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Review Article

A systematic review on genome-wide association studies exploring comorbidity in bipolar disorder

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ABSTRACT

Background: The comorbidities associated with bipolar disorder (BD) can worsen patients' prognosis and increase economic costs to society. Currently, efforts are being made to identify new endophenotypes characterized by the presence of BD and another concomitant condition.

Methods: We performed a search on PubMed and GWAS catalog databases to find genome-wide association studies carried out on patients with BD with any other comorbid condition. We extracted the associated SNPs that attained statistical significance and listed them to appraise their potential to define new BD endophenotypes based on the presence of comorbidities.

Results: Six articles fulfilled the inclusion criteria, and all included only patients with BD type-I (BDI). The identified comorbid conditions were migraine, externalizing disorders and eating disorders. BDI with comorbid migraine was associated with rs1160720 in the *NBEA* gene. BDI with comorbid anorexia or bulimia nervosa was associated with rs4854912 and rs13100379 in the *SOX2-OT* gene. BDI with comorbid substance abuse was associated with rs1039002 in the *PDE10A* gene, rs12563333 upstream of the *MARK1* gene, and rs13220542 downstream of the *MAP3K7* gene. BDI with comorbid alcohol dependence and substance abuse was associated with rs2727943, which is located between *CNTN4* and *CNTN6*. However, such associations were not strong enough to replicate.

Limitations: The main limitations are the small size and poor description of the samples used in the included articles.

Conclusions: Some genes involved in neurotransmission, stress response, neurogenesis and synaptic plasticity may be associated with comorbid BDI. However, evidence is too weak to consider new endophenotypes in BDI.

1. Introduction

Bipolar disorder (BD) is a group of chronic, severe and heterogenic psychiatric disorders characterized by the presence of mood swings that range from depressive to manic phases. This diagnosis includes two subtypes: bipolar disorder I (BDI), which is characterized by the presence of at least one manic episode, and bipolar disorder II (BDII), where the presence of at least one hypomanic and one major disorder episode are required for its diagnosis (Carvalho et al., 2020; Grande et al., 2016). BD is a highly heritable condition with genetic contributions explaining approximately 80% of its variability (Gordovez and McMahon, 2020). In addition, environmental factors play a critical role (Aldinger and

Abbreviations: BD, Bipolar Disorder; BDI, Bipolar Disorder type I; BDII, Bipolar Disorder type II; BiGS, Bipolar Genetics Study; CBD, Comorbid Bipolar Disorder; CBDI, Comorbid Bipolar Disorder type I; CNTN4, Contactin-4; CNTN6, Contactin-6; DIGS, Diagnostic Interview for Genetic Studies; DSM-X-R, Diagnostic and Statistical Manual of Mental Disorder Version X Revised; GABA, Gamma aminobutyric acid; GAIN, Genetic Association Information Network; GWAS, Genome-wide association study; ICD-DCR, Schizophrenia and Affective Disorders Schedule – Lifetime version (SADS-L) and diagnosed according to ICD-10 diagnostic criteria; MAP3K7, Mitogen-Activated Protein Kinase Kinase Kinase 7; MARK1, MAP/Microtubule Affinity-Regulating Kinase 1; NBEA, Neurobeachin; NHS, National Health Service; RDC, Research Diagnostic Criteria; PDE10A, Phosphodiesterase 10A; SABP, Schizo-Affective Bipolar Disorder; SNP, Single nucleotide polymorphism; SOX2-OT, SRY-Box Transcription Factor 2 Overlapping Transcript; UCL, University College of London.

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Schulze, 2017). A recent genome-wide association study (GWAS) in a large sample identified common variants located in 30 genes that explain about 25% of its heritability. Findings from the same study indicate the existence of an extensive polygenic architecture of this psychiatric condition, suggesting that BDI is more genetically correlated with schizophrenia, whereas BDII is more strongly correlated to major depression disorder (McIntyre et al., 2020; Stahl et al., 2019). Classic linkage and candidate genes studies identified genes associated with BD but with little consistency (Gordovez and McMahon, 2020).

BD could be highly disruptive and negatively impacts on occupational status, social, and family functioning. In this sense, a considerable proportion of adult patients cannot perform their jobs (Judd et al., 2008) and may present cognitive impairment (Samamé, 2013; Solé et al., 2016). With regards to pediatric and adolescent patients, BD also negatively affects their social, academic and family functioning (Wagner and Dineen Wagner, 2004).

In addition, the course of the illness may be worsened by the high frequency of comorbidities, which is defined as the presence of a concurrent disease in addition to the main BD diagnosis. A considerable economic burden is associated with bipolar disorder (Cloutier et al., 2018; Ferrari et al., 2016), and this burden substantially increases with the presence of any other comorbid condition (Hirschfeld and Vornik, 2005; McElroy, 2004). The percentage of psychiatric comorbidities in BD has been reported as 31% of cases (Vieta et al., 2001). However, when considering any condition, the percentage of comorbidity increases to 96.3% (Sylvia et al., 2015). In this sense, presence of comorbidity in patients with BD is associated with an earlier onset, lower remission rates, increased number of depressive episodes and a greater risk of suicidal behavior (Goes, 2015; Popovic et al., 2015; Vieta et al., 2001). In addition, comorbid conditions may also interfere with an accurate diagnosis, hampering treatment prescription and therefore reducing life expectancy (Chang et al., 2011; Crump et al., 2013; McIntyre et al., 2008, 2004; Popovic et al., 2015; Sylvia et al., 2015).

Comorbidities in BD have been proposed to be potential indicators of distinct subtypes of BD (Potash et al., 2007). Therefore, efforts are being made to identify more homogeneous groups of comorbid bipolar disorder (CBD) patients' phenotypes that may help to ensure a more accurate diagnosis and facilitate the design of more tailored subtype-based treatments. In this regard, genetic studies are useful to identify the genetic overlap associated with comorbid conditions that may define new endophenotypes.

With the goal of better understanding the genetics underlying subgroups of patients with BD presenting with any other comorbid diagnosis, we conducted this systematic review 1) to review GWAS performed on patients with BD presenting any other comorbidity, 2) to identify those genes associated with the aforementioned group of patients, and 3) to evaluate their potential to define new endophenotypes of BD.

2. Methods

This systematic review was performed following the PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009).

2.1. Study selection and data extraction

We performed a PubMed search (https://www.ncbi.nlm.nih.gov/pubmed/) on June 23, 2020. The text ((GWAS) OR (Genome-wide association study)) AND (comorb*) AND (bipolar disorder) was used as a search string. Additionally, on the same date, we searched the term "bipolar" in the GWAS Catalog (https://www.ebi.ac.uk/gwas/). No language, publication date or other restrictions were imposed in any of the searches.

The following inclusion criterion was selected with the aim of identifying relevant and homogenous studies: GWAS with a sample recruited exclusively with the inclusion criteria of comorbid bipolar disorder (CBD) (i.e., patients simultaneously suffering from BD and any other condition) independently of sample size, population background, age or sex. Exclusion criteria were as follows: (a) duplicate publications; (b) studies without GWAS data; (c) reviews, case reports, meeting reports, meta-analysis and conference abstracts; (d) linkage or candidate gene studies; (e) studies mainly investigating treatment outcome or drug-induced side effects; (f) GWAS assessing only BD without comorbidity; (g) studies based on genome-wide data assessing the genetic overlap between BD and other diagnostics; and (h) studies performed on schizoaffective bipolar disorder.

Eligibility assessment was performed by the first author and revised by all co-authors. Titles and abstracts of the retrieved studies were roughly screened and excluded if the content was not relevant for the purpose of the systematic review. The remaining articles were thoroughly examined and excluded if the methodology or design did not meet the eligibility criteria.

Finally, the following data were extracted into a table by the first author and checked by all the co-authors: sample size, phenotypes, study design, and most statistically significant single nucleotide polymorphisms (SNPs) with their P-values.

2.2. Summary measures and risk of bias

P-values approximating the consensual statistical significance (i.e., $P < 5 \times 10^{-8}$) were the primary measure of SNP association to CBD. However, to ascertain the validity of the results, size and homogeneity of the samples were also taken into consideration. Additionally, to reduce the bias from duplicate sample, we agreed to exclude all GWAS findings from replication analysis with discovery-sample overlap. We also were in agreement with exclusion of confirmation results in case of overlap with the discovery sample.

3. Results

3.1. Study selection and data extraction

PubMed and GWAS catalog databases provided 131 citations. After removal of duplicates, 119 remained. Following review of the abstracts, 99 articles were excluded because no sign of assessment of comorbidity in BD appeared, and 21 full-text articles were assessed for eligibility. Of those, 15 reports were discarded as these reports employed methodology other than GWAS. Eventually, 6 publications were identified for inclusion in the review. Fig. 1 depicts the flow-chart of the study selection process.

The characteristics of included studies are summarized in Table 1.

Of note, all included articles used a sample of patients with comorbid bipolar disorder type-I (referred as CBDI hereafter), and no study on comorbid bipolar disorder type-II patients was found. The identified comorbid conditions included one neurological disorder, i.e., migraine (Jacobsen et al., 2015), and two psychiatric disorders, i.e., eating disorders (Liu et al., 2016; Winham et al., 2014) and externalizing disorders (Kerner et al., 2011; Lydall et al., 2011; Swaminathan et al., 2015). The GWAS design varied among the studies, ranging from comorbid case-control, where cases were CBDI and controls were BDI without comorbidity, to case-only, where CBDI and BDI patients were compared, and case-control, where cases were BDI patients and controls were healthy individuals (Table 1). Regrettably, none of the studies were conducted separately in both sexes to assess whether gender differences influenced the results.

It is worth mentioning that one study also included a meta-analysis (Winham et al., 2014), and the suggestive associations were also taken into consideration. Furthermore, Kerner and colleagues evaluated a specific subgroup of patients with BDI who presented psychotic symptoms (Kerner et al., 2007).

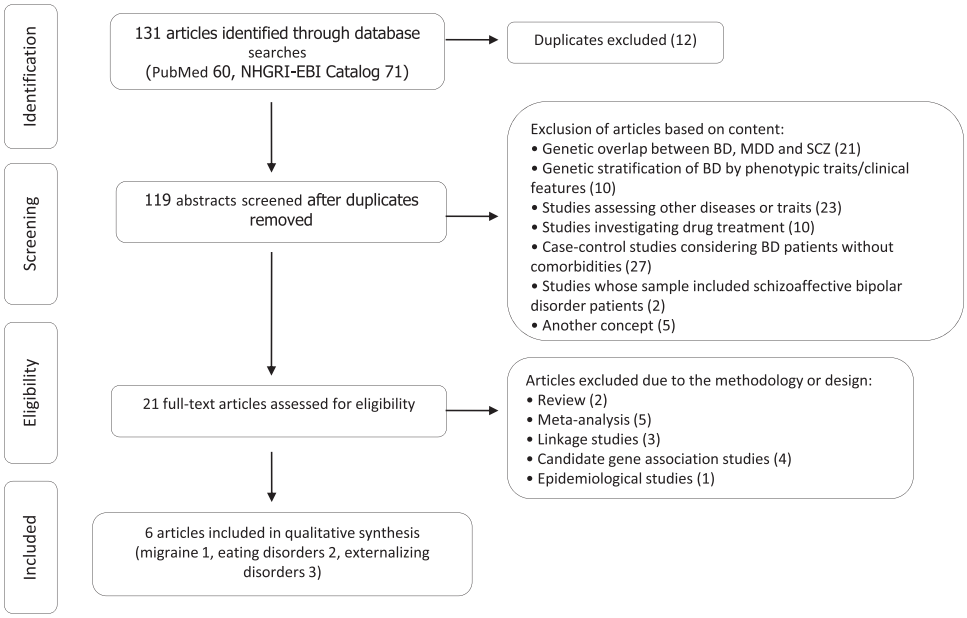

Fig. 1. Flow-chart of the study selection process.

Table 1
Material and methods of the selected articles.

Comorbid diagnosis	Study reference	Study design	Discovery sample	Replication sample	Diagnosis	Diagnostic procedure for BD	Diagnostic procedure for the comorbid condition in the discovery sample	Diagnostic procedure for the comorbid condition in the replication sample
Migraine	Jacobsen et al. J Affect Disord. 2015	Case-only	BiGS	GAIN + BiGS	BDI	DIGS	Self-reported	Self-reported
Eating disorders	Winham et al. J Affect Disord. 2014	Case-control Comorbid case-control Case-only	GAIN	Mayo Clinic Biobanks	BDI	DIGS, DSM-IV	Yes/No questionnaire	Clinical diagnostic
	Liu et al. J Affect Disord. 2016	Case-control Comorbid case-control Case-only	BiGS	–	BDI	DIGS, DSM-III-R, DSM-IV	Clinical diagnostic	–
Externalizing disorders	Swaminathan et al. J Affect Disord. 2015	Case-control Comorbid case-control Case-only	BiGS	–	BDI	DIGS	Clinical diagnostic	–
	Kerner et al. PLoS One, 2011	Comorbid case-control	GAIN	–	BDI	DSM-III-R, DSM-IV-R	Clinical diagnostic	–
	Lydall et al. Psychiatr Genet. 2011	Case-control Comorbid case-control	UCL + NHS	–	BDI	ICD-DCR, RDC, DSM-III-R	Clinical diagnostic	–

Summary of the characteristics of the included articles, stratified by comorbidity. BDI: Bipolar disorder type-I. BiGS: Bipolar Genetics Study. DIGS: Diagnostic Interview for Genetic Studies. DSM-III: Diagnostic and Statistical Manual of Mental Disorder Version III. DSM-III-R: Diagnostic and Statistical Manual of Mental Disorder Version III Revised. DSM-IV: Diagnostic and Statistical Manual of Mental Disorder Version IV. DSM-IV-R: Diagnostic and Statistical Manual of Mental Disorder Version IV Revised. GAIN: Genetic Association Information Network. ICD-DCR: Schizophrenia and Affective Disorders Schedule – Lifetime version (SADS-L) and diagnosed according to ICD-10 diagnostic criteria. NHS: National Health Service. RDC: Research Diagnostic Criteria. UCL: University College of London.

3.2. Summary measurements and risk of bias

SNPs approximating the consensual genomic statistical significance ($P < 5 \times 10^{-8}$) are summarized in Table 2. We also listed all suggestive SNPs ($P < 10{\times}10^{-5}$) in Supplementary Table 1. To facilitate comprehension, each study is contextualized in terms of comorbidity.

The validity of the results across all studies may be biased due to their small sample size. Additionally, the heterogeneous pool of patients with externalizing disorders and eating disorders may also interfere with the quality of the studies.

3.3. Description and main results of the included studies on the systematic review according to comorbidity

3.3.1. BDI with comorbid migraine

To date, only one case-only GWAS comparing BDI patients with and without a migraine diagnosis has been performed (Jacobsen et al., 2015), and one SNPs achieved the statistical significance threshold in the discovery sample. The SNP rs1160720 ($P = 2.97{\times}10^{-8}$) is located in the Neurobeachin (*NBEA*) gene, and several other neighboring SNPs in linkage disequilibrium with rs1160720 showed a trend for association

Table 2
Summary of the most significant SNP variants associated with comorbid diagnosis in patients with BD based on GWAS data.

Comorbidity	Reference	Study	Discovery sample size (CBD/BD/control)	Replication sample size (CBD/BD/control)	Chr	Base pair (GRCh38)	SNP	Gene	*P*-value
Migraine	Jacobsen et al. J Affect Disord. 2015	Case-only	460/914/-	289/697/-	13	35,312,538	rs1160720	*NBEA*	3.0×10^{-8}
Eating disorders	Liu et al. J Affect Disord. 2016	Comorbid case-control	184/-/1370	–	3	181,063,312	rs4854912	*SOX2-OT*	8.9×10^{-8}
					3	181,135,404	rs13100379	*SOX2-OT*	9.7×10^{-8}
Externalizing disorders	Kerner et al. PLoS One. 2011	Comorbid case-control (1)	283/-/1034	–	6	165,741,969	rs1039002	*PDE10A*	1.7×10^{-8}
					1	220,484,892	rs12563333	*MARK1*	5.9×10^{-8}
					6	90,909,043	rs13220542	*MAP3K7*	9.0×10^{-8}
		Comorbid case-control (2)	246/-/1034	–	3	1,856,289	rs2727943	*CNTN4/CNTN6*	3.3×10^{-8}

a. *P*-value obtained by Fisher exact test was considerably weaker (4.2×10^{-7} for rs11031481, 1.4×10^{-5} for rs9566845 and 1.5×10^{-5} for rs9566845).
b. SNP associated in the case-only meta-analysis where GAIN and Mayo samples were combined.
c. SNP associated in the CBD case-control meta-analysis where GAIN and Mayo samples were combined.
d. SNP associated in the case-only meta-analysis where discovery and replication GAIN samples were combined.
e. This replication sample consisted in 133 migrainous and 333 nonmigrainous individuals with attention deficit hyperactivity disorder (ADHD).

($P < 5 \times 10^{-5}$, Table S1). However, the association of rs1160720 was not validated in the replication sample.

3.3.2. BDI with comorbid eating disorders

We found one study performed in BDI patients with binge eating disorder (Winham et al., 2014) and another study performed in patients with anorexia nervosa or bulimia nervosa (Liu et al., 2016). The first study included case-only, case-control and comorbid case-control GWAS as well as a meta-analysis and a replication sample (Winham et al., 2014). However, no SNP reached statistical significance. The second study included case-control, comorbid case-control and case-only GWAS. In this study, two SNPs almost attaining statistical significance were found in the comorbid case-control GWAS: rs4854912 ($P = 8.9 \times 10^{-8}$) and rs13100379 ($P = 9.7 \times 10^{-8}$) within the SRY-Box Transcription Factor 2 Overlapping Transcript (*SOX2-OT*) gene.

3.3.3. BDI with comorbid externalizing disorder

Regarding externalizing disorders, some GWAS on comorbidities in BDI patients have been performed to date. Kerner and colleagues performed two comorbid case-control GWAS assessing substance abuse and alcohol dependence. More specifically, the first GWAS included BDI patients who presented a high probability of endorsing psychotic symptoms and substance abuse (including alcohol) but not dependence. This phenotype was significantly associated with rs1039002 ($p = 1.7 \times 10^{-8}$) located close to the Phosphodiesterase 10A (*PDE10A*) gene. Suggestive associations with rs12563333 ($P = 5.9 \times 10^{-8}$) and rs13220542 ($P = 9.0 \times 10^{-8}$) were also found. rs12563333 is located upstream of the MAP/Microtubule Affinity-Regulating Kinase 1 (*MARK1*) gene, and rs13220542 is located downstream of the gene encoding Mitogen-Activated Protein Kinase Kinase Kinase 7 (*MAP3K7*). The second GWAS included BDI patients with alcohol dependence and substance abuse/dependence). This phenotype was associated with the SNP rs2727943 ($P = 3.3 \times 10^{-8}$) located between the Contactin-4 (*CNTN4*) and Contactin-6 (*CNTN6*) genes. Additionally, Kerner and colleagues included a case-control GWAS with a subgroup of BDI patients ($N = 493$) with low probability of comorbidity and a case-control GWAS combining all the patient groups, but no significant associations were observed.

Lydall et al. (2011) performed a comorbid case-control GWAS using BDI patients with alcohol dependence as the case group. However, no marker survived conventional genome-wide significance.

Swaminathan et al. (2015) proposed that BDI patients suffering from alcohol abuse/dependence, drug abuse/dependence, pathological gambling, antisocial personality disorder, attention deficit hyperactivity disorder and conduct disorder could have a common genetic background and thus performed two case-only GWAS to assess their hypothesis. One GWAS compared BDI patients vs. BDI patients with any of the mentioned externalizing disorders, and another GWAS compared BDI patients vs. BDI patients with early onset of such externalizing disorders. However, no SNP attained statistical significance.

4. Discussion

Comorbidity in psychiatric patients is difficult to assess following the clinical classification of psychiatric disorders. Researchers are trying to identify genetic variants to help with clinical classification and define patient endophenotypes. There are two ways of approaching this aim. One method is performing GWAS where cases are patients suffering from the two diseases of study, and the second method is performing genetic correlation studies using GWAS data obtained from each disease independently. To the best of our knowledge, the present work is the first systematic review focused on the first type of study and suggests that genes involved in neurotransmission, stress response, neurogenesis and synaptic plasticity may be potentially associated with BDI patients presenting with comorbid conditions.

4.1. Migraine

Migraine is a common neurobiological headache disorder caused by increased excitability of the central nervous system (Silberstein, 2004), and its prevalence is greater in BD patients than the general population (Dilsaver et al., 2009). The only associated SNP found in the case-only GWAS of BDI patients with migraine involved the *NBEA* gene. Although such an association may represent a marker of the BDI plus migraine phenotype or of migraine itself, an analysis performed with migraine GWAS meta-analysis data showed no association of *NBEA* with migraine (Jacobsen et al., 2015). In addition, the possible role of *NBEA* in BDI was discarded by the PGC meta-analysis (http://www.broadinstitute.org/mpg/ricopili/), which did not show any association between NBEA and BDI. Thus, it is likely that the BDI with comorbid migraine condition represents an independent en-

dophenotype, but information is too limited to make a robust conclusion.

NBEA is a scaffold protein mainly expressed in the brain (Lauks et al., 2012) that is involved in the trafficking of vesicles containing gamma aminobutyric acid (GABA) and glutamate receptors from the post-Golgi site to the cellular membrane (Lauks et al., 2012; Nair et al., 2013). Disturbance of the glutamatergic system is believed to cause cortical spreading depression underlying migraine aura (Cutrer and Smith, 2013; Stuart et al., 2012), and some glutamate-related gene variants are associated with migraine (Anttila et al., 2010; Ligthart et al., 2011). Genetic variants in the glutamate system are also associated with the risk of suffering from BD (Kandaswamy et al., 2014, 2013; Poletti et al., 2015; Sklar et al., 2008). In addition, glutamate levels appear to be altered in BD patients (Ehrlich et al., 2015; Soeiro-de-Souza et al., 2015), and metabotropic glutamate receptors have been proposed as drug targets in some psychiatric condition (Blacker et al., 2017).

4.2. Eating disorders

Eating disorders are a heterogenous group of psychiatric conditions that usually are associated with dissatisfaction with subject's own body image and implies a perturbation of eating habits. Eating disorders include a broad spectrum of conditions, such as anorexia nervosa, bulimia nervosa and binge eating (Erzegovesi and Bellodi, 2016). Due to the elevated rates of eating disorders among patients with BD (McElroy et al., 2005, 2013) and vice-versa (Fornaro et al., 2020), efforts have been made to find common genetic risk factors underlying both pathologies.

Winham and colleagues performed a GWAS assessing BDI patients with comorbid eating disorders, but they did not found any common genetic marker associated (Winham et al., 2014). Alternatively, Liu and colleagues evaluated samples of BDI patients with comorbid anorexia/bulimia nervosa (Liu et al., 2016) based on the evidence that anorexia and bulimia nervosa share common genetic risk factors (Eckert et al., 1995; Tozzi et al., 2005). In this case, two SNPs in *SOX2-OT* yielded almost statistically significant associations in the comorbid case-control GWAS, suggesting that *SOX2-OT* may be implicated in BDI with comorbid anorexia/bulimia nervosa, BDI or anorexia/bulimia nervosa. However, the absence of an association of *SOX-OT* in the BDI case-control analysis allowed us to exclude its involvement in BDI. On the other hand, prior to this study, a case-control study of anorexia nervosa reported a suggestive association of *SOX2-OT* (Boraska et al., 2014). Thus, available information is not sufficient to determine whether *SOX2-OT* is involved in BDI with comorbid anorexia/bulimia nervosa (and thus it may represent an endophenotype) or rather it is a marker of anorexia nervosa.

SOX2-OT is a long non-coding RNA that may regulate the expression of SOX2 and is involved in embryonic and adult neurogenesis (Amaral et al., 2009) and various cancers (Li et al., 2020).

4.3. Externalizing disorders

Externalizing disorders relates to a group of psychiatric disorders characterized by the presence of disinibited or externally-focused symptoms, such as impulsivity, aggression, attention problems or delinquent behavior (McElroy et al., 2017). Evidence supports that some externalizing disorders occur in concomitance with BD, as it is the case of attention deficit hyperactivity disorder (O'Connell et al., 2019), substance abuse (Messer et al., 2017) and alcohol dependence (Di Florio et al., 2014). Within this context, three GWAS have been performed to find genetic markers that could explain the common pathogenesis of patients suffering from both BDI and externalizing disorders.

Kerner and colleagues found that the BDI with comorbid substance abuse phenotype was significantly associated with the *PDE10A, MARK1* and *MAP3K7* genes, and the BDI with comorbid alcohol dependence and substance abuse phenotype was significantly associated with the *CNTN4* and *CNTN6* genes (Kerner et al., 2011). The association of these genes with BDI was not supported by the case-control GWAS performed by Kerner and colleagues, where no statistically significant signal was found. However, we cannot rule out the implication of such genes in alcohol dependence or substance abuse. For instance, given that two intronic SNPs of *CNTN4* have been previously associated with alcohol use (Clark et al., 2015), the associated SNPs may be involved in alcohol dependence rather than in BDI with comorbid alcohol dependence and substance abuse. Therefore, information is not yet sufficient to determine whether BDI with comorbid alcohol dependence and substance abuse phenotype or BDI with substance abuse represent an independent endophenotype.

PDE10A is involved in the hydrolysis of the signaling molecules cAMP and cGMP, modulating intracellular signaling pathways. Differential expression of PDE10A isoforms in the striatum are present in BDI (Macmullen et al., 2016), and PDE10A is genetically associated with BDI (McDonald et al., 2012), which may explain the dysregulation of cAMP signaling observed in BDI (Gaspar et al., 2014). The involvement of PDE10A in alcohol abuse is widely accepted (Logrip, 2015; Logrip et al., 2014). Strikingly, Cerbera-Juanes and colleagues found that "low" and "heavy" drinkers presented different methylation patterns in the *PDE10A* gene (Cervera-Juanes et al., 2017).

MARK1 phosphorylates microtubule-associated proteins and is involved in synaptic plasticity and dendritic trafficking (Drewes et al., 1997), and comorbid nicotine- and alcohol-dependent patients are significantly associated with *MARK1* (Lind et al., 2010).

MAP3K7 is a serine/threonine protein kinase involved in the cell response to environmental stress (Chen, 2005), and ethanol feeding increases its DNA methylation and protein expression (Khachatoorian et al., 2013).

CNTN4 and CNTN6 are both members of a subgroup of the immunoglobulin superfamily. The CNTN family of proteins plays an important role in the formation and maintenance of specific neuronal networks in the brain (Yoshihara et al., 1995) as well as in behavioral neurodevelopmental disorders, including alcohol dependence and BDI (Oguro-Ando et al., 2017).

Lydall and colleagues aimed to find genetic markers of the BDI with comorbid alcohol dependence phenotype. However, no SNP attained statistically significant association (Lydall et al., 2011). Also, Swaminazam and colleagues tried to find common genetic markers among a pool of BDI patients with externalizing disorders, but no significance level was reached by any of the SNPs (Swaminathan et al., 2015). Thus, with the available information, it seems that neither BDI with alcohol dependence nor BDI with externalizing disorders patients are likely to define an endophenotype.

5. Limitations

The present work has some limitations. First, the main limitation of this review is the small sample size of included papers given that only the BDI case-control GWAS performed by Liu and colleagues approaches the consensually recommended minimum of 2000 cases and 2000 controls (Spencer et al., 2009). The second important limitation is the lack of replication to exclude false positives. This limitation could be explained by the small size of the replication samples, which lack the power to confidentially detect genetic variants with small effects. Third, the comorbid condition is occasionally self-reported (Table 1), which may suppose a recall bias. Fourth, in the case of GWAS assessing BDI with comorbid eating disorders and BDI with comorbid anorexia/bulimia nervosa, it is not clear whether people suffering from eating disorders have been excluded from the control group (Liu et al., 2016; Winham et al., 2014), which may interfere with the robustness of the results.

Furthermore, the genetic overlap among psychiatric disorders, and to a less extent, among psychiatric disorders and migraine, a neurological condition, may reflect the existence of common genetic pleiotropic loci conferring risk for multiple psychiatric disorders at a time or rather

the phenotypic overlap between some disorders (Anttila et al., 2018; Smoller et al., 2013). On this basis, we cannot exclude the possibility that the aforementioned associated SNPs may represent risk loci for a shared symptomatology given that BDI and eating disorders also share emotion dysregulation symptoms (McDonald et al., 2019) and BDI, eating disorder and externalizing disorder patients present impulsivity (Beauchaine et al., 2017; Kenny et al., 2019; Najt et al., 2007). Consistently, previous work has noticed the association between BD, impulsivity and the gene Glycogen Synthase Kinase 3 Beta (Jiménez et al., 2014), which is a gene involved in neurogenesis and neuroplasticity.

Finally, apart from a shared genetic background, common environmental triggers cannot be discarded. Childhood maltreatment and physical abuse are precursors of BDI, migraine and eating disorders (Daruy-Filho et al., 2011; Post and Leverich, 2006; Rayworth et al., 2004; Tietjen et al., 2010a, 2010b). Perinatal infection and postnatal stress are risk factors for BDI and alcohol dependence (Tay et al., 2018), and there is an overlap in the epidemiological risk factors for BDI and some externalizing disorders (Mitchell et al., 2019).

6. Conclusion

The available literature provides exciting evidence suggesting that genetics may help to diagnose psychiatric disorders. On this basis, clinical features have been used to cluster potential genetically homogenous CBDI patients in GWAS. Unfortunately, due to the reduced number of studies performed to date and their lack of power, the available literature is not yet sufficient to clearly define endophenotypes in BD based on comorbid conditions.

The findings summarized here should therefore be considered as the first step in a pathway leading to the understanding of the pathogenesis behind CBDI and precision psychiatry (Vieta, 2015). Further GWAS with larger samples and more homogenous phenotypes in terms of diagnosis and symptomatology are needed. Furthermore, it would be interesting to study whether the above list of SNPs associated with CBDs overlaps with the SNPs obtained from genetic correlation studies when available.

Finally, all the above reported genes fall into four different biological pathways: neurogenesis, neurotransmission, synaptic plasticity and stress response. Therefore, we hypothesize that a better understanding of these pathways may help disentangle the genetic complexity behind neuropsychiatric comorbid disorders in BDI patients. In any case, more research is required on functional studies to determine the molecular targets and mechanisms behind the identified genetic variants.

Declaration of Competing Interest

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The authors have nothing to disclose.

Author's contributions

Selena Aranda: Conceptualization, investigation and writing original draft. Ester Jiménez, Lourdes Martorell, Gerard Muntané and Eduard Vieta: writing, reviewing and editing the manuscript. Elisabet Vilella: Conceptualization, writing, reviewing and editing the manuscript.

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Supplementary materials

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