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Inês de Sousa Machado

The association between circadian clock gene polymorphisms and the
phenotype of Bipolar Disorder: a systematic review

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The association between clock gene polymorphisms and the phenotype of Bipolar Disorder

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Dedicatória

Aos meus pais, apoio incondicional, fundamentais nesta jornada

À minha tia, o meu maior exemplo de superação

The association between circadian clock gene polymorphisms and the phenotype of Bipolar Disorder: a systematic review

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Abstract

Objective: This systematic review explores the link between circadian clock gene polymorphisms and the phenotypic presentation of Bipolar Disorder (BD) in adult individuals. By combining findings from numerous studies, we aim to identify genetic factors that contribute and can eventually predict the clinical manifestations of BD.

Methods: Searches were conducted through PubMed, ScienceDirect and PsychInfo, according to PRISMA guidelines. We retrieved relevant literature on circadian clock genes, namely CLOCK, ARNTL, TIMELESS, PER3, GSK3-B, RORB, among others. 18 studies including SNP analysis and VNTR repetitions were considered and associations with specific BD traits were identified and synthesized.

Results: We found evidence of contribution of polymorphisms within circadian genes to the phenotypic presentation and the clinical characteristics of BD patients. Specifically, the CLOCK 3111 T/C SNP demonstrates a strong association with illness recurrence, evening activity, and sleep disturbances. Furthermore, the CRY2 SNP rs10838524 emerges as a robust predictor of the rapid cycling subtype of BD. Notably, no single genetic polymorphism exhibited a significant relationship with drug treatment response.

Conclusion: This systematic review sheds a light on the evolving understanding of circadian clock gene polymorphisms in the context of BD and its clinical and practical implications. The associations found emphasize the need for further research, giving an insight into possible individualized treatment approaches and refined risk assessment strategies for individuals with BD.

Keywords

“Bipolar Disorder”, “Circadian Clocks”, “Polymorphism, Genetic” “CLOCK proteins”, “Genetic Association Studies”

Introduction

Bipolar Disorder (BD) is a severe mental illness characterized by recurrent mania and depression episodes that are repetitive in nature. It significantly correlates with economic and psychosocial morbidity and affects about 1% to 2% of people worldwide, with a median age of onset of about 25 years (1).

Depending on the severity and frequency of the episodes, BD is classified into subtypes. Evidence of both acute major depressive episodes and acute manic episodes is required for the diagnosis of bipolar disorder; BD I is characterized by manic presentations leading to significant social or occupational impairment while BD II is characterized by hypomanic episodes, which are by definition a milder form of mania that is not always linked to functional impairment (2). Other subtypes of bipolar illness besides type I and type II are Rapid Cycling (more than four episodes of mania, depression, hypomania, or mixed state in one year) and Cyclothymia (hypomanic and subdepressive symptoms over a two-year period).

The high prevalence of mental and somatic comorbidities frequently has a negative impact on the course of the illness. Ultimately, the prognosis for bipolar disorder depends on how the illness manifests itself in each person. Particularly, comorbidities and psychotic symptoms appear to be detrimental to the prognosis.

Bipolar disorder can run in families, as numerous family studies have repeatedly shown. In comparison to relatives of unaffected controls, first-degree relatives of affected people have a roughly 10-fold higher risk of developing the disorder (3). Studies on twins have added to the body of evidence showing that genes play a significant role in the disorder's transmission within families (4). BD that manifests earlier seems to be more likely to run in families. (5)

The intricate interplay of genetic and environmental variables in the etiology of BD has been the focus of extensive research. Over the last two decades there have been made efforts to pinpoint individual susceptibility genes to the development of the disease. Several chromosomal areas have been suggested by linkage studies to include important genes, however, the findings have been mixed. It is now generally acknowledged that the genetic predisposition to BD results from the interaction of numerous genes, each of which has a relatively minor effect on overall risk. Thus, the focus of gene-finding research has shifted to association studies because they are more effective at detecting loci with small effects.

BD patients have been shown to have sleep abnormalities and circadian rhythm disorders. (6) Additionally, circadian rhythm disturbances are more noticeable in BD than other mood disorders, which suggests that they might be a phenotypic marker of BD. (6) The role of circadian rhythm dysregulation has emerged as a compelling avenue for exploration, with growing evidence suggesting that genetic variations in circadian clock genes may contribute to the manifestation and progression of BD.

The internal system that generates gene networks with a 24-hour cycle is what drives the circadian rhythmicity, controlled at the transcriptional level. Clock genes, which regulate rhythms in physiology and behavior, are found in these networks.

As we focus on individuals diagnosed with BD aged 18 years and older, this systematic review aims to provide a comprehensive synthesis of the existing literature pertaining to the association between circadian clock gene polymorphisms and the clinical and phenotypical presentation of BD.

The intervention examined in this systematic review involved the determination of circadian gene polymorphisms within the specified population. Through meticulous comparison of these polymorphisms, our objective is to unravel the genetic intricacies that may underlie the diverse clinical manifestations of BD. By systematically analyzing the outcomes reported in relevant studies, we aim to discern the relationships between specific polymorphisms and distinct clinical presentations, offering valuable insights into the heterogeneity of this complex disorder.

This review, therefore, serves as a critical examination of the existing evidence, seeking to identify consistent patterns and potential biomarkers associated with circadian clock gene polymorphisms in BD. As we bridge the gap between genetic variations and clinical outcomes, our findings may pave the way for a more nuanced understanding of the disorder, ultimately informing targeted therapeutic strategies and personalized treatment approaches for this specific population.

Methods

Following PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] guidelines, (7) we conducted a systematic review without a meta-analysis, of studies that assessed the role of genetic polymorphisms of circadian genes on the phenotype and clinical characteristics of BD patients. Studies were retrieved after a literature search including three electronic databases: PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), ScienceDirect (<https://www.sciencedirect.com/>) and PsychInfo (<https://psycinfo.apa.org>). The search was done from February 18 to April 3, 2023 using the following terms: “clock genes” OR “circadian genes” AND “bipolar disorder” OR “bipolar disorder phenotype”. Last search was carried in September 29, 2023. There were no language or publication year limits applied. Our target population were BD diseased adults aged 18 years or older. We excluded animal studies, since our focus was the human population in order to assess clinical and practical implications. The authors independently screened the studies found using the electronic databases.

The selection of studies was independently made by two reviewers, in two phases. Firstly, the articles were chosen by reading of their title and abstract. Secondly, the previously selected articles were fully read. Studies were selected for inclusion after analyzing the complete text and confirming one of the following criteria: i) publications concerning the influence of circadian genes in the presentation of BD in patients, and ii) articles connecting a single gene or a panel of genes to a clinical implication on BD patients. Exclusion criteria were i) studies that did not meet the previous criteria, ii) studies carried out on an animal model, iii) review articles, iv) studies that concerned other psychiatric disorders. The reference list of suitable papers was then supervised for further articles. Independently, both authors gathered the following information from the selected studies: authors' names, publication year, study size, polymorphism analysis and results, which were then synthesized in a table. [Table 2]

The qualitative analysis in this review was carried out independently by the two authors using a quality checklist established by Cosme D *et al* (8) for basic science studies. Each checklist criterion was graded 0, 1 or 2, respectively, if the information was not provided in the paper, limited information was offered, or the information was complete regarding each topic. To calculate the overall quality score for each study, the scores of all criteria were summed and divided by 28, which is the maximum obtained score for this checklist. This is shown on Table 1.

This review is registered in the PROSPERO International prospective register of systematic reviews under the registration number CRD42023449813 and can be assessed through https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=449813.

Results

The initial database search retrieved 1145 results in total. After initial screening through removal of duplicates and reading of title and abstract, 49 studies remained and were assessed for eligibility. After full text reading, 32 articles were excluded for not addressing the outcome of interest: 25 for relating circadian genes to the susceptibility of developing BD, 4 for relating clock gene polymorphisms to suicidal behaviour, and 3 for assessing structural brain changes related to circadian polymorphisms. Seventeen studies met the inclusion criteria and were therefore included in the final analysis. One additional study was identified through relevant citations of pertinent papers, leaving the final number of studies included at eighteen.

The PRISMA flow diagram [Fig 1.] explains the procedures followed in order to select the papers included in our review. The relevant data retrieved from the articles is summarized on Table 1.

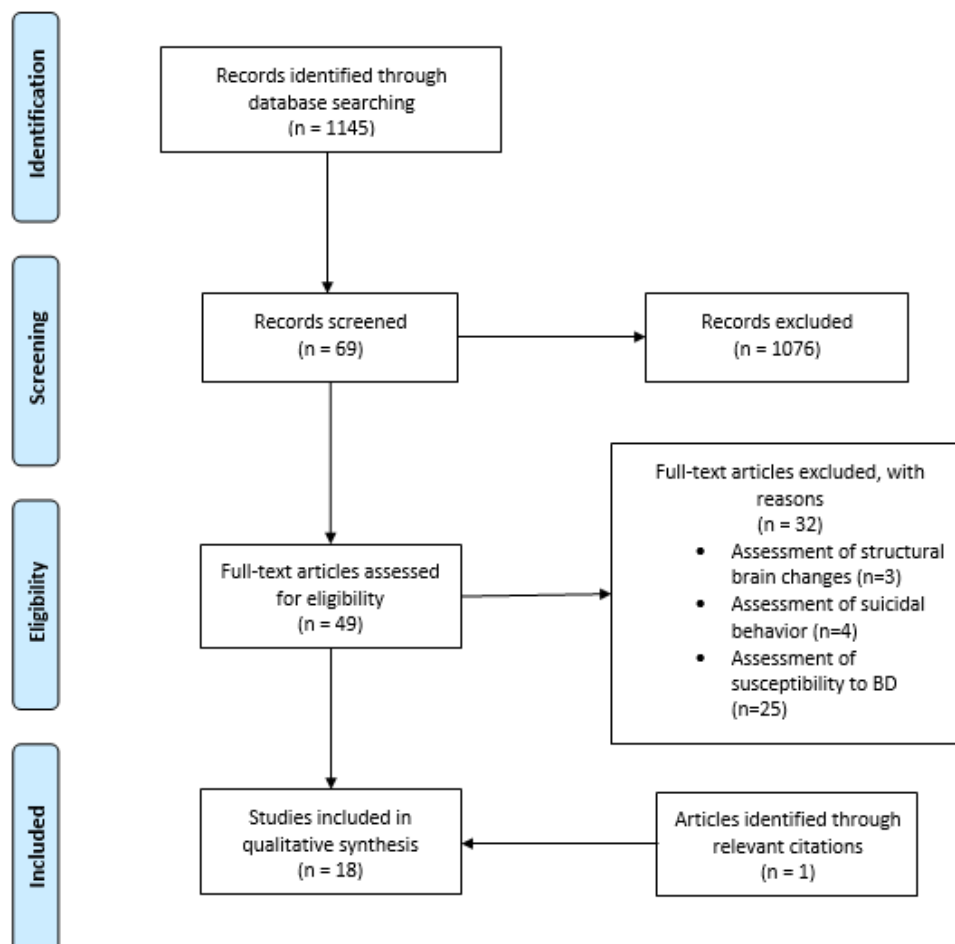


Fig.1 PRISMA flow diagram

Overall, the studies included 4117 participants, with sample sizes ranging from 39 (9) to 557 participants (10). All studies assessed adult individuals at least 18 years of age. The majority

included BD type I or BD types I and II and five studies did not differentiate by subtype of BD. (11-15) Most studies included both men and women, with four studies not differentiating by sex (9-11; 16).

Out of the eighteen studies included in the review, fifteen were from European countries (eight from Italy, three from France, three from Poland, one from Sweden), one was from South Korea and two were from the United States of America.

In what concerns the quality assessment done for all articles, three studies had a quality evaluation inferior to 50%. That can be attributable to the fact that those same articles were conference abstracts and many of the criteria relevant to the quality assessment score were missing. Fourteen of the studies (78%) were located in the upper quartile. The criteria with the lowest scores were the evaluation by independent observers; blinding; evidence of independent repetitions in the data collection, which is understandable given the design of the studies being mostly observation

	10. Accessible and transparent presentation of data throughout the paper (including the appropriate measures of precision/ variance)	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	11. Critical discussion of the results; comparison with relevant research on the field	1	1	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	12. Draw consistent conclusions based on the evidence presented in the paper	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	13. State the contribution to cumulative scientific knowledge and the practical implications of the findings	1	1	0	1	2	1	1	2	2	2	1	2	2	2	2	2	2	1	1
	14. Disclose conflicts of interest and declaring funding sources	0	0	0	0	0	1	1	1	1	2	2	2	2	2	2	2	2	2	2
Criteria overall score		1,214	1,286	0,928	0,786	1,429	1,643	1,786	1,714	1,786	1,917	1,786	1,786	1,714	1,714	1,786	1,714	1,714	1,571	1,714
Standard deviation		0,802	0,825	0,997	0,802	0,852	0,633	0,426	0,611	0,579	0,363	0,426	0,426	0,611	0,579	0,426	0,611	0,646	0,611	0,611
Maximum score		60,71%	64,29%	46,43%	39,29%	71,43%	82,14%	89,29%	85,71%	89,29%	92,86%	89,29%	89,29%	85,71%	89,29%	89,29%	85,71%	78,57%	85,71%	85,71%

Table 1. Quality Assessment of included Genetic Association Studies

Reference	Circadian gene	SNP	Phenotype	Association	Population	Study Size
Benedetti, F et al 2003	CLOCK	3111 T/C SNP	Illness Recurrence	Yes	Italian	101
Dallaspezia, S et al 2006	CLOCK	3111 T/C SNP	Evening Activity Sleep Disturbances	Yes	Italian	39
Lee, KY et al 2010	CLOCK	3111 T/C SNP	Evening Preference	Yes	South Korean	260
Maciukiewicz, M. et al 2014	CLOCK, ARNTL, TIMELESS and PER3	ARNTL SNPs rs11022778, rs37893327, rs10766075, rs11022778 CLOCK rs1801260	Main depression Appetite Disturbances Sleep Disturbances	Yes	Polish	511
Rybakowski, JK et al 2014	CLOCK, ARNTL, TIM, PER3	ARNTL SNPs rs1481892 rs7107287 rs1481892)	Anxious and Hyperthymic Temperament	Yes	Polish	70
Benedetti, F et al 2004	GSK3- β promoter	-50 T/C SNP	Later onset of illness Response to one night of sleep	Yes	Italian	60
Gonzaleza, R. et al 2019	GSKR- β and other genes	GSK3B SNP rs334555 RORB SNP rs7022435	Evening preference Rapid cycling Sleep Disturbances	Yes	American	66
Marino, E. et al. 2007	Per3	T1940G T3110C	Later onset of illness Response to SSRIs Novelty Seeking	Yes	Italian	512
Benedetti, F et al. 2008	Per3	VNTR of 4 or 5 repetitions	Later onset of bipolar illness	Yes	Italian	99
Dallaspezia, S. et al. 2015	Per3	VNTR of 4 or 5 repetitions	Sleep disturbances Depressive symptoms	Yes	Italian	105
Manchiaa, M. et al 2009	NR1D1 and DGKH	NR1D1 SNPs rs12941497 and rs9393347; DGKH SNPs rs9315885, rs1012053 and rs1170191	Response to lithium therapy	No	Sardinian	199

Table 2. Studies on genetic polymorphisms influencing BD phenotype and clinical characteristics

Campos-de-Sousa, S. et al 2010	Rev-erb- α	SNPs rs4794826, rs2314339, rs2071427, rs2269457, rs12941497, rs939347, and rs2071570	Response to lithium therapy	No	Sardinian	170
Sjöholm LK et al 2010	CRY2	CRY2 SNP rs10838524	Rapid Cycling	Yes	Swedish	557
Geoffroy, PA et al 2015	CRY2 and other genes	NPAS2 SNPs: rs6738097, rs12622050, rs2305159, rs1542179, and CRY2 rs1554338	Seasonal Pattern	Yes	French	269
McCarthy, MJ et al 2011	ARNTL, CLOCK, CRY1, CSKRB, NR1D1, PER2, PER3	3 SNPs in ARNTL, 3 SNPs in CLOCK, 1 SNP in CRY1, 1 SNP in CSK3B, 1 SNP in NR1D1, 1 SNP in PER2, 6 SNPs in PER3	Response to lithium therapy	No	American	282
Rybakowski JK et al 2013	CLOCK, ARNTL, TIM, PER3	9 SNPs of the CLOCK gene, 18 SNPs of the ARNTL gene, 6 SNPs of TIM gene, and 9 SNPs of the PER3 gene	Response to lithium prophylaxis	No	Polish	115
Étain, B et al 2014	TIM and other genes	TIM SNP rs774045 RORA SNP rs782931	Eveningness and Rigid Circadian Types	Yes	French	479
Geoffroy, P.A et al 2016	GSK3B and other genes	RORA rs17204573, rs4775355, rs7164773, rs1370431, rs782907	Response to lithium therapy	Yes	French	223

Table 2. Studies on genetic polymorphisms influencing BD phenotype and clinical characteristics

Overall, 27 different circadian genes were assessed for polymorphism associations with clinical and phenotypical characteristics of BD patients, which are further described below. CLOCK was the most frequently associated circadian gene, with 4 different articles associating CLOCK SNPs with sleep disturbances, chronotype preference, appetite disturbances and illness recurrence. Secondly, PER3 polymorphisms were found relevant among 3 articles for influencing novelty seeking, age of onset of illness, sleep

disturbances and chronotype preference. The detailed phenotypic associations found are described below.

We were unable to assess whether the subtype of BD was related to circadian gene polymorphisms given the absence of articles concerning only BD type II.

Phenotypic Associations

Lithium Response

The most frequent phenotypic association referred was lithium response, with polymorphisms among seven circadian genes demonstrating some degree of association with lithium prophylactic or therapeutic response. RORA and PPARGC1A SNPs had significant associations, RORA SNPs rs17204573, rs4775355, rs7164773, rs1370431 and rs782907 remaining significant after Bonferroni correction, although it was not replicated in a second sample. (17) Eight ARNTL SNPs and two TIM SNPs also had significant associations regarding the degree of prophylactic lithium response notwithstanding Bonferroni correction. (18) Two studies failed to show any association between lithium response and NR1D1 polymorphisms (14) (19), while another showed an association that did not remain significant after correction (16), as well as an additive effect and a trend towards epistasis along with GSK3-B. A CRY1 SNP was also associated with lithium response although it did not survive correction.

Sleep

Polymorphisms among five different genes were assessed for predisposing sleep variations among BD patients. A -50 C SNP on GSK3-B seemed to predict a higher relapse after recovery sleep, as well as better acute effects of total sleep deprivation on perceived mood. (20) The rs334555 SNP in this same gene was also associated with greater sleep efficiency while a RORB rs7022435 SNP showed increased sleep disturbances. (21) One study showed how a PER3 VNTR polymorphism influenced changes in total sleep time, the presence of a 4 repetition allele of the VNTR sequence having a reduction in total sleep time in comparison to both alleles having 5 repetitions. (13) Sleep disturbances were also associated with two different ARNTL polymorphisms, rs10766075 and rs3789327, while ARNTL rs11824092 SNP showed an additive effect with CLOCK rs11932595 increasing the appearance of sleep disturbances. (12) In one other study, CLOCK 3111 C SNP carriers had a significantly lower total sleep time and a significantly delayed sleep onset when compared to the CLOCK 3111 T SNP carriers. (9)

Chronotype and mood

Another frequent phenotypic association was with chronotype and mood, with polymorphisms among 5 different circadian genes demonstrating some degree of association. One study showed that evening preference was significantly superior in the CLOCK 3111 C SNP carriers than it was in the T SNP genotypes (22), and one other associated this same C SNP with increased evening activity. (9) GSK3-B rs334555 polymorphism also showed association with an evening chronotype. (21) The TIM rs774045 SNP AA/AG correlated to eveningness as well as a languid circadian rhythm, while RORA rs782931 GG/AG was significantly more frequent among rigid circadian types. (23) PER3 ex18TC C/C carriers were prone to have worse mood in the evening. (11)

Temperament

Four SNPs of the ARNTL gene were significantly associated with anxious temperament, namely, rs11022780, rs4146388 and, rs7107287 and rs1481892. However, only the last two remained significant after Bonferroni correction. Three SNPs of the ARNTL gene, rs1481892, rs4146388 and rs7107287, correlated to hyperthymic temperament, only rs1481892 SNP withstanding correction. Cyclothymic temperament showed association with two TIM SNPs, rs2291738 and rs10876890 that were disproven after correction. Lastly, PER3 rs228727 SNP seemed to be associated with depressive temperament, not withstanding Bonferroni correction as well. (15)

Age of onset

Two genes' SNPs correlated to age at onset of illness in BD patients. A GSK3-B promoter -50 C/C genotype showed a significantly later onset of BD when compared to -50 T/C and T/T. (20) Age of onset also significantly differed between the number of VNTR present in the *Per3* gene: earlier onset for 5/5 homozygotes, later onset for 4/4 homozygotes, while on heterozygotes illness showed at intermediate age. (24) Per3 exon 15 T1940G GG and Per3 exon 18 T/C CC genotypes also showed association with age at onset. (11)

Rapid cycling

Rapid cycling was nominally associated with GSK3-B SNP rs334555. (21) CRY2 SNP rs10838524 was also associated, being significantly overrepresented among BD patients with this subtype of disease, and withstanding Bonferroni correction. (10)

Other characteristics

Appetite disturbances were significantly related to ARNTL SNPs rs11022778, rs3789327 and CLOCK SNP rs1801260. (12) Depressive symptomatology was related to the same ARNTL SNPs rs11022778, rs3789327, and to SNP rs11022778. One study significantly associated the change of depressive symptoms during total sleep deprivation treatment to PER3 VNTR 5/5, (13) a gene which was also associated to the degree of response to SSRI treatment through PER3 SNP T1940G G/G. (11) PER3 variants were associated with novelty seeking among BD patients. (11) Illness recurrence significantly differed between CLOCK 3111 SNP T/C carriers, with the recurrence rate in homozygotes for the C variant being nearly double the one for the T

homozygotes. (25) Lastly, seasonal pattern was also assessed for association with circadian polymorphisms, with NPAS2 SNPs, rs6738097, rs12622050, rs2305159, rs1542179, and rs1562313 being significantly associated with seasonal pattern in BD patients. NPAS2 rs6738097 SNP and CRY2 rs1554338 SNP are also associated and seem to have an additive effect on the seasonal pattern phenotype. (26)

How does the circadian clock work?

Most essential functions follow daily regular cycles. The so-called circadian clock, an endogenous timing system, is required to regulate these circadian cycles and fluctuations. This clock's pacemaker is hypothesized to be situated in the suprachiasmatic nuclei (SCN) (27), which are immediately above the optic chiasm in the anterior-ventral region of the hypothalamus. The SCN imposes temporal structure through the synchronization of the organism's physiology with the external light-dark cycle perceived through the retina directly to the SCN via the retinohypothalamic tract. (28)

The currently accepted model which describes the intracellular clock mechanisms states that the transcription factors CLOCK and BMAL1 heterodimerize and bind to enhancer elements present in the promoters of circadian genes such as *Per* (29), *Cry* (30) and *Rev-erba/NR1D1*. (31) The PER and CRY proteins interact and inhibit the complex CLOCK-BMAL1, which establishes a negative feedback in their own transcription. (32) The modulators of this inhibition are CKI ϵ and CKI δ , which phosphorylate PER1, PER2, CRY1, CRY2 and BMAL1. (33) PGC-1 α stimulates the expression of genes such as *Bmal1/ARNTL* and *Rev-erba/NR1D1*, through coactivation of the ROR nuclear receptors. (34) Rev-erba, on the other hand, generates the positive feedback loop by repressing *Bmal1/ARNTL* transcription through ROR receptors. (35) PER and CRY then enter the nucleus and inhibit their own transcription through inhibition of CLOCK-BMAL1 heterodimer, also inhibiting *Rev-erba* and therefore activating the transcription of *Bmal1/ARNTL*. (36) TIM is an interacting partner of PER, on which PER is dependent to efficiently accumulate in the nucleus. (37) GSK3- β also plays an important role by regulating the nuclear entry of PER2 through dephosphorylation, contributing to the rhythmicity of the clock. (38) NPAS2 is another circadian gene that's a functional analog of Clock and can heterodimerize with BMAL1. (39)

Discussion

The results of our systematic review reveal notable patterns and consistencies across several studies. Namely, the association between the CLOCK 3111 T/C SNP and various aspects of BD such as illness recurrence, evening activity and sleep disturbances, suggesting a potential role of this polymorphism in influencing the clinical presentation of the disorder.

We found variable strength of correlation in our analysis. Some findings, such as the link between CRY2 SNP rs10838524 and the rapid cycling variant of BD appear to be robust. Others, such as the association between circadian genes SNPs and responsiveness to lithium medication lack significant evidence and show discrepant results. It may be hypothesized that, in what concerns some clinical characteristics such as treatment response, in a similar way to the predisposition of BD, the contribution of individual genes is less significant than the overall risk resulting from the interaction of different SNPs.

The identified associations may have clinical and practical implications. For once, the link between Per3 gene SNPs and later onset of illness could point to a role in the timing of symptom manifestation or treatment introduction; the individual susceptibility to depressive symptoms or sleep disturbances through ARNTL and CLOCK SNPs could help clinicians be more watchful to the emergence and treatment of such symptoms; evening activity and preferred circadian phase could help predict the individual's response to work scheduling or other disruptors of the circadian rhythm. Overall, understanding the genetic basis of specific clinical presentations in BD may help to enhance individual risk assessment and be the beginning to personalized treatment practices.

It is important to recognize the limitations of the studies included in our analysis. Variations in sample sizes, populations and methodologies were present and could contribute to the discrepancies found. Furthermore, the possibility of publication bias or selective reporting could influence the overall perception of data.

The inconsistencies and gaps found in the current literature suggest several possibilities for future research. Exploring the impact of circadian clock gene polymorphisms on specific symptom clusters and performing larger and more homogeneous studies may help clarify and refine our understanding of these associations.

These results are consistent with previously documented findings in the literature, such as the role of circadian genes in mood disorders and sleep abnormalities.

To sum up our findings, it is evident that circadian clock gene polymorphisms play a diverse role in the clinical manifestations of BD. The complexities and inconsistencies highlighted in this systematic review emphasize the need of having a full understanding of the genetic landscape in order to persuade more targeted and personalized treatment approaches.

In conclusion, the systematic review offers a complex perspective on the associations between circadian clock gene polymorphisms and the BD phenotype and clinical presentation. While some consistent patterns are found, the heterogeneity of the findings emphasizes the extensive genetic basis of this intricate condition. Continued research in this field is critical for unraveling the complexities and translating these results into practical clinical applications.

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Section/topic		#	Checklist item	Reported on page and paragraph/ table #
TITLE				
Title		1	Identify the report as a systematic review, meta-analysis, or both. - MANDATÓRIO	“The association between circadian clock gene polymorphisms and the phenotype of Bipolar Disorder: a systematic review” Título Página1
ABSTRACT				
Structured summary		2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. – SEGUIR RECOMENDAÇÕES DA REVISTA	Abstract Objective: This systematic review explores the link between circadian clock gene polymorphisms and the phenotypic presentation of Bipolar Disorder in adult individuals. By combining findings from numerous studies we aim to identify genetic factors that contribute and can eventually predict the clinical manifestations of BD. Methods: Searches were conducted through PubMed, ScienceDirect and PsychInfo, according to PRISMA guidelines. We retrieved relevant literature on circadian clock genes, namely CLOCK, ARNTL, TIMELESS, PER3, GSK3-B, RORB, among others. 18 studies including SNP analysis and VNTR repetitions were considered and associations with specific BD traits were identified and synthesized. Results: We found evidence of contribution of polymorphisms of circadian genes among several studies in what concerns the phenotypic presentation and the clinical characteristics of BD patients. CLOCK 3111 T/C SNP is strongly associated with illness recurrence, evening activity and sleep disturbances. CRY2 SNP rs10838524 is a strong predictor of a rapid cycling subtype. No individual genetic polymorphism was significantly related to treatment response. Conclusion: This systematic review sheds a light on the evolving understanding of circadian clock gene polymorphisms in the context of BD and its clinical and practical implications. The associations found emphasize the need for further research, giving an insight into possible individualized treatment approaches and refined risk assessment strategies for individuals with BD. Página 2
INTRODUCTION				
Rationale		3	Describe the rationale for the review in the context of what is already known. – MANDATÓRIO O rationale corresponde à justificação da importância da revisão sistemática	The intervention examined in this systematic review involved the determination of circadian gene polymorphisms within the specified population. Through meticulous comparison of these polymorphisms, our objective is to unravel the genetic intricacies that may underlie the diverse clinical manifestations of BD.



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			By systematically analyzing the outcomes reported in relevant studies, we aim to discern the relationships between specific polymorphisms and distinct clinical presentations, offering valuable insights into the heterogeneity of this complex disorder. This review, therefore, serves as a critical examination of the existing evidence, seeking to identify consistent patterns and potential biomarkers associated with circadian clock gene polymorphisms in BD. As we bridge the gap between genetic variations and clinical outcomes, our findings may pave the way for a more nuanced understanding of the disorder, ultimately informing targeted therapeutic strategies and personalized treatment approaches for this specific population. Página 4, Parágrafos 1 e 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). - MANDATÓRIO	“As we focus on individuals diagnosed with BD aged 18 years and older, this systematic review aims to provide a comprehensive synthesis of the existing literature pertaining to the association between circadian clock gene polymorphisms and the clinical and phenotypical presentation of BD.” Página 3 Parágrafo 8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. - FACULTATIVO	This review is registered in the PROSPERO International prospective register of systematic reviews under the registration number CRD42023449813 and can be assessed through https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=449813. Página 5 parágrafo 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. - MANDATÓRIO <i>É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.</i>	There were no language or publication year limits applied. Our target population were BD diseased adults aged 18 years or older. We excluded animal studies, since our focus was the human population in order to assess clinical and practical implications. The authors independently screened the studies found using the electronic databases. ... Studies were selected for inclusion after analyzing the complete text and confirming one of the following criteria: i) publications concerning the influence of circadian genes in the presentation of BD in patients, and ii) articles connecting a single gene or a panel of genes to a clinical implication on BD patients. Exclusion criteria were i) studies that did not meet the previous criteria, ii) studies carried out on an animal model, iii) review articles, iv) studies that concerned other psychiatric disorders. The reference list of suitable papers was



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			then supervised for further articles. Independently, both authors gathered the following information from the selected studies: authors' names, publication year, study size, polymorphism analysis and results, which were then synthesized in a table. [Table 1] Página 4, parágrafos 3 e 4	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. – MANDATÓRIO <i>Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov. Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.</i>	Studies were retrieved after a literature search including three electronic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (https://www.sciencedirect.com/) and PsycInfo (https://psycinfo.apa.org). The search was done from February 18 to April 3, 2023 using the following terms: “clock genes” OR “circadian genes” AND “bipolar disorder” OR “bipolar disorder phenotype”. Last search was carried in September 29, 2023. Página 4 parágrafo 3	then supervised for further articles. Independently, both authors gathered the following information from the selected studies: authors' names, publication year, study size, polymorphism analysis and results, which were then synthesized in a table. [Table 1] Página 4, parágrafos 3 e 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. – MANDATÓRIO <i>A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/alyork.ac.uk/issg-search-filters-resource/home)</i>	The search was done from February 18 to April 3, 2023 using the following terms: “clock genes” OR “circadian genes” AND “bipolar disorder” OR “bipolar disorder phenotype”. Página 4 Parágrafo 3	The search was done from February 18 to April 3, 2023 using the following terms: “clock genes” OR “circadian genes” AND “bipolar disorder” OR “bipolar disorder phenotype”. Página 4 Parágrafo 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). – MANDATÓRIO <i>As fases de selecção dos estudos</i>	The selection of studies was independently made by two reviewers, in two phases. Firstly, the articles were chosen by reading of their title and abstract. Secondly, the previously selected articles were fully read. Studies were selected for inclusion after analyzing the complete text and confirming one of the	The selection of studies was independently made by two reviewers, in two phases. Firstly, the articles were chosen by reading of their title and abstract. Secondly, the previously selected articles were fully read. Studies were selected for inclusion after analyzing the complete text and confirming one of the

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		<i>primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.</i>	following criteria: i) publications concerning the influence of circadian genes in the presentation of BD in patients, and ii) articles connecting a single gene or a panel of genes to a clinical implication on BD patients. Exclusion criteria were i) studies that did not meet the previous criteria, ii) studies carried out on an animal model, iii) review articles, iv) studies that concerned other psychiatric disorders. The reference list of suitable papers was then supervised for further articles. Independently, both authors gathered the following information from the selected studies: authors' names, publication year, study size, polymorphism analysis and results, which were then synthesized in a table. [Table 1] Página 4 parágrafo 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. – MANDATÓRIO <i>Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.</i>	The selection of studies was independently made by two reviewers, in two phases. Firstly, the articles were chosen by reading of their title and abstract. Secondly, the previously selected articles were fully read. Página 4 parágrafo 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. – MANDATÓRIO <i>Trata-se de descrever as variáveis para as quais foi obtida informação.</i>	Independently, both authors gathered the following information from the selected studies: authors' names, publication year, study size, polymorphism analysis and results, which were then synthesized in a table. Página 4 parágrafo 4
Risk of bias in individual studies / Risk of bias across studies	12/15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. – MANDATÓRIO <i>Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaiois clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é</i>	The qualitative analysis in this review was carried out independently by the two authors using a quality checklist established by Cosme D et al (8) for basic science studies. Each checklist criterion was graded 0, 1 or 2, respectively, if the information was not provided in the paper, limited information was offered, or the information was complete regarding each topic. To calculate the overall quality score for each study, the scores of all criteria were summed and divided by 28, which is the maximum obtained score for this checklist. Página 4 parágrafo 5



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		altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	Não Aplicável
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	Não Aplicável
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	Não Aplicável
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. – MANDATORIO	The initial database search retrieved 1145 results in total. After initial screening through removal of duplicates and reading of title and abstract, 49 studies remained and were assessed for eligibility. After full text reading, 32 articles were excluded for not addressing the outcome of interest: 25 for relating circadian genes to the susceptibility of developing BD, 4 for relating clock gene polymorphisms to suicidal behaviour, and 3 for assessing structural brain changes related to circadian polymorphisms. Seventeen studies met the inclusion criteria and were therefore included in the final analysis. One additional study was identified through relevant citations of pertinent papers, leaving the final number of studies included at eighteen Página 5 parágrafo 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. – MANDATORIO	Tabela 2



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Risk of bias within and across studies	19/22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). – MANDATÓRIO	Tabela 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. – FACULTATIVO . APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	Não Aplicável
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. – FACULTATIVO . MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE	Não Aplicável
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]). – FACULTATIVO . APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	Não Aplicável
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). – MANDATÓRIO	“The results of our systematic review reveal notable patterns and consistencies across several studies. Namely, the association between the CLOCK 3111 T/C SNP and various aspects of BD such as illness recurrence, evening activity and sleep disturbances, suggesting a potential role of this polymorphism in influencing the clinical presentation of the disorder. We found variable strength of correlation in our analysis. Some findings, such as the link between CRY2 SNP rs10838524 and the rapid cycling variant of BD appear to be robust. Others, such as the association between circadian genes SNPs and responsiveness to lithium medication lack significant evidence and show discrepant results. It may be hypothesized that, in what concerns some clinical characteristics such as treatment response, in a similar way to the predisposition of BD, the contribution of individual genes is less significant than the overall risk resulting from the interaction of different SNPs. “
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g.,	Página 13 Parágrafos 4, 5 “It is important to recognize the limitations of the studies included in our



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		incomplete retrieval of identified research, reporting bias). – MANDATÓRIO	analysis. Variations in sample sizes, populations and methodologies were present and could contribute to the discrepancies found. Furthermore, the possibility of publication bias or selective reporting could influence the overall perception of data. “ Página 14 Parágrafo 2
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. – MANDATÓRIO	“The inconsistencies and gaps found in the current literature suggest several possibilities for future research. Exploring the impact of circadian clock gene polymorphisms on specific symptom clusters and performing larger and more homogeneous studies may help clarify and refine our understanding of these associations. These results are consistent with previously documented findings in the literature, such as the role of circadian genes in mood disorders and sleep abnormalities. To sum up our findings, it is evident that circadian clock gene polymorphisms play a diverse role in the clinical manifestations of BD. The complexities and inconsistencies highlighted in this systematic review emphasize the need of having a full understanding of the genetic landscape in order to persuade more targeted and personalized treatment approaches.” Página 14 Parágrafo 3, 4, 5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. – SEGUIR RECOMENDAÇÕES DA REVISTA	The authors declare no funding for this study. Página 14 Parágrafo 7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Type	Maximum Word Count	Maximum no. of references	Abstract / Keywords
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PERSPECTIVES

Editorial	2000	5	No
Debate	1200	5	No

RESEARCH ARTICLES

Review Article	4000-7500	100	Yes
Original Article	5000	50	Yes

CORRESPONDENCE

Commentary	800	5	No
Letter	400	3	No

CLINICAL CORNER

Clinical Conundrum	800-1500	5	No
Clinical Curiosity	800-1500	5	No
Clinical Care	800-1500	5	No

REFLECTIONS

Musing	600	3	No
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Editorial: These should address contemporary topics of interest and provide thought-provoking discussion. The presentation of new hypotheses and novel ideas pertaining to psychiatry are welcome.

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- Key Message (50 words)
- Case Presentation
- Discussion
- Learning points (2-3 bullet points) - *optional*
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- Learning points (2-3 bullet points) - *optional*
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2. Voet D, Voet JG. *Biochemistry*. New York: John Wiley & Sons; 1990. 1223 p.

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