Genetic Factors Affecting Seasonality, Mood, and the Circadian Clock

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In healthy humans, seasonality has been documented in psychological variables, chronotype, sleep, feeding, metabolic and autonomic function, thermoregulation, neurotransmission, and hormonal response to stimulation, thus representing a relevant factor to account for, especially when considering the individual susceptibility to disease. Mood is largely recognized as one of the central aspects of human behavior influenced by seasonal variations. This historical notion, already mentioned in ancient medical reports, has been recently confirmed by fMRI findings, which showed that seasonality in human cognitive brain functions may influence affective control with annual variations. Thus, seasonality plays a major role in mood disorders, affecting psychopathology, and representing the behavioral correlate of a heightened sensitivity to factors influencing circannual rhythms in patients. Although the genetic basis of seasonality and seasonal affective disorder (SAD) has not been established so far, there is growing evidence that factors affecting the biological clock, such as gene polymorphisms of the core clock machinery and seasonal changes of the light-dark cycle, exert a marked influence on the behavior of patients affected by mood disorders. Here we review recent findings about the effects of individual gene variants on seasonality, mood, and psychopathological characteristics.

Keywords: seasonality, mood disorders, clock genes, circadian rhythm, seasonal affective disorder

INTRODUCTION

Seasonality is a central aspect of environmental variability, which has strongly influenced life on Earth by driving the development of biodiversity among living organisms and the evolution of extreme physiological adaptations and behaviors, such as migration and hibernation. In most species, periodic variations of environmental conditions, particularly those related to the light-dark cycle and depending on latitude, season, and time of day, require that internal timing mechanisms induce the adaption of behavioral or physiological functions to such changes (1).

Biological rhythms with an approximate 24-h period, close to the daily light-dark cycle, are known as circadian rhythms and defined by three fundamental properties: persistence of an ∼24-h rhythm, entrainability, and temperature compensation (2). The observation that these endogenous processes are also present among organisms such as cyanobacteria, which represent one of the earliest and most primitive species, suggests that circadian rhythms implicated a clear evolutionary advantage (1).
CLOCK GENES AND MOOD REGULATION

At the cellular level, circadian rhythms are generated by a core molecular clock consisting of multiple transcriptional/translational feedback loops (3). The transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle Arnt-like (ARNTL), or neuronal pas domain protein 2 (NPAS2) proteins, dimerize and initiate the expression of the clock proteins PERIOD (PER1, PER2, PER3), and CRYPTOCHROME (CRY1, CRY2). With rising accumulation, PER1-3 and CRY1/2 inhibit CLOCK:ARNTL (or CLOCK:NPAS2) activity and therefore block their own expression (3). An additional feedback loop is generated by CLOCK:ARNTL (or CLOCK:NPAS2) mediated transcription of REV-ERB and RORs, which in turn also regulate ARNTL transcription (see Figure 1).

As recently reviewed by Albrecht, there is already solid scientific evidence showing that the above-mentioned proteins “not only self-promote their own temporally fluctuating transcription, but also regulate the transcription of a large number of clock-controlled genes (CCGs) and/or modulate key molecular pathways via protein–protein interactions, such as the monoaminergic system, the HPA axis or neurogenic pathways” [(4), p. 1]. Several cellular processes in the brain are under the control of the circadian clock, including “differentiation, growth, motility and apoptosis, immune functions and neuroinflammation, neurogenesis, and neuroplasticity” [(5), p. 236]. A desynchronization of the circadian gene network and disruption of its downstream mechanisms has therefore widespread potential implications for a vast array of physiological processes.

Hamp et al. demonstrated that the functional triad of PER2, ARNTL, and NPAS2 and their encoded proteins, directly regulate the activation of the monoamine oxidase A gene (Maoa). In fact, the transcription and activity of the MAOA enzyme in the mesolimbic neurons is decreased in mice carrying a genetic deletion of the Per2 gene, causing an increase of the dopamine levels and an altered neuronal activity in the striatum, as well as behavioral changes (6, 7).

Dopamine is an important neurotransmitter in the reward system, and its levels in the nucleus accumbens show a circadian rhythmicity (6, 8). Considering that many other brain areas of the reward system, including the ventral tegmental area, prefrontal cortex, and amygdala, are also involved in both mood regulation and clock genes expression, this suggests that the entire reward circuit may be under the influence of the circadian clock, via dopamine metabolism (5).

Cryophoromes (CRY2 and CRY1) are key components of the molecular clock, which drive several functions of the circadian pacemaker (9) and are necessary for the development of intercellular networks in the suprachiasmatic nucleus (10). CRY2 and CRY1 proteins are functionally repressors of the transcription-translation loops, and inhibitors of the cyclic adenosine monophosphate signal pathway (11–14). Due to these important molecular properties at the circadian clock level, it has been suggested that CRY2 and CRY1 may play a major role in the metabolism of glucose and lipids (15, 16) and contribute to mood regulation on a daily basis, as well as to seasonal variations in mood and behavior (17).

Finally, PER3 is one of the most robustly rhythmic genes in humans and animals, playing a significant role in the temporal organization of peripheral tissues and being associated with diurnal preference, mental disorders, non-visual responses to light, as well as brain and cognitive responses to sleep loss/circadian misalignment (18). Some genetic variants are supposed to interfere with the stabilizing effect of PER3 on PERIOD1/2 proteins, which play critical roles in circadian timing. These findings suggest that PER3 may represent an important element of the missing molecular linkage between sleep and mood regulation by adapting these processes to seasonal changes (19).

CLOCK GENES IN MOOD DISORDERS

Several human population genetic studies have identified specific single nucleotide polymorphisms (SNPs) or variable number of tandem repeats (VNTR, see Supplementary Table 1) of different circadian clock genes that are associated with mood disorders (20, 21). These associations remain controversial, since most findings could either not be replicated or hold up to correction for multiple testing (22). From a pathophysiological point of view, recent experimental work, and mathematical models suggest that changes in period length and/or decreased amplitude of the circadian oscillation may depend on the impact of specific polymorphisms on the overall function in terms of structure and stability of a given clock protein (23). By as of yet poorly understood processes, the resulting functional changes of the clock-machinery and misalignment between clock-regulated functions and the environment can influence core psychopathological features of mood disorders, including the timing of onset and recurrence of illness episodes, individual symptomatology, and response to treatments (5).

Depressive Disorder

In depressive disorder (DD) (7), two TIMELESS polymorphisms have been found to be associated with excessive daytime fatigue among women, as well as a two-way interaction of TIMELESS and ARNTL (rs1868049) with early-morning awakening among men (24). Lavebratt et al. demonstrated that RORA, PER2, and NPAS2 are associated with DD and the onset of depression within 3 years independently from financial strain (25). Both an increased or decreased PER3 transcriptional activity may implicate a higher risk for MDD. In particular, Shi and colleagues identified a missense mutation in hPER3 (hPER3-P856A), which slightly lengthens the circadian period and is related to MDD in females, by likely driving changes in clock-controlled genes as opposed to SCN timing. Moreover, the authors describe other sex-dependent associations of common polymorphisms with a CLOCK variant protective of MDD in males and NPAS2 polymorphisms with association of MDD especially in females (26). NPAS2 and CRY1 were also linked with DD in a study by Soria et al. (27), with the latter finding replicated by Hua et al. (28), who, instead, did not find any association of CRY2...
FIGURE 1 | Molecular mechanisms of the circadian clockwork. Following the dimerization of the transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle Arnt-like (ARNTL) or neuronal PAS domain protein 2 (NPAS2) proteins, the expression of the clock proteins period (PER1, PER2, PER3) and cryptochrome (CRY1, CRY2) is initiated. The PER and CRY proteins interact with the serine/threonine kinases casein kinase 1 (CK1δ/ε) and form a complex allowing nuclear translocation. In the nucleus they act as inhibitors of CLOCK:ARNTL (or CLOCK:NPAS2) activity and therefore block their own expression. An additional feedback loop is generated by CLOCK:ARNTL (or CLOCK:NPAS2) mediated transcription of REV-ERB and ROR-related orphan receptor A/B (RORA/B), which in turn also regulate ARNTL transcription. Up to 10% of the human genome is under the influence of the molecular clock (clock-controlled genes, CCG). RORE: ROR response element.

(rs10838524) with major depressive disorder (MDD). However, Kovanen et al. suggested that CRY2 and the protein kinase C delta binding protein (PRKCDBP, or CAVIN3) variants may represent risk factors for MDD (29). Finally, the best association between a SNP and MDD based on genome-wide association studies has been found for NR1D1 (30).

Bipolar Disorder
The observation that patients with bipolar disorder (BD) show alterations in circadian rhythms, and recurrent fluctuations of mood and sleep disturbances (31) has suggested a possible dysfunction of the biological clock in the pathogenesis of BD (32). Moreover, since heritability in BD is estimated to be as high as 85% (33), an increasing interest in identifying genetic risk factors has supported different association studies looking at the link between BD and some core clock genes (7).

Significant SNPs associations with bipolar 1 disorder were found for TIMELESS and ARNTL (34), as well as for NPAS2, RORB 9, and CRY2 (35). Gonzalez et al. performed a family-based association study of circadian genes and BD in a Latino
population, reporting nominal associations between SNPs of CSNK1E, ARNTL, CSNKID, CLOCK, as well as statistically significant associations between CSNK1E and ARNTL haplotypes and BD, with either increased susceptibility or protective effect against the development of the disorder respectively (36). Shi et al. demonstrated the three-way interaction of BHLMHE40, TMEM165 (transmembrane protein 165), and CSNK1E with bipolar disorder (37), while McGrath et al. focusing their analysis on the RORA and RORB genes, found that 4 RORB SNPs were associated with bipolar 1 disorder (38). Etain et al. indicated a significant association of TIMELESS and of RORA with BD (39), while Lee et al. found CLOCK 3111T/C to have significant allelic and genotypic associations with the disease (40). GSK3beta was associated with bipolar type 2 disorder in women (41). General associations of NR1D1 (42) and of VIP (27) with BD were also reported. In genome-wide association studies, the associations of ARNTL, GSK3beta, RORB, and CRY 2 gene variants with BD have gained further support (30, 43).

Genetic polymorphisms influencing clock genes functions have shown major effects on the phenotypic clinical features of disease (44). A SNP in CLOCK gene, which is known to influence diurnal preference in healthy subjects (45), also impacts on bipolar patients, leading to worsening of insomnia, higher evening activity and delayed sleep onset. Carriers of the allelic C variant also showed a higher episode recurrence rate and different neuropsychological performance (46–48), while the G allele of the same polymorphism has been linked with symptoms of appetite disturbances in females (49). A correlation with violent suicide attempts was shown for other SNPs in CLOCK and TIMELESS, while the latter is also associated with the lifetime number of suicide attempts and a positive family history of suicide (50). A VNTR of PER3 gene was shown to influence the general age of onset, as well as a postpartum depressive onset of the disorder (51, 52). PER3 was also linked to an increased preference for the evening hours in daily activity among BD patients (42). Maciukiewicz et al. observed further associations between SNPs of ARNTL variants with sleep, appetite and depressive dimensions in BD (49).

A functional SNP in the promoter region of the GSK3beta gene (nt −171 to +29), which also shows a general association to impulsivity and suicide risk among patients with bipolar disease, was found to influence the age at onset of BD, as well as the response to treatment with antidepressant, lithium salts and chronotherapeutics (53–55). This polymorphism was recently shown to also influence white matter microstructure of bipolar patients under ongoing lithium treatment (56) and gray matter volumes in areas critical for the generation and control of affect implicated in BD pathophysiology (57).

Other polymorphisms influencing treatment response, such as the mood stabilizer effect of lithium salts (variant in the promoter of NR1D1) and a general association with positive treatment response (CRY1) have been described (58). Finally, Sjöholm et al. identified two risk haplotypes and one protective haplotype in the CRY2 gene associated with rapid cycling in BD (59) (see Supplementary Table 1).

**GENETICS OF SEASONALITY AND SEASONAL AFFECTIVE DISORDER**

The interplay between mood variations and seasonal rhythms in humans has received renewed interest since the diagnosis of Seasonal Affective Disorder (SAD) was proposed by Rosenthal in 1984, as “a condition characterized by recurrent depressive episodes that occur annually at the same time each year” ([60], p. 72). The observation that many adults experience a “ subsyndromal SAD”, with milder vegetative symptoms in the fall/winter months (61, 62), suggested that “seasonality may be a dimensional process rather than a discrete syndrome” ([63], p. 315).

**Serotonergic Genes**

Although the genetic basis of seasonality and SAD has not yet been completely identified, several studies suggest that both conditions have an inherited component (64–66). From a pathophysiologival point of view, the typical symptoms of SAD, such as overeating, carbohydrate craving, weight gain, and oversleeping, point to a dysfunction of the serotonergic system (66). Moreover, the serotonin level in the human hypothalamus shows seasonal variations, with a general decrease during the winter season (67). The serotonin hypothesis is also supported by the large therapeutic evidence that selective serotonin reuptake inhibitors (SSRIs) and bright light therapy are effective in winter SAD (68–71), with reversion of this effect by rapid tryptophan depletion (70, 72).

Therefore, the first pioneer genetic studies focused on the molecular components of the serotonergic system (73). Rosenthal et al. showed that the short (s), as opposed to the long (l), allele of the 5-HT transporter linked polymorphism (5-HTTLPR) contributes to the trait of seasonality and is a risk factor for SAD (74). First reports showing an association of this variant with general susceptibility and several features of the clinical course among patients with SAD (75–77) could not be corroborated by a meta-analysis by Johansson et al., but the authors concluded that the polymorphism may have an effect on seasonal behavioral traits (78, 79).

Recent Positron Emission Tomography (PET) studies showed a significantly higher activity of serotonin transporter binding potential in several brain regions, during fall and winter, compared to spring and summer, in healthy volunteers (80, 81). Furthermore, “the first [11C]DASB PET longitudinal study investigating whole-brain seasonal 5-HTT fluctuations in both patients with SAD and in healthy individuals reported that a whole-brain seasonal change in 5-HTT predicted symptom severity in patients with SAD, an effect primarily driven by females with the short 5-HTTLPR genotype (S’ carriers)” ([82], p. 2), (83). These findings were later confirmed by other groups (83, 84).

The serotonin 5-HT2A receptor gene has also been proposed as major candidate gene in association studies of seasonality
and SAD (85, 86). In particular, it has been suggested that “downregulation of 5-HT2A receptors may underlie the therapeutic effects of SSRIs” [(64), p. 656], (87) and the effectiveness of light therapy in the treatment of SAD has also been linked to an alteration of the sensitivity of 5-HT2A receptors (76). Moreover, specific sequence polymorphisms in the coding region of the serotonin 5-HT2A receptor gene have been found to be associated with the clinical features and course of depressive disorder or directly with seasonality and SAD (64, 86, 88–90).

**Circadian Genes**

Apart from an extensive connection between SAD and the serotoninergic system, genes of the core clock family have also been implicated in the disease. After a first report of a SNP in NPAS2 being linked to SAD (91), Partonen et al. found further SNPs of PER2, ARNTL, and NPAS2 to be associated with seasonality and SAD (92, 93).

Kim et al. also reported an association of NPAS2 and ARNTL, especially with the metabolic components of seasonality (body weight and appetite). In addition, they found increased seasonal variations of mood and behavior among individuals carrying a CLOCK polymorphism previously implicated in bipolar disorder (40, 46–48, 94). These recent findings are in contrast with a previous work from the same group, showing that the same SNP of CLOCK is not associated with seasonal fluctuations in a sample of Korean college students (95).

Furthermore, another recent investigation highlighted the impact of two rare genetic variants of the PERIOD3 gene (PER3) on a circadian phenotype and a seasonal mood trait, which may be especially critical under conditions of short photoperiod (e.g., during the winter season) (19).

**Other Genetic Findings**

Environmental light detection in humans is mediated by melanopsin containing intrinsically photosensitive retinal ganglion cells (ipRGCs), which are located in the inner retina (96–98). Some polymorphisms of the melanopsin gene may be linked to a greater sensitivity to light, thus determining functional variations in ipRGC activity. During shortened photoperiods (e.g., during the winter months) this may contribute to inter-individual differences in sleep and alertness (99, 100). A missense variant (P10L) in the melanopsin (OPN4) gene, which has also been found in SAD patients, has been proposed to contribute to changes in melanopsin sensitivity (99). Reduced retinal light sensitivity, especially during the winter months, as a pathophysiological hypothesis of SAD (101–103) recently gained first supporting evidence. A study by Roecklein et al. found a reduced post-illumination pupil response (PIPR) in SAD patients, compared with controls, in winter but not in summer (104).

A study by Delavest et al. investigating the rs2072621 polymorphism of the X-linked GPR50 gene, a member of the G protein-coupled melatonin receptor subfamily, found an association with SAD in females, thus providing the first potential gender-specific molecular link between the hormone melatonin and SAD (105).

Yang et al. studied the relationship between ST8SIA2 and NCAM1, two genes forming the polysialic acid neural cell adhesion molecule (NCAM) complex in the SCN, and circadian preferences, as well as seasonality, in healthy adult Korean subjects. The association of 8 SNPs of ST8SIA2 and 2 SNPs of NCAM1 with seasonality remained significant after correction for multiple testing (106).

Another study by Nam et al. found that the GNB3 (G-protein β3 subunit) C825T polymorphism, which is associated with various medical conditions (107, 108) and psychiatric disorders, including recurrent winter depression or SAD (109, 110), also plays a role in seasonal variations in mood, body weight, energy level, and appetite, particularly in females.

**CONCLUSIONS**

Gene polymorphisms of the core clock machinery and seasonal changes of the light-dark cycle substantially impact on the behavior of patients with mood disorders. The relationship between biological clock and behavior suggests a specific sensibility of these patients to psychobiological factors that can modify the circadian timing system, such as environmental synchronizers (light phase and seasonal photoperiod changes), and conditions directly perturbing the clock (sleep deprivation, or phase advance/delay). These factors can trigger or worsen the severity of mood disorders, but also be successfully exploited to treat manic and depressive episodes (111).

Current models of circadian homeostasis suggest that the hierarchical control exerted by the SCN on circadian rhythms of behavior, physiological functions, and on peripheral clocks (112), interacts with homeostatic mechanisms that also contribute to these phenomena. In rodents, a similar dependence of behavior on clock gene mutations occurs in the absence of other regulators of circadian rhythmicity, such as melatonin, and is abolished when these homeostatic components are restored (113). Therefore, we suggest that the high sensitivity of mood-disordered patients to clock gene variants is underpinned by a deficit in homeostatic mechanisms regulating the circadian timing system. Recent discoveries in humans of yet unknown circulating substances affecting the circadian phenotype and overcoming the timing of the clock gene machinery (114, 115), lead to hypothesize that a systematic investigation of these mechanisms will shed new light on the nature of circadian disruption in mood disorders.

**AUTHOR CONTRIBUTIONS**

Both authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, writing, or revision of the manuscript. In particular: CG conceived, designed and drafted the manuscript. FB drafted and critically reviewed the manuscript. CG and FB approved the final version of the manuscript.
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REFERENCES

1. Hut RA, Beersma DGM. Evolution of time-keeping mechanisms: early emergence and adaptation to photoperiod. Philos Trans R Soc Lond B Biol Sci. (2011) 366:2141–54. doi: 10.1098/rstb.2010.0409
2. Takahashi JS. Circadian Clocks. New York, NY: Kluwer Academic; Plenum Publishers (2001).
3. Albrecht U. Timing to perfection: the biology of central and peripheral circadian clocks. Neuron (2012) 74:246–60. doi: 10.1016/j.neuron.2012.04.006
4. Albrecht U. Molecular mechanisms in mood regulation involving the circadian clock. Front Neurol. (2017) 8:30. doi: 10.3389/fneur.2017.00030
5. Benedetti F, Terman M. Much ado about...a moody clock. Biol Psychiatry (2013) 74:236–7. doi: 10.1016/j.biopsych.2013.05.037
6. Hampp G, Ripperger JA, Houben T, Schmutz I, Blex C, Perreau-Lenz S, et al. Regulation of monoamine oxidase a by circadian-clock components implies clock influence on mood. Curr Biol. (2008) 18:678–83. doi: 10.1016/j.cub.2008.04.012
7. Partonen T. Circadian clock genes and mood disorders. In: López-Muñoz F, Srinivasan V, de Berardis D, Álamo C, Kato TA, editors. Melatonin, Neuroprotective Agents and Antidepressant Therapy. New Delhi: Springer (2016), p. 319–34.
8. Hood S, Cassidy P, Cossette MP, Weigl Y, Verwey M, Robinson B, et al. Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via activation of D2 dopamine receptors. J Neurosci. (2010) 30:14046–58. doi: 10.1523/JNEUROSCI.2128-2010.10.10
9. Lamia KA, Papp SJ, Yu RT, Barish GD, Uhlenhaut NH, Jonker JW, et al. Cryptochromes mediate circadian repression of the glucocorticoid receptor. Nature (2011) 480:532–6. doi: 10.1038/nature10700
10. Ono D, Homna S, Homna K. Cryptochromes are critical for the development of coherent circadian rhythms in the mouse suprachiasmatic nucleus. Nat Commun. (2013) 4:1666. doi: 10.1038/ncomms2670
11. Dardente H, Fortier EE, Martineau V, Cermakian N. Cryptochromes impair phosphorylation of transcriptional activators in a general mechanism for circadian repression. Biochem J. (2007) 402:255–36. doi: 10.1042/BJ20060827
12. Oztürk N, Song SH, Özgün S, Selby CP, Morrison LR, Partch C, et al. Structure and function of animal cryptochromes. Cold Spring Harb Symp Quant Biol. (2007) 72:119–31. doi: 10.1101/sqb.2007.72.015
13. Ye R, Selby CP, Chiou YY, Ozkan-Dagliyan I, Gaddameedhi S, Santer A. Dual modes of CLOCK:BMAL1 inhibition mediated by cryptochrome and period components implies clock influence on mood. Curr Biol. (2011) 21(Suppl. 4):R746–58. doi: 10.1016/j.cub.2011.07.007
14. Etain B, Milhiet V, Bellivier F, Leboyer M. Genetics of circadian rhythms and mood spectrum disorders. Eur Neuropsychopharmacol. (2011) 21(Suppl. 4):S67–82. doi: 10.1016/j.euroneuro.2011.07.007
15. Kelly MA, Rees SD, Hydrie MZ, Shera AS, Bellary S, O’Hare JP, et al. Circadian gene variants and susceptibility to type 2 diabetes: a pilot study. PLoS ONE (2012) 7:e32670. doi: 10.1371/journal.pone.0032670
16. Machicao F, Peter A, Machann J, Königrainer I, Böhm A, Lutz SZ, et al. Glucose-raising polymorphisms in the human clock gene cryptochrome 2 (CRY2) affect hepatic lipid content. PLoS ONE (2016) 11:e0154563. doi: 10.1371/journal.pone.0154563
17. Kovánen L, Donner K, Kaumisto M, Partonen T. CRY1 and CRY2 genetic variants in seasonality: A longitudinal and cross-sectional study. Psychiatry Res. (2016) 242:101–10. doi: 10.1016/j.psychres.2016.05.044
18. Archer SN, Schmidt C, Vendewalle G, Dijk DJ. Phenotyping of PER3 variants reveals widespread effects on circadian preference, sleep regulation, and health. Sleep Med Rev. (2017) 40:109–26. doi: 10.1016/j.smrv.2017.10.008
19. Zhang L, Hirano A, Hsu PK, Jones CR, Sakai N, Okuro M, et al. A PERIOD3 variant causes a circadian phenotype and is associated with a seasonal mood trait. Proc Natl Acad Sci USA. (2016) 113:E1536–44. doi: 10.1073/pnas.1600039113
20. Lavebratt C, Sjöholm LR, Partonen T, Schalling M, Forsell Y. PER2 variation is associated with depression vulnerability. Am J Med Genet B Neuropsychiatr Genet. (2010) 153B:570–81. doi: 10.1002/ajmg.b.30120
21. Zhang L, Hirano A, Hsu PK, Jones CR, Sakai N, Okuro M, et al. A PERIOD3 variant causes a circadian phenotype and is associated with a seasonal mood trait. Proc Natl Acad Sci USA. (2016) 113:E1536–44. doi: 10.1073/pnas.1600039113
22. Lavebratt C, Sjöholm LR, Partonen T, Schalling M, Forsell Y. PER2 variation is associated with depression vulnerability. Am J Med Genet B Neuropsychiatr Genet. (2010) 153B:570–81. doi: 10.1002/ajmg.b.30120
23. Soria V, Martínez-Amorós E, Escaramís G, Valero J, Pérez-Egea R, García C, et al. Differential association of circadian genes with mood disorders: CR1 and NPAS2 are associated with unipolar major depression and CLOK and VIP with bipolar disorder. Neuropsychopharmacology (2010) 35:1279–89. doi: 10.1038/nnnp.2009.230
24. Hua P, Liu W, Chen D, Zhao Y, Chen L, Zhang N, et al. Cry1 and Tef gene polymorphisms are associated with major depressive disorder in the Chinese population. J Affect Disord. (2014) 157:100–3. doi: 10.1016/j.jad.2013.11.019
25. Kovanen L, Donner K, Kaumisto M, Partonen T. CRKDBP (CAYIN3) and CRY2 associate with major depressive disorder. J Affect Disord. (2017) 207:136–40. doi: 10.1016/j.jad.2017.08.034
26. Byrne EM, Heath AC, Madden PA, Pergadia ML, Hickie IB, Montgomery GW, et al. Testing the role of circadian genes in conferring risk for psychiatric disorders. Am J Med Genet B Neuropsychiatr Genet. (2014) 165B:254–60. doi: 10.1002/ajmg.b.32230
27. Riemann D, Voderholzer U, Berger M. Sleep and sleep-wake manipulations in bipolar depression. Neuropsychobiology (2002) 45(Suppl. 1):7–12. doi: 10.1159/000049255
28. Dallapiccola B, Benedetti F. Chronobiology of bipolar disorder: therapeutic implications. Curr Psychiatry Rep. (2015) 17:606. doi: 10.1007/s11920-015-0606-9
29. McQuinn P, Rüdijk F, Andrew M, Shannon P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry (2003) 60:497–502. doi: 10.1001/archpsyc.60.5.497
30. Mansour HA, Wood J, Logue T, Chowdari KV, Dayal M, Kupfer DJ, et al. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. Genes Brain Behav. (2006) 5:150–7. doi: 10.1111/j.1601-183X.2005.00147.x

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2018.00481/full#supplementary-material
42. Kripke DF, Nievergelt CM, Joo E, Shekhtman T, Kelsoe JR. Circadian rhythms in bipolar disorder. *J Affect Disord.* (2015) 168:367–75. doi: 10.1016/j.jad.2015.07.014

43. Le-Niculescu H, Patel SD, Bhat M, Kuczenski R, Faraone SV, Tsuang MT, et al. Association between circadian clock gene and age at onset of bipolar disorder. *Neuropsychobiology* (2009) 53:203–10. doi: 10.1016/S0165-0327(98)00194-3

44. Dallaspezia S, Benedetti F. Melatonin, circadian rhythms, and the clock genes in bipolar disorder. *Chronobiol Int.* (2014) 31:807–14. doi: 10.3109/07420528.2014.96445

45. Katzenberg D, Young T, Finn L, Lin L, King DP, Takahashi JS, et al. CLOCK sodium channel gene polymorphism is associated with age at onset of bipolar disorder. *Frontiers in Endocrinology* (2018) 9:481.

46. Serretti A, Cusin C, Benedetti F, Mandelli L, Pirovano A, Zanardi R, et al. Association between circadian genes, bipolar disorders and chronotypes. *Chronobiol Int.* (2006) 23:531–6. doi: 10.1159/000090070

47. Benedetti F, Serretti A, Pontiggia A, Bernasconi A, Lorenzi C, Colombo C, et al. Lithium and GSK3-beta promoter gene variants influence winter microstructure in bipolar disorder. *Neuropsychopharmacology* (2013) 38:313–27. doi: 10.1038/npp.2012.172

48. Benedetti F, Poletti S, Radaelli D, Locatelli C, Pirovano A, Lorenzi C, et al. Lithium and GSK-3beta promoter gene variants influence corticol gray matter volumes in bipolar disorder. *Psychopharmacology* (2015) 232:1325–36. doi: 10.1007/s00213-015-4004-z

49. Maciukiewicz M, Dmitrzak-Weglarz M, Wilkosz M, Leszczynska-Rodziewicz A, Kapelski P, et al. Association analysis of the GSK-3beta promoter gene with age at onset of bipolar disorder. *Biol Psychiatry* (2009) 65:11V–81. doi: 10.1016/j.biopsych.2008.08.007

50. Pawlak J, Dmitrzak-Weglarz M, Maciukiewicz M, Wilkosz M, Leszczynska-Rodziewicz A, Zaremba D, Skibinska M, et al. Analysis of genetic association and epistasis interactions between circadian clock genes and symptom dimensions of bipolar affective disorder. *Chronobiol Int.* (2014) 31:770–8. doi: 10.3109/07420528.2014.899244

51. Carlson A, Svennerholm L, Winblad B. Seasonal and circadian monoamine variations in human brains examined post mortem. *Acta Psychiatr Scand.* (1989) 80:675–85. doi: 10.1111/aps.1989.61.x280.75

52. Dallapiccia S, Lorenzi C, Pirovano A, Colombo C, Smeraldi E, Benedetti F. Circadian clock gene Per3 variants influence the postpartum onset of bipolar disorder. *Eur Psychiatry* (2011) 26:138–40. doi: 10.1016/j.eurpsy.2010.11.009

53. Dallapiccia S, Lorenzi C, Pontiggia A, Serretti A, Colombo C, et al. A single nucleotide polymorphism in glycogen synthase kinase 3-beta promoter gene influences age at onset of bipolar disorder. *Neuropsychobiology* (2004) 355:37–40. doi: 10.1159/00004.10.021

54. Dallapiccia S, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. *Neuropsychobiology* (2004) 355:123–6. doi: 10.1159/00004.10.050
of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry (2006) 163:803–12. doi: 10.1176/appi.2006.163.5.805
71. Pau CU, Masand PS, Peindl K, Mannelli P, Han C, Marks DM, et al. An open-label, rater-blinded, flexible-dose, 8-week trial of escitalopram in patients with major depressive disorder with atypical features. Prim Care Companion J Clin Psychiatry (2008) 10:205–10. doi: 10.4088/PCC.v10n0305
72. Spillmann MK, Van der Does AJ, Rankin MA, Vuolo RD, Alpert JE, Nierenberg AA, et al. Trypophan depletion in SRR1-recovered depressed outpatients. Psychopharmacology (2001) 155:123–7. doi: 10.1007/s002130000669
73. Partonen T. Chapter 7: Circadian systems biology in seasonal affective disorder. In: Timo Partonen, Pandi-Perumal SR, editors. Seasonal Affective Disorder: Practice and Research. 2nd ed. Oxford: Oxford University Press (2009).
74. Rosenthal NE, Mazzanti CM, Barnett RL, Hardin TA, Turner EH, Lam GK, et al. Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. Mol Psychiatry (1998) 3:175–7. doi: 10.1038/sj.mp.4000360
75. Praschak-Rieder N, Willeit M, Praschak-Rieder N, Neumeister A, Zill P, Stastny J, et al. Serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. Mol Psychiatry (2003) 8:942–6. doi: 10.1038/sj.mp.4001392
76. Willeit M, Praschak-Rieder N, Neumeister A, Zill P, Leisch F, Stastny J, et al. A polymorphism (5-HTTLPR) in the serotonin transporter promoter gene is associated with DSM-IV depression subtypes in seasonal affective disorder. Mol Psychiatry (2003) 8:942–6. doi: 10.1038/sj.mp.4001392
77. Thirry N, Willeit M, Praschak-Rieder N, Zill P, Hornik K, Neumeister A, et al. Serotonin transporter promoter gene polymorphic region (5-HTTLPR) and personality in female patients with seasonal affective disorder and in healthy controls. Eur Neuropsychopharmacol. (2004) 14:53–8. doi: 10.1016/S0924-977X(03)00064-6
78. Johannson C, Willeit M, Levitin R, Partonen T, Smedh C, Del Favero J, et al. The serotonin transporter promoter repeat length polymorphism, seasonal affective disorder and seasonality. Psychol Med. (2003) 33:785–92. doi: 10.1017/S0033291703007372
79. Sher L, Greenberg BD, Murphy DL, Rosenthal NE, Hamer DH. Pleiotropy of the serotonin transporter gene for seasonality and in healthy controls. Eur Neuropsychopharmacol. (2004) 14:53–8. doi: 10.1016/S0924-977X(03)00064-6
80. Johansson C, Willeit M, Levitin R, Partonen T, Smedh C, Del Favero J, et al. Serotonin transporter promoter repeat length polymorphism, seasonal affective disorder and seasonality. Psychol Med. (2003) 33:785–92. doi: 10.1017/S0033291703007372
81. Buhr, B.S., Halberg, R.J., Halberg, F., Goldsmith, S., Thomasius, R., Petersen, K., et al. Correction for age necessary in SPECT or PET of the central serotonin transporter in depressed outpatients. J Nucl Med (2008) 10:205–10. doi: 10.4088/JNPC.v10n0305
82. Enoch MA, Goldman D, Barnett R, Sher L, Mazzanti CM, Rosenthal NE. Association between the serotonin transporter promoter polymorphism, −1438G/A. Mol Psychiatry (1999) 4:89–92. doi: 10.1038/sj.mp.4000439
83. Arias B, Giutierrez B, Pintor L, Gastó C, Fanás L. Variability in the 5-HT(2A) receptor gene is associated with seasonal pattern in major depression. Mol Psychiatry (2001) 6:239–42. doi: 10.1038/sj.mp.4000818
84. Levitan RD, Masellis M, Basile VS, Lam RW, Jain U, Kaplan LS, et al. Polymorphism of the serotonin-2A receptor gene (HTR2A) associated with childhood attention deficiency hyperactivity disorder (ADHD) in adult women with seasonal affective disorder. J Affect Disord. (2002) 71:229–33. doi: 10.1016/S0165-0327(01)00372-X
85. Johannson C, Willeit M, Smedh C, Ekholm J, Paunio T, Kieseppa T, et al. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. Neuropsychopharmacology (2003) 28:734–9. doi: 10.1038/sj.npp.1301001
86. Partonen T, Treulein J, Alpman A, Frank J, Johannson C, Depner M, et al. Three circadian clock genes Per2, Arntl, and Npas2 contribute to winter depression. Am Med. (2007) 99:229–38. doi: 10.1008/s07853980701278795
87. Kovanen L, Saarikoski ST, Aromaa A, Lönqvist J, Partonen T. ARNTL (BMAL1) and Npas2 gene variants contribute to fertility and seasonality. PLoS ONE (2010) 5:e10007. doi: 10.1371/journal.pone.0001007
88. Kim HI, Lee HJ, Cho CH, Kang SG, Yoon HK, Park YM, et al. Association of CLOCK, ARNTL, and Npas2 gene polymorphisms and seasonal variations in mood and behavior. Chronobiol Int. (2015) 32:785–91. doi: 10.1080/07420528.2015.1049613
89. Paik JW, Lee HJ, Kang SG, Lim SW, Lee MS, Kim L. CLOCK gene 311C>T polymorphism is not associated with seasonal variations in mood and behavior in Korean college students. Psychiatry Clin Neurosci. (2007) 61:124–6. doi: 10.1111/j.1440-1819.2007.01621.x
90. Berenson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science (2002) 295:1070–3. doi: 10.1126/science.1067262
91. Hattar S, Liao H, Takao M, Berenson D, Yau K. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science (2002) 295:1065–70. doi: 10.1126/science.1066969
92. Ruby NE, Brennan TJ, Xie X, Cao V, Franken P, Heller HC, et al. Role of melanopsin in circadian responses to light. Science (2002) 298:2211–3. doi: 10.1126/science.1067601
93. Roecklein KA, Rohan KJ, Duncan WC, Rollag MD, Rosenthal NE, Lipsky RH, et al. A missense variant (P101L) of the melanopsin (OPN4) gene in seasonal affective disorder. J Affect Disord. (2009) 114:279–85. doi: 10.1016/j.jad.2008.08.005
94. Roecklein KA, Wong PM, Franzen PL, Hasler BP, Wood-Vasey WM, Ninomiya KV, et al. Melanopsin gene variations interact with season to predict sleep onset and chronotype. Chronobiol Int. (2012) 29:1036–47. doi: 10.1080/07420528.2012.706766
95. Terman M, Reme C, Rafferty B, Gallin P, Terman J. Bright light therapy for winter depression: potential ocular effects and theoretical implications. Photochem Photobiol. (1990) 50:781–92. doi: 10.1111/php.1990.50.6.781
96. Hebert M, Beattie CW, Tam EM, Yatham LN, Lam RW. Electroretinography in patients with winter seasonal affective disorder. Psychiatry Res. (2004) 127:27–34. doi: 10.1016/j.pysres.2004.03.006
97. Gagné A-M, Hébert M. Atypical pattern of rod electroretinogram modulation by recent light history: a possible biomarker of seasonal affective disorder. Psychiatry Res. (2011) 187:370–4. doi: 10.1016/j.pysres.2010.08.010
98. Roecklein K, Miller M, Donofry S, Dupont C, Hasler B, Krebs MO. Association of the intronic rs2072621 polymorphism of the X-linked GPR50 gene with seasonal affective disorder. J Affect Disord. (2009) 127:379–81. doi: 10.1016/j.jad.2009.01.011
99. Yang SY, Baek JH, Cho Y, Cho EY, Choi Y, Kim Y, et al. Effects of genetic variants of ST8SIA2 and NCAM1 genes on seasonal mood changes and
circadian preference in the general population. Chronobiol Int. (2017) 35:1–11. doi: 10.1080/07420528.2017.1410827

107. Holtmann G, Siffert W, Haag S, Mueller N, Langkafel M, Senf W, et al. G-protein beta 3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. Gastroenterology (2004) 126:971–79. doi: 10.1053/j.gastro.2004.01.006

108. Jacobi I, Hilgers KE, Schlaich MP, Siffert W, Schmieder RE. 825T allele of the G-protein beta3 subunit gene (GNB3) is associated with impaired left ventricular diastolic filling in essential hypertension. J Hypertens (1999) 17:1457–62. doi: 10.1097/00004872-199917100-00014

109. Willeit M, Praschak-Rieder N, Zill P, Neumeister A, Ackenheil M, Kasper S, et al. C825T polymorphism in the G protein beta3-subunit gene is associated with seasonal affective disorder. Biol Psychiatry (2003) 54:682–6. doi: 10.1016/S0006-3223(03)00169-0

110. Johansson C, Willeit M, Aron L, Smedh C, Ekholm J, Paunio T, et al. Seasonal affective disorder and the G-protein beta-3-subunit C825T polymorphism. Biol Psychiatry (2004) 55:317–9. doi: 10.1016/S0006-3223(03)00640-1

111. Wirz-Justice A, Benedetti F, Terman M, editors. Chronotherapeutics for affective disorders. In: A Clinician's Manual for Light and Wake Therapy. 2nd ed. Basel: Karger (2013). p. 32.

112. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Genet. (2008) 9:764–75. doi: 10.1038/nrg2430

113. Shimomura K, Lowrey PL, Vitaterna MH, Buhr ED, Kumar V, Hanna P, et al. Genetic suppression of the circadian Clock mutation by the melatonin biosynthesis pathway. Proc Natl Acad Sci USA. (2010) 107:8399–403. doi: 10.1073/pnas.1004368107

114. Brown SA, Kunz D, Dumas A, Westermark PO, Vanselow K, Tilman-Wahnschaffe A, et al. Molecular insights into human daily behavior. Proc Natl Acad Sci USA. (2008) 105:1602–7. doi: 10.1073/pnas.0707772105

115. Pagani L, Schmitt K, Meier F, Izakovic J, Roemer K, Viola A, et al. Serum factors in older individuals change cellular clock properties. Proc Natl Acad Sci U S A. (2011) 108:7218–23. doi: 10.1073/pnas.1008882108

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