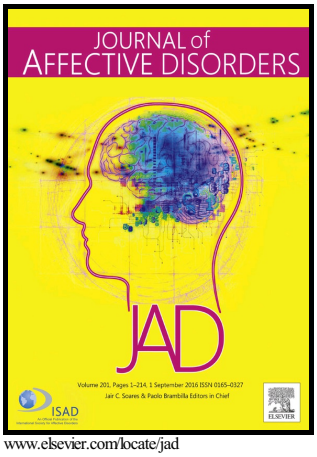

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The role of clock genes in the etiology of Major Depressive Disorder

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ABSTRACT

Background

Circadian rhythms are largely dysregulated in Major Depressive Disorder (MDD). The present review provides a summary of the findings about the role of clock genes in the etiology of MDD.

Methods

A careful search of articles on Pubmed, PsycINFO, Isi Web of Knowledge was performed in order to obtain a comprehensive review about the topic.

Results

The studies reported contrasting results about the association of different single nucleotide polymorphisms (SNPs) in clock genes and MDD. The most consistent result reported the

association between SNP rs2287161 of CRY1 and MDD development.

Limitations

Most of the published papers on the topic show bias as a prevalence of Asian ethnicity or not blinded conditions of laboratory experiments with respect to subjects' conditions (healthy controls or MDD).

Conclusion

Further epigenetic and genome-wide studies are necessary to have a more clear idea about the role of clock genes in the etiology of MDD.

Keywords: Major Depressive Disorder (MDD), Genetics, Clock genes

1. Main Body

Major Depressive Disorder (MDD) is characterized by several circadian abnormalities, although sleep-wake rhythm is certainly the most disrupted one (Turek, 2007). Common biological factors are probably involved both in mood symptoms and alteration of circadian rhythms of MDD patients, and this hypothesis is supported by the fact that: a) not all subjects with insomnia develop depression and b) vice versa hypnotic agents (e.g., zolpidem or ramelteon) do not address depressive symptoms (Turek, 2007). Clock genes dysregulation has been evocated as an important factor associated with the development of both insomnia and mood symptoms (Monteleone et al., 2011). Probably insomnia and environmental factors such as work shift (Romano et al., 2017) cause changes in the expression of clock genes, which in turn determines the mood symptoms (Monteleone et al., 2011). Alternatively particular polimorphisms of clock genes may confer susceptibility to circadian abnormalities (e.g. sleep dysregulation) in MDD (Mendlewicz, 2009). Of note, not only the clock genes regulate sleep-wake rhythms, but also the propensity and timing of wakefulness; in addition a research has demonstrated as the abnormal expression of the clock gene

Rev-erbα (retinoic acid-related orphan receptor alpha) inhibits dopamine synthesis and consequently weakens dopamine neurotransmission (Chung et al., 2014). From a biological point of view, the two main molecules involved in the regulation of circadian rhythms are represented by protein Period (PER) and Cryptochrome (CRY). PER and CRY expression is regulated by the proteins CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Brain and muscle Arnt-like protein-1) whose transcription is in turn controlled by Rev-erbα. Finally PER may be inactivated by phosphorylation driven by casein kinase 1 epsilon (CK1ε) (Turek, 2007; Monteleone et al., 2011). All these genes regulate the internal clock in the suprachiasmatic nuclei of hypothalamus; this internal clock is in turn maintained in synchrony with the 24-h solar day by different molecules including melatonin or metabolic peptide hormones (Tsang et al., 2016).

Purpose of the present review is to summarize the available findings about the role of clock genes in the etiology of MDD. In particular, we focused on the core clock genes that control the internal center clock in the suprachiasmatic nuclei. A careful search of articles on Pubmed, PsycINFO, Isi Web of Knowledge was performed in order to obtain a comprehensive review about the topic. The words MDD and unipolar depression have been matched with the terms “clock gene” and “circadian gene”. No restriction criteria were established for study design. Exclusion criteria consisted of: 1) animal studies; 2) samples with patients affected by a mood disorder different from MDD (e.g. bipolar depression); 3) off topic articles (e.g. those investigating the role of clock genes on antidepressant response). Only papers in English were included.

Table 1 summarizes the results of the included studies and their effect sizes and it provides an evaluation of the quality of included studies according to Qualitative Assessment Tool for Quantitative Studies (Effective Public Health Practice Project).

Four hundred and forty-one papers were initially identified, 190 were duplicates and 237 were excluded for above mentioned criteria. Fourteen papers satisfied the inclusion criteria (Figure 1).

The first study about the role of polymorphisms of clock genes in the etiology of MDD was

published in 2008. The authors failed to find an association between single nucleotide polymorphisms (SNPs) of the nuclear receptor of Rev-erbα (NR1D1) and the diagnosis of MDD (Kishi et al., 2008). A subsequent study by the same research group confirmed these preliminary results as it failed to find any association between six tagging SNPs in CLOCK gene and MDD (Kishi et al., 2009). In contrast, the C allele in SNP rs2287161 of CRY1 gene was found to be more frequent in MDD subjects than in healthy controls, while the G allele in SNP rs11123857 of Neuronal PAS domain-containing protein 2 (NPAS2) gene was found to be more commonly associated with MDD patients than controls (Soria et al., 2010). NPAS2 is a transcriptional factor that acts similarly to CLOCK protein (Soria et al., 2010). Another research group found the SNP rs10997875 of sirtuin 1 (SIRT1) gene to be associated with the diagnosis of MDD. SIRT1 is an enzyme which regulates clock gene transcription in response to stress and aging (Kishi et al, 2010). In addition, definite haplotypes of the ubiquitin-specific peptidase 46 (USP46) gene have been found to be more frequent in subjects affected by MDD than in healthy controls (Fukuo et al., 2011). This protein is of particular interest because USP46 mutant mice have been found to have abnormalities in circadian behavioural rhythms (Fukuo et al., 2011). In contrast, a study by the same Japanese research group failed to find any association between CLOCK gene variants and MDD (Kishi et al. 2011) and these results were confirmed by a more recent research (Crisafulli et al., 2013). Similarly, a subsequent study did not find the polymorphisms of CK1ε to be associated with a diagnosis of MDD (Matsunaga et al., 2012). Another research group measured the expression of RNA of different clock genes both in the brain of dead patients with MDD and healthy controls, and cyclic patterns were found to be much weaker in depressed patients than in controls as a consequence of shifted peak timing and probably disrupted phase relationships between the single circadian genes (Li et al., 2013a). Similar results were reported by another research that found disrupted diurnal rhythmic expression of clock genes such as PER, CRY, BMAL1, NPAS2 in subjects affected by MDD than in healthy controls (Li et al., 2013b). Furthermore, a study found

that MDD cases had higher frequency of the C allele in rs2287161 of CRY1 and of the T allele in rs738499 of Thyrotroph embryonic factor (TEF) than healthy controls (Hua et al., 2014). Of note, TEF is a clock-related gene that was found to contribute to the onset of sleep disturbances and mood symptoms in Parkinson disease (Hua et al., 2014). In contrast, a large-sample size study failed to find significant evidence for an association between MDD and different SNPs of both a core (n=21) and expanded (n=323) list of circadian genes (Byrne et al., 2014). In a more recent study the influence of gender and glucocorticoids on clock gene expression was hypothesized, and an association between SNP rs228697 of Per3 gene and MDD was reported in females, while between SNP rs1801260 of CLOCK gene and MDD in males (Shi et al., 2016). Finally, in a large Finnish sample MDD was found to be associated with the following SNPs: rs2292910 in CRY2, rs7123390 in CRY2 and rs 1488864 in PRKCDBP (Protein Kinase C Delta Binding Protein) (Kovanen et al., 2017). Of note PRKCDBP regulates the quantity of PER2 and CRY2 by reducing their metabolic stability (Kovanen et al., 2017).

Most of association studies failed to find significant results between SNPs of clock genes and MDD, while abnormalities in the expression of these genes have been reported for different genes (Li et al., 2013b) in depressed subjects versus healthy controls. This result may be explained by the fact that alterations in the expression of clock genes might arise by epigenetic regulators which in turn are strongly influenced by environmental and lifestyle factors (e.g. pollution), hormones and inflammation (Romano et al., 2017). It is thought that irregular lifestyle of predisposed subjects ultimately determines deficit in hippocampus neurogenesis by the mediator role of internal clock (Abrecht, 2017). One exception is represented by SNP rs2287161 of CRY1 which might confer a higher susceptibility to circadian dysregulation (e.g. early or delayed sleep phase) (Patke et al., 2017) and MDD. One study reporting this association has an intermediate quality, while the other a low one; the reported effect sizes (d) are similar: 0.23 and 0.31 respectively (small/medium effect size) (Soria et al., 2010; Hua et al., 2014). Of note, loss of CRY1 gene in mice resulted in a

shortening of circadian cycle independently from light (Xu et al., 2015). If we consider published data about this topic for other mood disorders, it is surprising that few researches investigated the role of clock genes in the etiology of seasonal affective disorder (both unipolar and bipolar one). One of the best quality paper reported a specific polymorphism of NPAS2 gene (471 Leu/Ser) to be more frequently associated to the diagnosis of seasonal affective disorder (Johansson et al., 2003). This finding has not been subsequently replicated, and with regard to major depressive disorder 2 (Byrne et al., 2014; Shi et al., 2016) out of three association studies failed to find an association between polymorphisms of NPAS2 and depressive illness. In contrast, more data have been published with regard to bipolar disorder; of note, polymorphisms of the gene of Aryl Hydrocarbon Receptor Nuclear Translocator Like Protein (ARNTL) and CRY2 would seem to increase susceptibility to bipolar illness or propensity to lithium response, while variants of Per3 have been associated with severe forms of bipolar disorder (Abreu and Bragança, 2015). It is interesting to notice that polimorphisms of CRY1 would seem to be more associated with a diagnosis of MDD, and variants of CRY2 with bipolar disorder. Previous research has demonstrated that dysregulation of CRY1 causes early sleep phase (typical of MDD), while abnormalities in the expression of CRY2 provoke delayed sleep phase (typical of bipolar disorder) (Okamura et al., 1999).

Finally, we have to consider that most of the published papers on the topic show bias as a prevalence of Asian ethnicity or not blinded conditions of laboratory experiments with respect to subjects' conditions (healthy controls or MDD). These factors. together with the heterogeneity of studied polymorphisms. prevented form performing a meta-analysis of the available results. In addition. the samples of depressed patients in the different studies are extremely heterogeneous: in some cases first-episode major depressive patients have been selected (Li et al., 2013b), in other cases subjects with a major depressive episode of different severity or assessed with different diagnostic tools. For sure future research should focus on epigenetic aspects (e.g. methylation or microRNA) or genome-wide studies to get a better idea about the role of clock genes in MDD. If

the role of clock genes will be identified as relevant for at least specific subgroups of patients, new therapeutic strategies such as chronotherapeutics or social rhythm therapies will be decisive in ameliorating outcome of these subjects .

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Contributors

Dr Buoli thought about the topic of the article, calculated the effect sizes and contributed to write the review

Drs Grassi, Serati, Pergoli and Cantone contributed to write the manuscript

Professors Altamura and Bollati revised the manuscript

Role of the Funding Source

No funding sources were received to prepare the present manuscript

Conflict of interest

Prof. Altamura has served as a consultant or on Advisory Boards for Roche, Merck, Astra Zeneca, Bristol Myers Squibb, Janssen/Cilag and Lundbeck

Dr Buoli has served as Lundbeck consultant

Drs Serati, Grassi, Pergoli, Cantone and Prof. Bollati do not have any conflict of interest to declare

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Figure 1. Prisma Diagram for systematic reviews

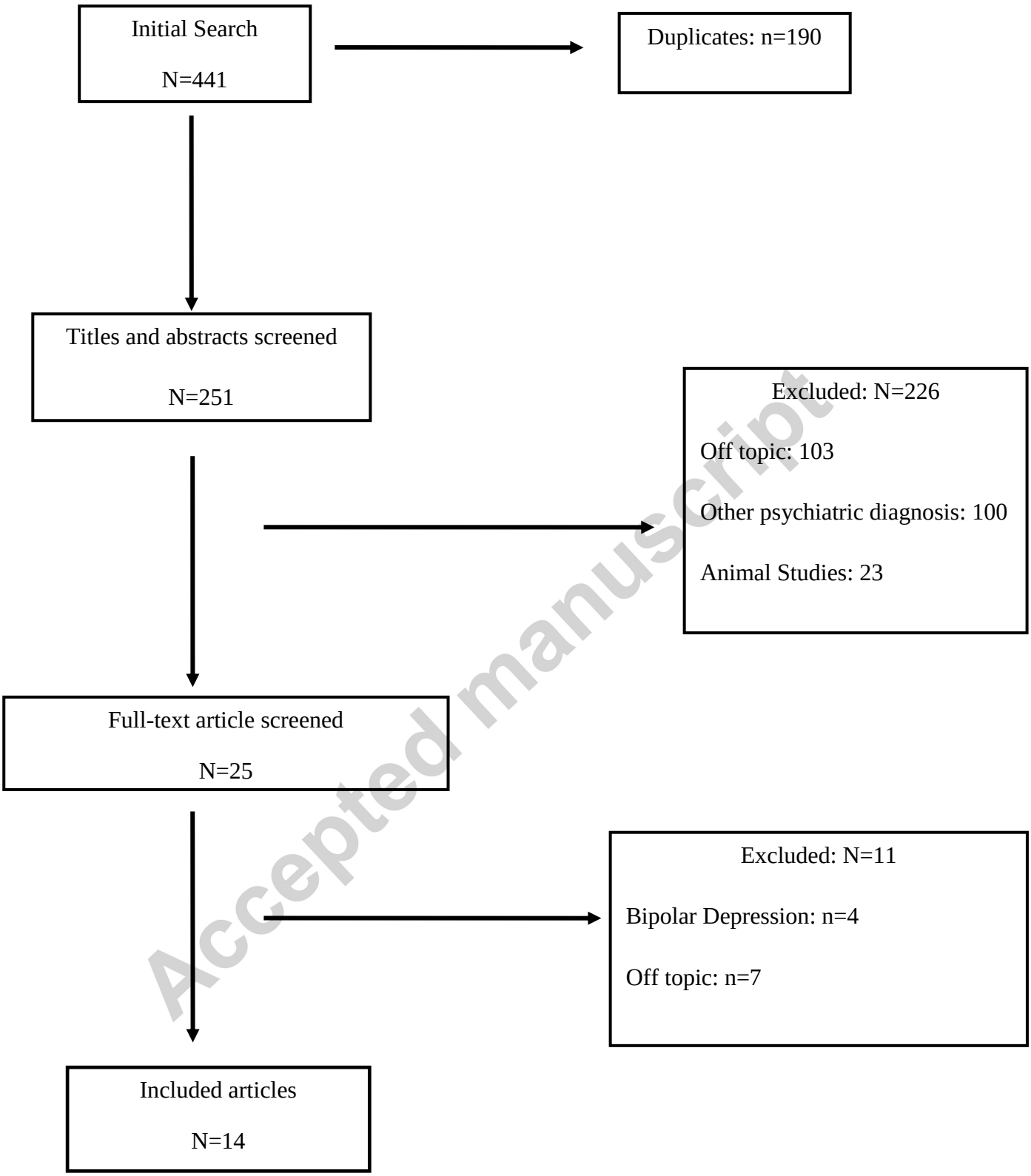

Table 1. Clock Genes and Major Depressive Disorder (MDD)

Study	Site	Quality Global Rating	Genes	Sample (N)	Primary Outcomes	Effect size (d)
Kishi al., 2008 (association study)	Japan	3	NR1D1	682 MDD: 322 HC: 360 (all Asians)	Frequency of A allele in SNP rs939347 in MDD subjects versus healthy controls	N.S. 0.02
					Frequency of G allele in SNP rs2071427 in MDD subjects versus healthy controls	N.S. 0.03
					Frequency of A allele in SNP rs3744805 in MDD subjects versus healthy controls	N.S. 0.02
Kishi et al., 2009 (association study)	Japan	3	CLOCK	1119 MDD: 324 HC: 795 (all Asians)	Frequency of G allele in SNP rs11939815 in MDD subjects versus healthy controls	N.S. 0.06
					Frequency of A allele in SNP rs11931061 in MDD subjects versus healthy controls	N.S. 0.08
					Frequency of A allele in SNP rs11133385 in MDD subjects versus healthy controls	N.S. 0.04
					Frequency of G allele in SNP rs3736544 in MDD subjects versus healthy controls	N.S. 0.06
					Frequency of T allele in SNP rs1801260 in MDD subjects versus healthy controls	N.S. <0.01
					Frequency of T allele in SNP rs3749474 in MDD subjects versus healthy controls	N.S. 0.03
Soria et al., 2010 (association study)	Catalonia (Spain)	2	CRY1 NPAS2	775 MDD: 335 HC: 440 (all Caucasians)	Frequency of C allele in SNP rs2287161 of CRY1 in MDD subjects versus healthy controls	0.23
					Frequency of G allele in SNP rs11123857 of NPAS2 in MDD subjects versus healthy controls	0.23
Kishi et al., 2010 (association study)	Japan	3	SIRT1	1216 MDD: 450 HC: 766 (all Asians)	Frequency of T allele in SNP rs10997875 in MDD subjects versus healthy controls	0.18

Fukuo et al., 2011 (association study)	Japan	3	USP46	1224 MDD: 432 HC: 792 (all Asians)	A-A-C haplotype in MDD patients versus healthy controls	0.23
					G-A-A-C haplotype in MDD patients versus healthy controls	0.20
Kishi et al., 2011 (association study)	Japan	3	CLOCK	1028 MDD: 139 HC: 889 (all Asians)	Frequency of G allele in SNP rs3736544 in MDD subjects versus healthy controls	N.S. 0.1
					Frequency of T allele in SNP rs1801260 in MDD subjects versus healthy controls	N.S. 0.04
					Frequency of T allele in SNP rs3749474 in MDD subjects versus healthy controls	N.S. 0.03
Matsunaga et al., 2012 (association study)	Japan	3	CSNK1D* CSNK1E*	2164 MDD: 452 HC: 1712 (all Asians)	Frequency of T allele in SNP rs4789846 of CSNK1D gene in MDD subjects versus healthy controls	N.S. 0.09
					Frequency of C allele in SNP rs135745 of CSNK1E gene in MDD subjects versus healthy controls	N.S. 0.09
Crisafulli et al., 2013 (association study)	Genetic analyses conducted in Italy, but sample from Korea	3	ABCB1, ABCB4 TAP2, CLOCK CLPX1, CLPX2, SYN2, NRG1, 5HTR1A, GPRIN2	315 MDD: 145 HC: 170 (all Koreans)	Several SNPs	None was statistically significant

Li et al., 2013a (expression study)	United States of America	1	Different Including BMAL1, PER1-2-3, NR1D1, DBP, BHLHE40, BHLHE41	89 MDD: 34 (33 Caucasians, 1 Asian) HC: 55 (50 Caucasians, 2 Asians, 2 African Americans, 1 Pacific Islander)	Deviations of the predicted time of death according to clock gene transcription in MDD patients versus controls (indirect measure of the intensity of cyclic patterns and expressions of clock genes)	0.13
Li et al., 2013b (expression study)	China	2	Expression of PER1, PER2, PER3, CRY1, BMAL1, NPAS2, GSK-3β	24 MDD: 12 HC: 12 (all Chinese)	Expression of PER1 in MDD subjects versus healthy controls	1.6
					Expression of PER2 in MDD subjects versus healthy controls	0.20
					Expression of PER3 in MDD subjects versus healthy controls	0.51
					Expression of CRY1 in MDD subjects versus healthy controls	1.3
					Expression of BMAL1 in MDD subjects versus healthy controls	0.23
					Expression of NPAS2 in MDD subjects versus healthy controls	1.6
					Expression of GSK-3β in MDD subjects versus healthy controls	2.6
Hua et al., 2014 (association study)	China	3	CRY1, CRY2, TEF	590 MDD: 105 HC: 485 (all Chinese)	Frequency of C allele in SNP rs2287161 of CRY1 gene in MDD subjects versus healthy controls	0.31
					Frequency of A allele in SNP rs10838524 of CRY2 gene in MDD subjects versus healthy controls	N.S. 0.20
					Frequency of T allele in SNP rs738499 of TEF gene in MDD subjects versus healthy controls	0.44

Byrne et al., 2014 (association study)	Analyses performed in Australia, but cases from around the world (Psychiatric Genomics Consortium)	2	Numerous circadian genes including CRY2, CSNK1D, CSNK1E, DBP, NPAS2, PER 1-2-3, NR1D1	18759 MDD: 9240 HC: 9519 (all Caucasians)	Several SNPs	None was statistically significant
Shi et al., 2016 (association study)	United States of America	2	ARNTL, CLOCK, NPAS2, PER3	1368 MDD: 592 HC: 776 (all Caucasians)	Frequency of minor allele in SNP rs70965440 of ARNTL gene in MDD subjects versus healthy controls	N.S. 0.06
					Frequency of minor allele in SNP rs1801260 of CLOCK gene in MDD subjects versus healthy controls	N.S. 0.07 Males: 0.24
					Frequency of minor allele in SNP rs4851377 of NPAS2 gene in MDD subjects versus healthy controls	N.S. 0.1
					Frequency of minor allele in SNP rs34705978 of NPAS2 gene in MDD subjects versus healthy controls	N.S. 0.07
					Frequency of minor allele in SNP rs228697 of PER3 gene in MDD subjects versus healthy controls	0.15 Females: 0.13 Males: N.S. 0.12
					Frequency of minor allele in SNP rs17031614 of PER3 gene in MDD subjects versus healthy controls	0.13
Kovanen et al., 2017 (association study)	Finland	2	CRY2, PRKCDBP	4537 MDD: 383 HC: 4154 (all Finnish)	Frequency of minor allele in SNP rs1488864 of PRKCDBP gene in MDD subjects versus healthy controls	0.25
					Frequency of minor allele in SNP rs7123390 of CRY2 gene in MDD subjects versus healthy controls	0.14
					Frequency of minor allele in SNP rs2292910 of CRY2 gene in MDD subjects versus healthy controls	0.14

Legend:

ABCB1: ATP Binding Cassette Subfamily B Member 1

ABCB4: ATP Binding Cassette Subfamily B Member 4

ARNTL: Aryl Hydrocarbon Receptor Nuclear Translocator Like Protein

BHLHE40: Basic Helix-Loop-Helix Family Member E40

BHLHE41: Basic Helix-Loop-Helix Family Member E41

BMAL1: Brain and Muscle ARNTL Protein-1

CLOCK: Circadian Locomotor Output Cycles Kaput

CLPX1: Caseinolytic Mitochondrial Matrix Peptidase Chaperone Subunit 1

CLPX2: Caseinolytic Mitochondrial Matrix Peptidase Chaperone Subunit 2

CRY1: Cryptochrome 1

CRY2: Cryptochrome 2

CSNK1D: Casein Kinase 1 Delta

CSNK1E: Casein Kinase 1 Epsilon

d: Cohen's d effect size

DBP: Albumin D Box-Binding Protein

GPRIN2: G Protein Regulated Inducer Of Neurite Outgrowth 2

HC: healthy controls

MDD: Major Depressive Disorder

N: number

NPAS2: Neuronal PAS domain-containing protein 2

NR1D1: Nuclear receptor of Rev-erbα

NRG1: Neuroregulin1

N.S: not statistically significant

PER 1-2-3: Period 1-2-3

PRKCDBP: protein kinase C delta binding protein

SIRT1: Sirtuin1

SNP: single nucleotide polymorphism

SYN2: Synapsin 2

TAP2: Antigen Peptide Transporter 2

TEF: Thyrotroph Embryonic Factor

USP46: Ubiquitin-Specific Peptidase

5HTR1A: Serotonin Receptor 1A

*The most statistically significant SNPs have been reported

Global rating (Effective Public Health Practice Project) was performed according to these criteria:

1) Selection Bias (sample size power and number of subjects who agreed to participate into the study)

2) Study Design (randomized versus non-randomized trials)

3) Confounders (Yes/No)

4) Blinding (Yes/No)

5) Data collection methods (self reported data, observations by investigators or medical records)

6) Presence of description of numbers and reasons for withdrawals and drop-outs

Case reports and case series have not been included

Rate:

1=strong (no weak ratings according to above criteria)

2= moderate (one weak ranting according to above criteria)

3= weak (two or more weak ratings according to above criteria)

Highlights

- Clock genes are thought to be involved in circadian abnormalities of Major Depressive Disorder
- Abnormalities in the expression of clock genes have been reported in depressed subjects
- SNP rs2287161 of CRY1 might confer a higher susceptibility to circadian dysregulation in Major Depression
- Lifestyles, hormones or pollution are hypothesized to regulate the expression of clock genes of depressed patients