-Hodgkin lymphoma by altering the expression of CRY2-controlled genes related to the immune and hematologic systems, thus potentially promoting cancer development [82]. Similarly, research on human bone osteosarcoma revealed that *CRY2* knockdown decreased *TP53* and increased *c-MYC* and *CCND1* expression, leading to enhanced cell migration and proliferation [83]. *CRY2* missense mutations associated with cancer risk in The Cancer Genome Atlas (TCGA) [84], including Asp^{325}His and Ser^{510}Leu, promoted proliferation and *c-MYC* expression while downregulating p53 target genes [84]. The Asp^{325}His mutation reduced CLOCK:BMAL1 transcriptional activity, resulting in loss of rhythmicity, whereas Ser^{510}Leu exhibited a lengthened period compared to wild-type *CRY2* [84]. These findings support the emerging idea that CRY2 may contribute to tumor suppression through its role in regulating c-MYC turnover and interaction with CLOCK:BMAL1.

Conversely, a candidate-gene association study identified the *PER1* SNPs rs2289591 as being significantly associated with an elevated risk of glioma and rs885747 with the risk of prostate cancer [71,85]. Interestingly, a nested case–control study with 2056 noise-exposed factory workers showed that rs2585405 was associated with susceptibility to noise-induced hearing loss [86] (Table 1). Two *PER2* variants, rs7602358 and rs934945, seem to have conflicting roles in different types of cancer. rs7602358 is associated with an increased risk of prostate cancer, whereas rs934945 is linked to an elevated risk of breast cancer, but both variants exhibit a protective effect against liposarcoma [71,78,87,88]. The rs7602358 variant is located upstream of *PER2* in its regulatory region, whereas rs934945 is located within the CRY binding domain [87]. However, further research will be necessary to determine whether these variants significantly alter *PER2* expression or the PER2 interaction with CRY1. Different haplotypes among *PER3* SNPs are paradoxically associated with survival in cancer patients [41]. For instance, rs228729 is a potential biomarker for predicting 5 year overall survival in gastric cancer patients, and rs2640908 is significantly associated with overall survival in unresectable HCC patients and low prostate cancer risk [89,90]. The rs2640908 location in the exonic splicer enhancer region suggests a potential impact on mRNA sequence, protein structure, and overall activity [40,80,89].

CK1ε polymorphisms have also been significantly associated with oral cancer (rs135745, [91]), an increased risk of prostate cancer (rs1534891, rs1997644), and an elevated testosterone to dihydrotestosterone ratio in serum (rs1005473, Table 3) [71,92]. Although replication is lacking, these studies suggest that CK1ε may regulate circulating sex hormone levels, a known risk factor for prostate cancer [71]. Consequently, polymorphisms may predispose individuals to cancer in hormone-dependent organs such as the prostate and collectively contribute to an increased or decreased risk when interacting with other endogenous physiological and environmental risk factors.

Other diseases and disorders associated with circadian polymorphisms

Circadian genes regulate key physiological processes such as gluconeogenesis, lipogenesis, and adipocyte differentiation. Consequently, SNPs in some of these genes have been linked to the

risk of cardiovascular disease and metabolic disorders including diabetes, dyslipidemia, and obesity (reviewed in [93]).

Two functional haplotypes in the *BMAL1* promoter, rs11022775 and rs7950226, were found to alter its expression and thus the transcriptional regulation of congenic regions identified in the etiology of human hypertension and type 2 diabetes [94] (Table 3). The *CLOCK* SNP rs4580704 was associated with a significantly reduced risk of type 2 diabetes, lower body weight, decreased likelihood of hyperglycemia, and reduced inflammation and dyslipidemia [95–97] (Table 3). Conversely, multiple case–control studies established that the *CLOCK* SNPs rs10002541, rs1801260, and rs3749474 are associated with an increased risk of obesity and dyslipidemia and are predicted to influence *CLOCK* expression [95,98–105].

Variants affecting glucose metabolism and energy homeostasis were uncovered in *CRY1*, *CRY2*, and the melatonin receptor 1B (*MTNR1B)* through a large GWAS by the Glucose and Insulin-Related traits Consortium [106]. Season-dependent associations were observed between *CRY1* (rs8192440, also linked to diurnal rhythm of cluster headache episodes [107]) and *CRY2* (rs11605924) variants and fasting/post-challenge glucose concentrations, which are standard measures of glucose tolerance and insulin sensitivity [108] (Table 2). Furthermore, *CRY1* and *CRY2* SNPs were implicated in the regulation of liver triglycerides, emphasizing their involvement in metabolic processes and susceptibility to conditions such as type 2 diabetes and obesity [109–113] (Table 2). One exonic *PER2* SNP, rs35333999, was associated with both an evening chronotype and myocardial infarction, and led to increased body temperature and melatonin levels, indicating an overall shift in circadian period [114,115]. Among *PER3* SNPs, different haplotypes – rs707467, rs228697, and rs2797685 – were associated with diabetes, extreme obesity, and immune-related diseases, respectively [71,116–118], and the five-repeat allele of *PER3* rs57875989 VNTR showed a higher association with diabetes [119] (Table 1).

Of note, polymorphisms in *PER2* have been associated with autoimmune disorders such as rheumatoid arthritis (RA) and lupus [120,121] (Table 1). RA is a condition known to exhibit circadian patterns of symptoms, where joint pain and stiffness often peak in the early morning [122]. A case–control study identified that *PER2* rs2304674 is associated with the pathogenesis of RA through a bidirectional relationship between inflammation and the expression of circadian genes [120,123]. In a different case–control study, *PER2* rs11894491 was found to be significantly associated with an increased risk of systemic lupus erythematosus [121].

Lastly, *CLOCK* SNPs have been associated with male infertility, initially observed in animal models and later confirmed in humans [124,125] (Table 3). A case–control study encompassing men with idiopathic infertility found that *CLOCK* SNPs are linked to poor sperm quality and mobility [124,125]. Intriguingly, these same SNPs were also correlated with elevated levels of serum testosterone and follicle-stimulating hormone (FSH), implying a potential hormonal basis for their impact on fertility.

Concluding remarks

The polymorphisms and genes discussed in this review were selected based on their clinical relevance and supporting statistical significance. It is important to note that this compilation should not be considered to be exhaustive. Although hundreds to thousands of SNPs in many of these genes are cataloged in the National Institute for Biotechnology (NCBI) SNP Database, their impact on human health remains largely unexamined. The emerging view arising from the association studies highlighted in the present report is that the location of polymorphisms is

Outstanding questions

What are the detailed molecular mechanisms by which specific SNPs in circadian genes influence the development or progression of a disease condition?

How do circadian gene SNPs exert tissue-specific effects, and what are the implications for diseases that affect different organ systems?

How do gene–environment interactions, including lifestyle factors and external cues, modulate the impact of circadian gene SNPs on disease susceptibility?

What strategies need to be developed to study causality between specific circadian gene SNPs and diseases, and to distinguish causal SNPs from those that are merely correlated?

Can insights from circadian gene SNP research be translated into novel therapeutic strategies for preventing or treating diseases?

How do genetic variations in circadian genes contribute to disease susceptibility in diverse populations?

Can longitudinal studies be conducted to track the impact of circadian gene SNPs on disease development over time?

How might the integration of other omic data contribute to a comprehensive understanding of the signaling pathways affected by circadian gene SNPs?

Is there a relationship between epigenetic modifications and circadian gene SNPs in disease etiology?

one of the most important determinants of functional and phenotypic effects. A major challenge arises in establishing the functional significance of the identified SNP in gene regulation or protein function, and in experimentally establishing a functional link between a SNP and a disease, ideally using different animal models (see Outstanding questions). SNPs may act as both *cis*- and *trans*-acting elements that regulate gene expression by modulating promoter occupancy, transcription factor activation, mRNA secondary structure and stability, and post-transcriptional modification (reviewed in [126]). Although many of the indicated association studies identified relevant risk-associated SNPs, few have confirmed these correlations in animal models or provided in-depth molecular mechanism analysis. Lastly, it should be acknowledged that intronic GWAS loci may not necessarily affect the closest gene; further variant-to-gene mapping is often necessary to identify effector genes [130,131].

The presence of a given SNP alone is typically insufficient to produce the associated phenotype, as demonstrated by the conflicting results observed for some SNPs across different types of cancers. In the case of complex conditions such as cancer, the presence of SNPs is one of many factors that influence cancer etiology. As demonstrated by the synergistic effect between *PER3* variants, smoking, and the risk of prostate cancer, external environmental factors likely play an important role in determining whether a particular genotype influences a cancerous phenotype. Circadian disruption resulting from chronic nightshift work is one well-studied risk factor for cancer and has also been shown to have synergistic interactions with mutations in circadian genes. Therefore, polymorphisms in circadian genes should be viewed as potential indicators of predisposition to a particular condition rather than a diagnostic cause. Future work will be necessary to determine whether the plethora of variants identified from association studies are truly indicative of their respective associated conditions or the result of other factors that were not sufficiently controlled within the study design.

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Declaration of interests

The authors have no interests to declare.

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