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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Genetic endophenotypes for insomnia of major depressive disorder and treatment-induced insomnia

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Abstract

Major depressive disorder (MDD) is primarily hinged on the presence of either low mood and/or anhedonia to previously pleasurable events for a minimum of 2 weeks. Other clinical features that characterize MDD include disturbances in sleep, appetite, concentration and thoughts. The combination of any/both of the primary MDD symptoms as well as any four of the other clinical features has been referred to as MDD. The challenge for replicating gene association findings with phenotypes of MDD as well as its treatment outcome is putatively due to stratification of MDD patients. Likelihood for replication of gene association findings is hypothesized with specificity in symptoms profile (homogenous clusters of symptom/individual symptoms) evaluated. The current review elucidates the genetic factors that have been associated with insomnia symptom of MDD phenotype, insomnia symptom as a constellation of neuro-vegetative cluster of MDD symptom, insomnia symptom of MDD as an individual entity and insomnia feature of treatment outcome. Homozygous CC genotype of 3111T/C, *GSK3B*-AT/TT genotype of rs33458 and haplotype of *TPH1* 218A/C were associated with insomnia symptom of MDD. Insomnia symptom of MDD was not resolved in patients with the A/A genotype of *HTR2A*-rs6311 when treated with SSRI. Homozygous short (SS) genotype-*HTTLPR,* GG genotype of *HTR2A*-rs6311 and CC genotype of *HTR2A*-rs6313 were associated with AD treatment-induced insomnia, while val/met genotype of *BDNF*-rs6265 and the TT genotype of *GSK-3beta*-rs5443 reduced it. Dearth of association studies may remain the bane for the identification of robust genetic endophenotypes in line with findings for genotypes of *HTR2A*-rs6311.

Keywords Endophenotype · Genetic polymorphism · Major depressive disorder · SSRI · Antidepressants · Insomnia

Introduction

Major depressive disorders (MDD) are the fourth largest global disease burden affecting over 4% of adults globally (Ferrari et al. 2013). MDD is defined as at least 2 weeks of low mood and/or loss of interest in addition to a combination of disturbances in appetite, sleep, psychomotor agitation or retardation, lethargy, diminished decision-making ability as well as feeling of worthlessness, poor concentration or suicidal ideation features (American Psychiatric Association 2013). Impairment in social, occupational and general functioning is also characteristically associated with depression (American Psychiatric Association 2013). Currently, evaluations of symptom severity and its associated changes during treatment are done using validated instruments. A major challenge in polythetic ailment such as MDD has been in the array of symptoms, some of which are polar opposites of one another, which could potentially contribute in making such a diagnosis. Such diagnostic heterogeneity is a key limiting factor for the evaluation of etiological as well as predictive factors for MDD and its treatment outcome (Trivedi et al. 2016; Trivedi 2013; Kapur et al. 2012; Morgan and Gartlehner 2011; Cipriani et al. 2005, 2009; Krueger and Bezdjian 2009; Olbert et al. 2014; Strauss and Smith 2009; Westen et al. 2004).

Different analytical approaches have indicated that clinical features of MDD can be categorized into three clusters,

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thus suggesting a modest degree of heterogeneity of symptoms. A study of 132 Japanese patients utilized the factor analysis approach to define three symptom clusters, namely: dysphoria, retardation and vegetative symptoms as major symptom categories for MDD. Sadness, pessimism and suicidal thoughts constituted the dysphoria cluster of MDD symptoms. The retardation cluster of MDD symptoms which comprised of lassitude, inability to feel, apparent sadness, and concentration difficulties while reduced sleep, reduced appetite as well as increased inner tension were categorized as vegetative cluster of symptoms (Suzuki et al. 2005; Takahashi et al. 2017). A five-cluster symptom classification of MDD features had also been reported in the literature. The clusters included: (1) "typical MDD", characterized by common HAMD17 symptom profile with baseline mean (SD) HAMD-17 score of 19.9 (3.59). (2) "Sleep/sexual/somatic" cluster, characterized by higher scores for items of general somatic symptoms, genital symptoms as well as early, middle and late insomnia, symptoms on the HAMD17 scale. (3) "Lack of insight" cluster, characterized by higher scores for the insight item on the HAMD17 scale. (4) "Gastrointestinal/weight loss", cluster characterized by higher scores in: gastrointestinal symptoms and weight loss items on the HAMD17 scale. (5) "Mild MDD" cluster is characterized with very low severity of MDD symptomatology [baseline mean (SD) HAM-D 17 score of 11.3 (3.38)] (Schacht et al. 2014). Beneficial treatment outcome for one component of the cluster may be masked by a "no effect" outcome on other cluster members and hence masking the opportunity to identify novel factors associated with better treatment outcome for that specific symptoms (Chekroud et al. 2017; Fried and Nesse 2015; Olbert et al. 2014). Focus on evaluating the association between potential genetic factors and individual or homogenous cluster of MDD symptoms, rather than the entire constellation of heterogeneous MDD symptoms, could improve diagnostic accuracy and treatment outcomes (Chekroud et al. 2017).

There is sufficient evidence that selective serotonin reuptake inhibitors (SSRIs) and other antidepressants (AD) have varying success against different symptom clusters (Chekroud et al. 2017). Low mood and cognitive challenges associated with MDD appear to be better resolved by SSRI (Higuchi et al. 2008; Uher et al. 2009a) while the neurovegetative cluster of symptoms, which is chiefly characterized by insomnia, is best resolved with nortriptyline, a tricyclic antidepressant (TCA) (Uher et al. 2009a). Insomnia is a neurovegetative feature of MDD that is reported to predate, persist and herald the recurrence of depression (Murata et al. 2013). Worsening of insomnia following SSRI treatment in some patients and not others has also been reported; a clear manifestation of inter-individual difference (Morehouse et al. 2011; Murata et al. 2013; Thase et al. 2010). In fact, insomnia has been reported by patients as one of the key reasons for non-compliance to SSRI treatment (Ratcliffe et al. 2014; Garfield et al. 2014; Laje et al. 2009; Uher et al. 2009b). In the pharmacological treatment of depression, compliance to treatment in terms of dose and schedule is very vital to achieve the desired treatment outcome (Jiang et al. 2015; Popp et al. 2006). Different phenotypes such as: insomnia symptom associated with MDD diagnosis, insomnia symptoms of MDD diagnosis resolving following SSRI treatment and SSRI treatment-induced insomnia are appropriate phenotype for determination of endophenotypes related to insomnia. Endophenotype is a reliable, heritable and measurable biological feature that reflects the function of a biological system (Tan et al. 2008; Wong et al. 2011). The actual biological phenomena underlying a disease and its associated features are more closely correlated with endophenotypes than clinical phenotypes (Tan et al. 2008; Wong et al. 2011).

Genetic differences have been implicated regarding inter-individual variations in susceptibility for MDD and its treatment outcome (Murata et al. 2013; Serretti et al. 2005). Identifying the genetic factors that predispose to symptoms such as insomnia in MDD patients and persistence or worsening of the insomnia following SSRI treatment can contribute immensely to achieving the goals of personalised medicine (Gorzalka et al. 2001; Murphy et al. 2003).

The current paper focuses on reviewing the key genetic factors that have shown an association with insomnia as a symptom of MDD, as a feature of the neurovegetative cluster of MDD symptom, as well as a feature of treatment outcome, potentially paving way for endophenotype identification. A schematic diagram describing the insomnia literature reviewed in the current study for the identification of genetic endophenotypes is represented in Fig. 1.

Methods

We searched for articles reporting human studies, published in English language, without any restriction on ethnicity or race, using search words such as pharmacogenetics, pharmacogenomics, insomnia, anhedonia, adverse effects, depression, MDD, *HTR1A, HTR2A, HTTLPR, rs23351, BDNF, TPH, GSK-3β* and *CLOCK*. The search was restricted to articles published from the year 2000 to July 2018. The step–by-step approach carried out in identifying the appropriate literature to be reviewed in this study is presented in Fig. 2. The flow of literature search is presented in Fig. 2.

Selection of publication

A total of 4506 articles and conference proceedings were identified by the search strategy. A detailed search for all or some of the following: the articles titles, keywords or

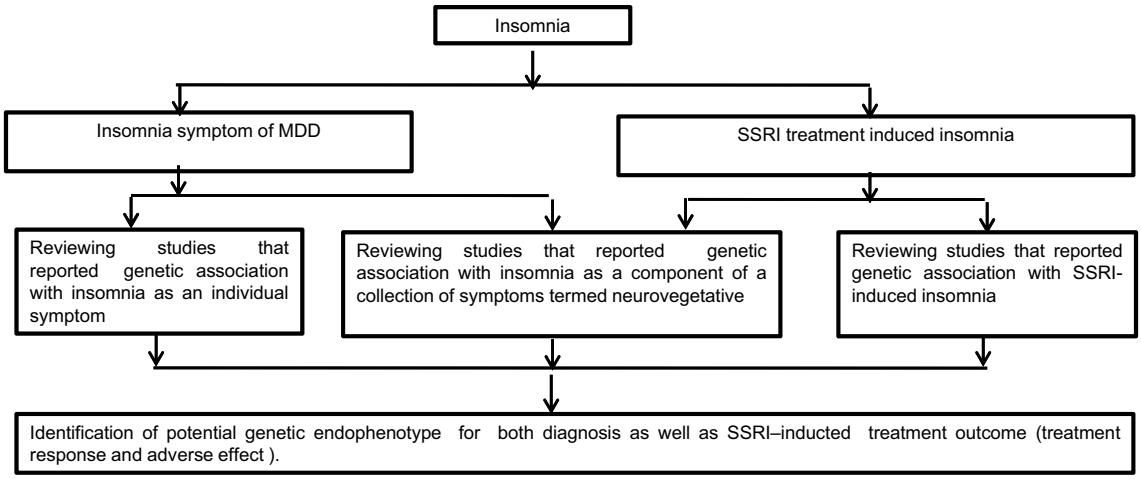

Fig. 1 Schematic diagram describing the insomnia literature reviewed in the current study for identification of genetic endophenotypes

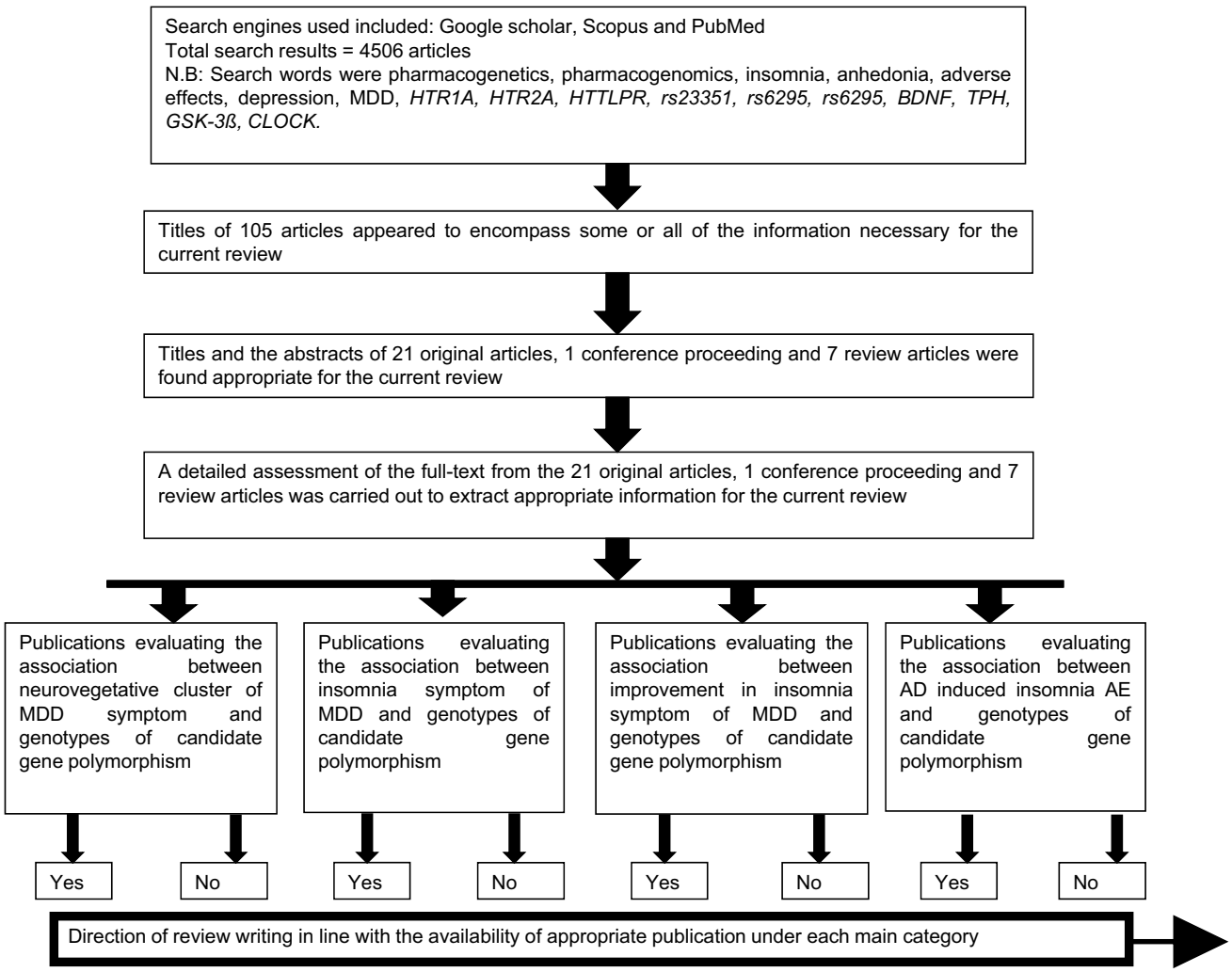

Fig. 2 Flow chart describing the procedures as well as the flow of write-up for each candidate gene. *AD* antidepressant, *MDD* major depressive disease, *AE* = adverse effect, *Yes* there are publication for this category of evaluation in the data base, *No* there are no publications for this category of evaluation in the data base

abstracts, in that order, found 105 articles potentially relevant to this review. The titles and abstracts of these 105 articles were evaluated closely and only 22 original articles were identified as those which reported studies with relevant information for the current review (Table 1). The full-text of these articles was assessed and appropriate data were retrieved and reviewed. There were six genes that were discovered to have been evaluated for association with at least one of the following features of insomnia either as an individual feature, as a component of MDD phenotype, as a component of the neurovegetative cluster of MDD symptoms, or as a component of AD treatment outcome.

Single nucleotide polymorphisms associated with insomnia of MDD and its treatment

Serotonin transporter gene polymorphism and SSRI-induced insomnia

The serotonin transporter gene located on Chromosome 17q11.1-q12, *SLC6A4* contains a number of polymorphisms. Some common polymorphisms in the *SLC6A4* gene include 5*HTTLPR* polymorphism in the promoter region, *HTTVNTR* in the intron and rs25531 polymorphism, which is in linkage disequilibrium with *HTTLPR* (Heils et al. 1996; Lencz and Malhotra 2008; Lesch et al. 1996).

An evaluation of the association between neurovegetative cluster of MDD symptoms which include insomnia and genotypes of the 5*HTTLPR* polymorphism among 132 Japanese MDD patients failed the test of statistical significance (Kamata et al. 2011). Pharmacogenetic evaluation for association of the serotonin transporter polymorphisms (5*HTTLPR* and *HTTVNTR*) with treatment response for neurovegetative symptom cluster in Japanese unipolar MDD patients also did not pass the test of statistical significance even after adjusting for severity of depression (Takahashi et al. 2017). The failure to analyze the data in line with the type of antidepressant used ($n = 80$, milnacipran and $n = 80$, fluvoxamine) may have accounted for the failure of the test of statistical significance reported in the pharmacogenetic study.

Increased prevalence and severity of a general adverse effect cluster of symptom (encompassing all types of AE symptoms) in MDD patients on paroxetine treatment were reported to be significantly associated with homozygous short allele S/S of 5*HTTLPR* polymorphism (Murphy et al. 2004). A trend for higher incidence of insomnia, somnolence, agitation, anxiety and asthenia, with SS and SL genotypes of 5*HTTLPR* polymorphism among Caucasian patients has also been reported (Smits et al. 2007). There is a report of association for 5*HTTLPR*-SS genotype with increased risk for SSRI-induced insomnia (Perlis et al. 2003). Nevertheless, there are no studies that evaluated the role of serotonin transporter gene polymorphisms with insomnia feature of MDD as an individual symptom as well as its resolution following AD treatment.

Expression of the encoded serotonin transporter protein is highest among patients with the long (L) allele of 5*HTTLPR* polymorphism (Lam et al. 2013). The difference in expression of the serotonin transporter protein (5-HTT) is commonly projected as the reason for difference in treatment with antidepressants. Persistently high level of serotonin in the synaptic cleft of patients with the low expressing SS genotypes of 5*HTTLPR* polymorphism is believed to be responsible for SSRI-induced insomnia (Wilson and Argyropoulos 2005).

Serotonin 2A receptor gene (*HTR2A*) polymorphism and SSRI-induced insomnia

The *HTR2A* gene in humans, located on chromosome 13 (13q14–21), is 20kbp in size and consists of exons separated by two introns only (Chen et al. 1992). The *HTR2A*-rs6311 polymorphism in the promoter region and the *HTR2A*-rs6313 polymorphism in the non-coding region of the *HTR2A* gene were reportedly in complete linkage disequilibrium (Arranz et al. 1998; Erdmann et al. 1996; Spurlock et al. 1998). The T allele of *HTR2A*-rs6313 polymorphism corresponded to the high-activity mutant A allele of *HTR2A*-rs6311 polymorphism (Lencz and Malhotra 2008).

Increased reports of neuro-vegetative cluster of MDD symptoms which include insomnia had been observed in patients with the A-allele of *HTR2A*-rs6311 polymorphism (Kamata et al. 2011). An evaluation of the association of genotypes of *HTR2A*-rs6311 polymorphism with treatment response for the neuro-vegetative cluster of MDD symptoms failed to pass the test of statistical significance irrespective of the level of severity of symptoms (Takahashi et al. 2017). The *CC* genotype and the C-allele of *HTR2A*-rs6313 polymorphism were discovered to be significantly associated with the severity of insomnia symptom of MDD and not its treatment response in another evaluation (Kato et al. 2009). The results remained the same after re-analyzing the data based on a patient's ethnicity (Japanese or Italian) and adjusting the association evaluations with socio-demographic results (Kato et al. 2009). An evaluation of the association between the genotypes of *HTR2A*-rs6311 polymorphism and the response of insomnia symptom of MDD to AD treatment with citalopram was not statistically significant (Choi et al. 2005). In another study, the resolution of insomnia symptom of MDD was significantly associated with the AA genotype of *HTR2A*-rs6311 and not the GG genotype following treatment with mirtazapine (Kang et al. 2007). The precise mechanism through which genotypes of *HTR2A*-rs6311 polymorphism get involved in mirtazapine action for modulating insomnia symptoms of MDD in some patients and not others was not clear. This is especially

Table 1 List of articles reviewed in the current study

Gene/SNP	Reference	Sample size	Characteristics	Remarks
TPH	Myung et al. (2012)	$N=241$	1. SSRIs were prescribed to 153 patients (88 fluoxetine, 32 paroxetine, 33 sertraline), SNRIs to 25 patients (7 milnacipran, 18 venlafaxine), NRI (nortriptyline) to 15 patients and NaSSa (mirtazapine) 2. At least 19 years of age	1. Unrelated Korean Unipolar MDD patients 2. Association evaluation was for individual adverse effect example insomnia
	Kamata et al. (2011)	$N=132$	1. MDD patients, 1. $\pm$ 12.6 years	1. Japanese 2. Evaluating vegetative-symptom cluster of MDD, which includes insomnia 3. Case–control study
	Du et al. (2001)	$N=135$(MDD), 196 (controls)	1. MDD 2. 40.08 $\pm$ 9.43 years	1. Caucasian 2. Case–control study
BDNF	Zou et al. (2010)	$N=305$	1. Fluoxetine 2. $\geq$ 18 years 3. MDD	Ethnic Chinese
	Tsai et al. (2003)	$N=152$	1. Fluoxetine 2. $\geq$ 18 years 3. MDD	Ethnic Chinese
	Choi et al. (2006)	$N=83$	1. Citalopram 2. $\geq$ 18 years 3. MDD	1. Koreans 2. MDD-insomnia
	Kang et al. (2007)	$N=243$	1. Mitrazapine medication. 2. MDD 3. Valine/valine-rs6265 = 48.8 $\pm$ 2.0 year 4. Valine/methionine-rs6265 = 51.6 $\pm$ 1.3 year 5. Methionine/methionine-rs6265 = 50.8 $\pm$ 2 year	1. Koreans 2. MDD-insomnia was evaluated at baseline and after 8 weeks of Mirtazapine treatment 3. Result was not significant
GN3-B	Keers et al. (2011)	N (escitalopram) = 460, $N=358$ (nortriptyline), (total study $N=795$)	1. Mean age 42.3 $\pm$ 11. 8 2. Escitalopram/nortriptyline	
	Costemale-Lacoste et al. (2018)	$N=432$ (but only 27 patients were genotyped)	1. MDD	1. METADAP cohort a 6-month prospective real-world treatment study in psychiatric settings 2. Case–control study

Table 1 (continued)

Gene/SNP	Reference	Sample size	Characteristics	Remarks
HTR2A	Murphy et al. (2003)	$N = 122$ (total study $N = 246$)	1. Patients were ≥ 65 years 2. Paroxetine	1. Conducted in USA (mainly Caucasian)
	Kato et al. (2006)	$N = 39$ (total study $N = 100$)	1. Paroxetine 2. Recurrent MDD diagnosis	1. Japanese patients 2. Association for patients on fluvoxamine failed the test of significance
	Kato et al. (2009)	N (Japanese) = 80, N (Italian) = 123 (total study $N = 246$)	1. Paroxetine/fluvoxamine = 57/146 2. MDD	1. Italian subsamples show statistically significant difference for severity of insomnia
	Kang et al. (2007)	$N = 101$	1. Mirtazapine 2. MDD 3. AA-*HTR2A* = 49.65 ± 15.39; GA-*HTR2A* = 50.77 ± 16.91; GG-*HTR2A* = 50.03 ± 14.55	Koreans
	Choi et al. (2006)	$N = 71$	1. Citalopram 2. MDD 3. 52.66 ± 15.66 years	Koreans
	Takahashi et al. (2017)	N (Fluvoxamine) = 80, N = (milnacipran) = 80; (total study $N = 160$)	1. 69 years 2.MDD 3. Fluvoxamine/milnacipran	1. Japanese
HTTLPR	Smits et al. (2007)	$N = 209$	1. 18–64 years 2. MDD patients 3. SSRI medication	1.Caucasians 2. The association was only a trend (not actually statistically significant)
	Murphy et al. (2004)	$N = 122$ (total study $N = 246$)	1. Patients were ≥ 65 years 2. Paroxetine	1. Conducted in USA (mainly Caucasian)
	Perlis et al. (2003)	37, (total study $N = 50$)	1. Fluoxetine 2. MDD 3. 18-65 years	1. Analysis was restricted to Caucasian-non latinos
	Kato et al. (2006)	Total study $N = 100$	1. Paroxetine and fluvoxamine 2. Recurrent MDD diagnosis	1. Japanese patients 2. Association for patients on SSRI failed the test of significance
	Takahashi et al. (2017)	N (Fluvoxamine) = 80, N = (milnacipran) = 80; (total study $N = 160$)	1. 69 years 2. MDD 3. Fluvoxamine/milnacipran	Japanese
	Kamata et al. (2011)	$N = 132$	1. MDD patients 2. ± 12.6 years	1. Japanese 2. Evaluating vegetative-symptom cluster of MDD, which includes insomnia 3. Case–control study

Table 1 (continued)

Gene/SNP	Reference	Sample size	Characteristics	Remarks
CLOCK	Serretti et al. (2005)	$N = 178$	1. Mean age = 52.6 ± 12.6 years 2. MDD/BD (90/88) 3. SSRIs (Fluvoxamine)	1. Caucasians
	Serretti et al. (2010)	$N = 100$	1. MDD 2. 18–60 years	1. Mexicans
	Utge et al. (2010)	N (MDD) = 384; N (control) = 1270	1. MDD	1. Caucasians 2. Case–control study
	Voinescu et al. (2009)	$N = 27$	1. 23–71 years 2. MDD	1. Caucasian 2.Case–control study 3. Association for insomnia was not observed

SNP single nucleotide polymorphism, *MDD* major depressive disorder, *SSRI* selective serotonin reuptake inhibitors, *SNRI* serotonin norepinephrine reuptake inhibitors, *NRI* norepinephrine reuptake inhibitors, *NaSSA* noradrenergic and specific serotonergic antidepressant, *Val* valine, *Met* methionine, *BDNF* brain-derived neurotrophic factors, *GN3-b* guanine nucleotide beta-3, *TPH* tryptophan hydroxylase gene, *HTR2A* serotonin 2A gene, *HTTLPR* serotonin transporter gene, *CLOCK* Circadian locomotor output cycles kaput

because mirtazapine has serotonin 2A receptor (5HTR2A) and histamine 1 (H1) blocking effect which collectively promotes sedation while the activation of 5HTR2A in the central nervous system promotes insomnia (Kang et al. 2007; Marek et al. 2003; Pullar et al. 2000; Landolt et al. 1999; De Boer 1996). The absence of an association between the improvement of insomnia symptom of MDD following SSRI treatment with genotypes of *HTR2A*-rs6311 downplays the genotypes' role in SSRI treatment response but not their role in the severity of the symptoms.

The most severe form of MDD was reported among patients with the *CC* genotype of *HTR2A*-rs6313 (Kato et al. 2009). In addition, patients with the *CC* genotype at the rs6313 position of the *HTR2A* had an increased risk for gastrointestinal upset, dizziness and insomnia (Murphy et al. 2003). However, patients treated with mirtrazepine, an antidepressant that blocks 5HTR2A receptors, did not exhibit any significant adverse effect irrespective of the presence of *CC* genotype of the *HTR2A* gene (Murphy et al. 2003). Thus, it is possible that the 5HTR2A receptor blocking activity of mirtrazepine eliminates any effect of the *CC* genotype of *HTR2A* gene that promotes the development of adverse effects including insomnia (Murphy et al. 2003). Patients on paroxetine who have the *GG-HTR2A*-rs6311 genotype were associated with higher incidence and severity of a generalized adverse effects phenotype (Kato et al. 2006). Thus, genotypes of *HTR2A*-rs6311, which are in linkage disequilibrium with genotypes of *HTR2A*-rs6313, have shown association with insomnia in different facets of MDD and its treatment; however, more studies are extremely needed to make possible the robust determination of endophenotype status of these genotypes.

The precise mechanism through which the *HTR2A*-rs6311 genotypes influence the development of adverse effects is expected to be similar to that of genotypes of *HTR2A*-rs6313, since they are in complete linkage disequilibrium. The high level of receptor protein expression exhibited by each of the mutant allele T for rs6313 and A for rs6311 may account for the role of the wild-type alleles (C-rs6313 and G-rs6311) in adverse effect (Murphy et al. 2003). The wild-type genotypes were associated with low expression of receptor protein, thus ensuring rapid activation of the entire receptors with generation of serotonergic neurotransmission vital for 5HTR2A activities (Polesskaya and Sokolov 2002).

PER3-circadian locomotor output cycles kaput (*CLOCK*) gene and STEI

The *CLOCK* gene is located in chromosome 4 and is a regulatory gene of the circadian rhythm (Steeves et al. 1999; Musiek and FitzGerald 2013). Period circadian regulator 2 and 3 (PER 2, 3) as well as cryptochrome circardian clock 1 (CRY) are coding regions in the CLOCK gene that have

been associated with numerous phenotypes including sleep abnormalities (Kripke et al. 2009; Patke et al. 2017; Soria et al. 2010; Viola et al. 2007). This *CLOCK* gene encodes proteins that are vital for transcriptional inhibition of the circadian regulatory gene and it is highly expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus, hippocampus, pyriform cortex and cerebellum following repeated administration of selective serotonin reuptake inhibitors (SSRI) (Johansson et al. 2003).

Eveningness in health and insomnia symptom of MDD has been significantly associated with the *CC* genotype of *CLOCK*-rs1801260 (T3111C), TIMELESS polymorphisms (TIMELESS-rs1082214) or its haplotype (rs7486220-rs1082214) (Katzenberg et al. 1998; Utge et al. 2010). There is a study that reported the absence of association between the insomnia symptom of MDD and genotype of *CLOCK*-rs1801260 as well as the presence of an association between the *CC* genotype of rs1801260 and the persistence of insomnia symptom in MDD patients treated with SSRI (Serretti et al. 2005). Nevertheless, the role of *CLOCK* gene polymorphism in determining AD-induced insomnia has not been reported in the literature. The definitive role of *CLOCK* gene polymorphism as an endophenotype marker can only be evaluated further following additional assessment with the entire facets of insomnia of MDD and its treatment outcome.

The mechanism through which this polymorphism modulates insomnia of MDD symptom or its persistence during treatment may putatively be associated with the enhanced expression of the CLOCK protein by the C-allele of rs1801260 polymorphism (Ozburn et al. 2016).

Brain-derived neurotrophic factor (*BDNF*) gene polymorphism and STEI

Several studies focusing on determining the association between *BDNF* gene polymorphism and sleep pattern among healthy volunteers, untreated and treated MDD patients have been conducted (Meerlo et al. 2009; Novati et al. 2008; Rechtschaffen et al. 1989; Zou et al. 2010). Evaluation of the association between genotypes of *BDNF*-rs6265 and the insomnia symptom of MDD diagnosis among 243 Korean patients failed the test of statistical significance (Kang et al. 2010). Korean MDD patients with the valine/methionine (val/met) genotype for the *BDNF*-rs6265 polymorphism, when treated with citalopram, had a statistically significant improvement in insomnia symptom of MDD (Choi et al. 2006). In a study involving152 ethnic Chinese patients that were treated with fluoxetine, the evaluation for association between improvement in insomnia symptom of MDD and genotypes of *BDNF*-rs6265 polymorphism was not statistically significant (Tsai et al. 2003). A similar result was obtained when the same evaluation for association was carried out among 243 Korean MDD patients treated with Mirtazapine (Kang et al. 2010). This suggests that the *BDNF*-rs6265 polymorphism plays a key role in citalopram (not fluoxetine or mirtazapine) treatment-related improvement of insomnia symptom of MDD. This may be attributable to the role of BDNF-rs6265 polymorphism in the synthesis of BDNF protein as well as in its optimal activity in promoting neurogenesis which was vital for the remission of depression symptoms including insomnia (Meerlo et al. 2009).

A pharmacogenetic assessment revealed a significantly reduced risk for the development of SSRI-induced insomnia among Chinese depressed patients treated with fluoxetine who had the Met allele (Val/Met: adjusted OR = 0.40, $p = 0.017$; Met/Met: adjusted OR = 0.32, $p = 0.010$; Val/Met + Met/Met: adjusted OR = 0.37, $p = 0.004$) (Zou et al. 2010). This is the same allele (Met) of *BDNF*-rs6265 that was associated with citalopram treatment response for the insomnia symptom of MDD. This polymorphism is putatively vital to both the resolution of insomnia symptom of MDD as well as to the reduced risk for SSRI treatment-induced insomnia.

The role of Met allele as a predictor of both resolution of insomnia symptom of MDD and as a protector against AD-induced insomnia lends credence to the potential role of genetic markers such as Met allele as endophenotype of MDD symptom and its treatment outcome.

Glycogene synthase kinase-3β (GSK-3b) polymorphisms and insomnia

One of the components of the molecular clock with serine threonine kinase activity is called glycogene synthase kinase-3β gene and has proven to have a number of polymorphisms such as rs6808874, rs6782799, rs334558 and rs2319398 (Keers et al. 2011).

An evaluation of the association between insomnia symptoms of MDD and the minor allele of *GSK-3β* rs334558 AT/TT was observed to be statistically significant in a multicentric, realworld observational cohort (Costemale-Lacoste et al. 2018). In the literature, the evaluation of the role of the *GSK-3β* rs334558 AT/TT in AD treatment response was not statistically significant (Costemale-Lacoste et al. 2018). A pharmacogenetic assessment revealed that the TT genotype of *GSK-3β*-rs5443 polymorphism was not significantly associated with SSRI treatment-induced insomnia (Keers et al. 2011). Thus, this AD-induced insomnia associated with genotypes of *GSK-3β*-rs5443 polymorphism is unlikely to be a manifestation of an improved serotonergic neurotransmission only.

Tryptophan hydroxylase gene polymorphism

The rate-limiting step in serotonin synthesis is catalyzed by tryptophan hydroxylase (TPH), which is either in TPH1 or TPH2 isoform, the latter being responsible for serotonin biosynthesis within the pineal gland (Hamon et al. 1981; Patel et al. 2004). Genetic polymorphisms have been identified within the *TPH* gene and they may play a role in modulating the rate of serotonin biosynthesis which is associated with inter-individual variation (Myung et al. 2012).

The evaluation of association between neurovegetative cluster of MDD symptoms and genotypes of the *TPH1* 218A/C, polymorphism among 132 Japanese MDD patients was not statistically significant (Kamata et al. 2011). An association study in homogeneous Chinese cohort of unipolar MDD patients revealed that *TPH1* haplotype G–G–C–C–G–G–G–C (rs7933505–rs211102–rs1799913–rs1800532–rs10488683–rs211105–rs17794760–rs172423) is strongly associated (uncorrected $p = 1.55e{-5}$, Bonferroni corrected $p = 6.21e{-5}$) with middle insomnia symptom of MDD and not the early or terminal insomnia symptoms (Myung et al. 2012). An earlier study for the evaluation of the association of insomnia symptom of MDD in a Caucasian cohort of 135 MDD patients with genotypes of TPH1-218A/C polymorphisms was not statistically significant (Du et al. 2001). The difference in the findings of these two studies reinforces the hypothesis that haplotype evaluation is more efficient for the identification of risk alleles compared to single gene's evaluation with phenotypes (Dawson et al. 2002; Niu et al. 2002; Yu and Schaid 2007; Zhang and Zhao 2006; Zhao et al. 2000). There are no studies in the literature that evaluated the association of TPH polymorphism with either a response to the treatment for insomnia symptoms of MDD or the antidepressant treatment-induced insomnia adverse effect.

Summary

Genotypes of serotonin transporter gene polymorphism (*HTTLPR*-SS), genotype of *HTR2A*-rs6311 and *HTR2A*-rs6313 are not found to be associated with treatment response to neurovegetative cluster of MDD symptom. Insomnia symptom of MDD has an association with *TPH1* haplotype GGCCGGGC, *AT/TT* of *GSK-3β*-rs33458, *CC* of *CLOCK*-rs1801260, TIMELESS-rs1082214, TIMELESS-rs7486220-rs1082214 haplotype and *CC* of *HTR2A*-rs6313 in the literature. The *AA* of *HTR2A*-rs6311 in patients treated with mirtazapine, val/met of BDNF-rs6265 in patients treated with citalopram and *CC* of CLOCK-rs1801260 in patients on fluvoxamine, were established to be associated with AD treatment outcome regarding the fate of insomnia symptom of MDD. Genotypes of *HTTLPR-SS*, *CC* genotype of *HTR2A*-rs6313 (which is in linkage disequilibrium with *GG* of *HTR2A*-rs6311), *CC* genotype of *CLOCK*- rs1801260, val/met genotype of *BDNF*- rs6265 and *TT* of *GSK-3β*-rs5443 were found to be associated with SSRI treatment-induced insomnia. Thus, the polymorphisms of *HTR2A*-rs6311 and *CLOCK*-rs1801260 have association with the insomnia symptom of MDD, its treatment response and treatment-induced insomnia adverse effect. Replication of association findings between candidate genes with phenotypes of specific symptom of MDD and its treatment response with/without treatment-induced adverse effect (of similar phenotype with the specific symptom) may identify appropriate endophenotype markers. This proves to be a vital step towards facilitating the attainment of the goal for the actualization of personalized medicine.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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