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Genetic biomarkers for differential diagnosis of major depressive disorder and bipolar disorder: a systematic and critical review.

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Authors' Contribution: a-Study Design; b-Literature Search; c-Data Collection; d-Data Selection; e-Data Interpretation; f-Manuscript Preparation; g-English Review.

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Abstract

Depressive symptoms are present in the depressive mood state of bipolar disorder (BPD) and major depression disorder (MDD). Often, in clinical practice, BPD patients are misdiagnosed with MDD. Therefore, genetic biomarkers could contribute to the improvement of differential diagnosis between BPD and MDD. This systematic and critical review aimed to find in literature reliable genetic biomarkers that may show differences between BPD and MDD. This systematic review followed the PRISMA-P method. The terms used to search PubMed, Scopus, PsycINFO, and Web of Science were depress*, bipolar, diagnos*, genetic*, biomark*. After applying the selection criteria, N=27 studies were selected, being n=9 about biomarkers for BPD; n=15, about MDD; and n=3 for distinguishing MDD from BPD. A total of N=3086 subjects were assessed in the selected studies (n= 486 in BPD group; n=1212 in MDD group; and n=1388, healthy control group). The articles were dated up to June 2017. Of the N=27 studies, n=16 assessed gene, n=1 miRNA, n=2 lcnRNA and n=3 protein expressions, n=4 methylation, and n=4 polymorphisms. Some studies applied more than one of these genetic analyses. To find reliable genetic biomarkers we have taken into account the methodological care during the studies development and their validity. The genetic biomarkers selected are related to genes that play a fundamental role in synaptic plasticity, neurogenesis, mood control, brain ageing, immune-inflammatory processes and mitochondrial respiratory chain. BDNF gene expression was one of the genetic biomarkers that highlighted because of its capacity of distinguishing BPD and MDD groups, and being adequately reproduced by more than one selected study.

Key-Words: depression, bipolar, diagnosis, genetic biomarker.

1. INTRODUCTION

Major depressive disorder (MDD) and bipolar disorder (BPD) are distinct psychiatric disorders, but both have in common the occurrence of depressive symptoms [1,2]. BPD is characterized by recurrent episodes of depression and elevation of mood (mania and/or hypomania), being in a depressive state more frequent, longer and disabling than hypo/manic state in BPD [3-7]. Bipolar patients are more likely to have a family history of BPD, greater number of affective episodes, psychiatric hospitalization, suicide attempts, and earlier onset of the disease than unipolar depressed patients [8-11]. Also, they have more comorbid psychiatric disorders, especially anxiety and substance use disorders, and clinical disorders, such as diabetes, hypertension and cardiovascular disease, which can explain the higher mortality rates among patients with BPD ([12]. Although there are etiological, neurological and physiological differences between MDD and BPD in clinical practice, the presentation of depressive episodes in bipolar patients may not differ substantially from patients with unipolar depression [1,13-15], which may be the cause many BPD patients being misdiagnosed with MDD [16]. Clinical studies have shown about 40%-50% of BPD patients are firstly erroneously diagnosed with MDD and the correct diagnosis use to be delayed 8-10 years [17,18]. Thus, the misdiagnosis of BPD as MDD may lead to grave consequences in the treatment of bipolar patients, as a history of treatment-resistant depression [2,19, 20]. In this sense, it is important to study biomarkers that can help in clinical practice to distinguish MDD and [21,22].

Based on this, the main goal of the present systematic and critical review is to analyze genetic biomarker candidates and the methods applied by studies for

searching them. Not only the capacity of differentiating groups was taken into account, but the biomarkers validity and the methodological care to avoid bias.

2. METHODS

2.1 Search

The present systematic review followed PRISMA-P method [23,24]. The research was conducted using the terms depress*, bipolar, diagnos*, genetic*, biomark* (the terms were truncated to enlarge the research, including terms with the same word beginning, but with distinct suffixes) in the following databases: PubMed, Scopus, PsycInfo, and Web of Science.

The limits set were for language (only English), subjects' species (only humans), subjects' age (18-65 years old) and for study design (reviews or systematic reviews or meta-analysis or case reports or study protocols excluded). No limits were set for the time frame (articles published up to June 2017), neither subjects' gender.

2.2 References Selection

In the first selection, repeated articles, articles that investigated only non-genetic biomarkers, or any other disorders but not depression/MDD/BPD, or response to treatment or prognosis instead of diagnosis, or reviews or systematic reviews or meta-analysis or case reports or study protocols were excluded. The subjects may or may not be having psychiatric medications.

After this, a second and refined selection was made, excluding the following articles: those that did not specify the subtype of depression (unipolar or bipolar; or belonging to MDD or BPD); or those that have analyzed unipolar and bipolar data

as one single group; those that presented bias in the subjects' selection (e.g. ; studies that did not assessed possible and/or some significant psychiatric disorders in control group); or studies that did not controlled appropriately for potential confounding factors (e.g. gene expression may be decreased because of subjects' alcohol addiction, and not because of the depression level).

2.3 Data Management

For references and data management was used an open source bibliography reference manager Jabref. This software uses native file format BibTeX, the standard LaTeX bibliography format, and is available in <http://jabref.sourceforge.net/>.

3. RESULTS

3.1 Articles Eligibility and Selection

The search combining all the keywords and limits resulted in a total of N=792 articles (n=316 articles were found in PubMed; n=200, in Scopus; n= 165, in PsychInfo; and n=111, in Web of Science). After filtering all article duplicates, there were N=523 articles left. It was applied the first exclusion criteria in these articles, n=448 were excluded, and n=75 articles were left. The first exclusion, the excluded articles followed these criteria: a) n=237 articles which issue was not depression and/or MDD and/or BPD; b) n=102 reviews and/or metanalysis; c) n=56 articles about non-genetic biomarker; d) n=37 articles about treatment and/or prognosis, instead of diagnosis; e) n=7 which only subjects were animals; f) n=3

which subjects were younger than 18 or older than 65 years-old; g) n=6 were study protocols, without any results.

The second refined selection, n=48 excluded articles followed these criteria: a) n=22 did not specify the subtype of depression that was being studied or assessed unipolar and bipolar data together, as one single group; b) n= 15 bias in subjects selection and/or not adequate applied methods for subjects' diagnosis as bipolar or unipolar or control; c) n=9 confounding factor (e.g. the results are product of another factor); d) n=2 assessed MDD and/or BPD data as only one group.

In the end, there were N=27 articles left. These articles went through qualitative analysis. The results of all process of selection and exclusion criteria are detailed in Figure 1.

INSERT Figure 1

3.2 General Study Characteristics

From the selected articles (N=27), n=9 were about biomarkers for BPD; n=15, MDD; and n=3, BPD and MDD. All the chosen articles were case-control studies. There were n=5 studies that, besides case-control design, were also cohorts. In these cases, the data used to compose this systematic review was the transversal data, when participants ingressed in the study. The studies sample ranged from N=18 [25] to N=876 [26] subjects. Most articles presented female and male subjects, except for Akarsu et al. [27] that presented one group composed only by

men and Teyssier et al. [28], which all blood samples were from women. All subjects were in adult age. Of the 27 studies, most of them (n=16) applied a molecular method for searching genetic biomarkers was gene expression. The sum of all subjects resulted in N=3086, which n=486 are BPD, n=1212 MDD, and n=1388 healthy controls (HC).

3.3 Subjects' Diagnosis Confirmation

For subjects' diagnosis confirmation, n=12 studies applied The Structured Clinical Interview for DSM-IV Axis I (SCID-I) [27-38] and/or n=5 The Mini International Neuropsychiatric Interview (MINI) [28, 40-42]; n=2 Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [22, 43]; and n=2 others structured diagnosis interviews [44,45]. Others n=8 (29.63%) articles did not apply any structured diagnosis interviews, but the diagnosis by consensus of psychiatrists/psychologists using the Fourth Edition (DSM-IV; [46]) or Text-Revision of Fourth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; [47]) [25,26,48-52] or the World Health Organization International Classification of Diseases (WHO-ICD-10; [53] [54].

3.4 Genetic Biomarkers

There is considerable heterogeneity in the literature concerning possible genetic biomarkers candidates. The results will be presented below considering the diagnosis (BPD, MDD, or BPD and MDD) and the analysis patterns applied.

3.4.1 Genetic Biomarkers for BPD

Of N=27 articles selected, n=9 (30%) assessed genetic biomarkers candidates for BPD. Of these 9 studies, n=6 applied gene expression; n=1, protein expression; n=2, methylation; n=3, polymorphisms. There is n=1 article that assessed genetic biomarker candidate applying more than one analysis method [45]. Also, n=4 studies validated their results [25, 36, 40, 43]. The total sample in those studies was n= 641 subjects (n=306 BPD and n=335 HC).

Table 1 summarizes those n=9 studies, showing the genetic analysis applied, the subjects and their mood state (in the case of BPD patients), the results (candidates that found difference between groups), if the results were validated or not, and the bias.

INSERT Table 1

3.4.1.1 Gene Expression in BPD

Of the n=6 studies of this section, n=4 found upregulation [27,36,40,42] and n=3 [36,40,43] found downregulation in gene expression of BPD compared to HC. Two studies [27,45] found no difference in gene expression between groups.

Both Akarsu et al. [27] and Munkholm et al. [43] assessed NDUFV2 gene expression in BPD sample. NDUFV2 is a gene that belongs to subunits of mitochondrial complex I [27]. Akarsu et al. [27] isolated messenger ribonucleic acid (mRNA) from blood samples obtained from BPD patients in the manic state matched to HC. BPD samples presented higher NDUFV1, NDUFV2, and

NDUFS1 mRNA levels. UQCRC1 mRNA levels did not differ BPD from HC. They also compared mRNA levels between BPD with psychotic features to BPD without psychotic features, but no difference was found. Munkholm et al. [43] compared the gene expression of BPD patients to HC, and BPD among each other. So, they assessed mRNA levels of 19 candidate genes in peripheral blood mononuclear cells (PBMC). They observed downregulation in TOGG1 and POLG gene expression in BPD compared to HC. When comparing BPD samples from different mood states among themselves, NDUFV2 gene expression was upregulated in the depressed state compared to the euthymic state. Later, composite gene expression score was constructed (more details, vide Munkholm et al. [43]), which provided results corresponding to a moderately accurate test.

Zhang et al. [42] applied quantitative polymerase chain reaction (qPCR) to assess mRNA levels of p11 in BPD (BPD-I and BPD-II) remitted patients and HC. p11 mRNA was over-expressed in BPD patients, but there was no difference in p11 expression between BPD-I and BPD-II. Kato et al. [40] performed qPCR to assess gene expression in lymphoblastoid cells (LCL) sample from BPD-I, and HC. 17 candidate genes were measured, but only three were selected - ANK3, RASGRP1 and POLG1. In BPD-I patients, ANK3 showed higher expression levels, whereas POLG1 and RASGRP1 showed lower levels compared to controls. BPD-I sample could be discriminated from controls with 44% sensitivity (moderate) and 81% specificity (high).

Padmos et al. [36] assessed inflammatory gene expression signature, after having selected 22 discriminating inflammatory genes through whole genome analysis. There were 19 aberrantly expressed genes in BPD patients – PDE4B,

IL1B, IL6, TNF, TNFAIP3, PTGS2, PTX3, MAPK6, DUSP2, NAB2, ATF3, BCL2A1, EMP1, CCL2, CCL7, CCL20, CXCL2, CCR2, and CDC42. All these 19 genes were upregulated in BPD (all mood states) compared to HC sample, except for CCL2 that was downregulated. Comparing euthymic BPD to HC, almost all those 19 genes (except for CCL2 and EMP1) were upregulated. Other BPD mood states samples presented upregulation when compared to euthymic bipolar state: manic (MAPK6 and CCL2 genes) and depressive (MAPK6, CCL2, IL6, PTX3, EMP1, and BCL2A1) mood states. Although all these aberrant gene expressions between BPD and HC, and among BPD mood states, when authors assessed positivity for the genes signature, they observed the strongest correlations for Phosphodiesterase 4B (PDE4B) gene expression which is related to proinflammatory processes, chemokinesis, and cell survival mRNA signature.

Kittel-Schneider et al. [45] compared the influence of the nitrinergic system in BPD patients and HC. Nitric Oxide Synthase 3 (NOS3) gene expression between BPD and HC groups did not differ. After splitting BPD sample according to the mood states and BPD type (I and II) to compare with HC, they still did not find a difference in NOS3 gene expression.

3.4.1.2 Protein Expression in BPD

Kazuno et al. [25] observed increased protein expression in BPD compared to HC. They performed a comparative proteomic analysis from LCL cells of monozygotic twins discordant for BPD applying two-dimensional differential in-gel electrophoresis (2D-DIGE) and validated comparing BPD and HC. They found approximately 200 protein spots differentially expressed between BPD patient and the co-twin. BPD samples presented up-regulation in phosphoglycerate mutase 1

(PGAM1). PGAM1 promotes glycolysis and ATP production via the TCA cycle and the electron transport system [25,51].

3.4.1.3 Methylation in BPD

Both Nohesara et al. [35] and Ghadirivasfi et al. [33] observed hypomethylation in salivary DNA from BPD subjects compared to HC applying bisulphite DNA sequencing and quantitative methylation-specific polymerase chain reaction (qMSP). The hypomethylation found by Nohesara et al. [35] was in catechol-O-methyltransferase (MB-COMT) promoter. Ghadirivasfi et al. [33] observed the hypomethylation in serotonin receptor Type-2A Gene (HTR2A) T102C polymorphic site.

3.4.1.4 Polymorphisms in BPD

N=3 studies assessed polymorphisms in BPD, but no one of them found differences compared to HC. Kittel-Schneider et al. [45] genotyped samples for rs2070744, rs1799983 and the NOS3 Intron 4 variable number tandem repeat (VNTR) (as a three-marker haplotype) in NOS3 gene, and NOS1 ex 1c, NOS1 ex 1f (two genetic variants of the NOS1 gene). The Allele 4c of the VNTR was not detected in this study. There was no haplotypes significantly over or underrepresented in BPD. Both Ghadirivasfi et al. [33] and Nohesara et al. [35] genotyped their study samples by conventional methods using enzymatic restriction (RFLP) of PCR product and did not find differences in polymorphisms frequencies between BPD and HC. Ghadirivasfi et al. [33] assessed HTR2A - 1438 A/G and T102C polymorphisms and Nohesara et al. [35] assessed COMT Val/Met.

3.4.2 Biomarkers for MDD

Of N=27 articles selected, n=15 (55.55%) assessed genetic biomarkers candidates for MDD. Of those 15 studies, n=8 applied gene expression; n=1, microRNA (miRNA) expression; n=2, long non-coding RNAs (lncRNAs) expression; n=1, protein expression; n=2, methylation; n=3, polymorphisms. There is a n=2 article that assessed genetic biomarker candidate is applying more than one analysis method [32,49]. Also, n=9 studies validated their results [29,30,32,37-40,49,52]. The total sample in those studies was n= 1799 subjects (n=988 MDD and n=811 HC). Table 2 summarizes those n=15 studies, showing the genetic analysis applied, the subjects and the severity of symptoms (in the case of MDD patients), the results (candidates that found a difference between groups) if the results were validated or not, and the bias.

INSERT Table 2

3.4.2.1 Gene Expression in MDD

Of the n=8 studies that assessed gene expression in MDD, n=3 found upregulation, n=2 downregulation and n=1 found up and downregulation when compared to HC. n=2 studies found no difference between groups.

Rizavi et al. [50] investigated mRNA levels of cytokines and their membrane-bound receptors in the lymphocytes of MDD and HC. They observed that mRNA levels of IL1 β , IL6, TNF- α , as well as IL1R1 and IL1RA, TNFR1 and TNFR2 were higher in MDD patients. However, for IL1R2, IL6R, and IL6STU (or called Gp130), there was

no difference in mRNA levels between groups. Yi et al. [38] compared expression profile among drug-free first-episode subjects with subsyndromal symptomatic depression (SSD - unipolar) (mild to moderate symptoms), MDD (moderate to more severe symptoms), and HC. They combined the most differentially expressed genes from each set of gene expression signatures, followed by trained and tested the multiple combinatorial gene signatures. There were 48 gene expression signatures determined with 100% accuracy. They observed differential expression of the following genes: ABL1, BRE, AP3B1, C19orf6, CAPRN1, CCND2, CD84, COG3, CTNS, FDPS, FGD3, GCHFR, GINS4, INPP4A, KALRN, KTI12, LHX9, MEF2A, NEK8, NOP56, NRAS, PA2G4, PDE6B, PIK3AP1, PNN, PRKAR2A, PRKCB, PURA, RHOQ, RPL4, SCFD2, SENP1, SH3YL1, SLC16A3, SOCS4, STAT5B, STRN, TERF2, TMBIM6, TMEM97, VARS, WWP2, ZCCHC3, ZNF785, ZNF791, GRK6, BDNF, and COX5B. They highlighted BDNF, COX5B and GRK6 as the most significantly differential genes. Numata et al. [49] main study focus were methylation (we will better describe this article in below in section 3.5.2.5 – methylation), but they also assessed GSK3B gene expression. They found a significantly higher GSK3B expression level in patients with MDD than HC.

Watanabe et al. [52], assessed leukocyte gene expression profiles of 40 candidate genes. After a pilot study and the development of a linear discriminant function to differentiate MDD from HC. PDGFC, SLC6A4, ARHGAP24, and HDAC5 genes were upregulated, and PRNP gene was downregulated. A pilot study presented overall 80% sensitivity and 92% specificity; and the replication test had overall 85% sensitivity and 89% specificity respectively. According to authors, this was the first leukocyte gene expression-based test for MDD involving a customized

PCR array plate and demonstrates confirmed sensitivity and 80% specificity or greater.

Milanesi et al. [41] assessed V-erb-b2 erythroblastic leukaemia viral oncogene homolog 3 (ErbB3) and fibroblast growth factor receptor 1 (Fgfr1) mRNA expression levels. MDD leucocyte samples presented reduced ErbB3 mRNA levels than HC samples. No difference was found in Fgfr1 mRNA expression levels.

Garbett et al. [32] assessed differential mRNA expression was applying microarray and identified 162 differentially expressed gene probes in MDD that reported > 50% change, of which 139 unique known genes (25 overexpressed and 114 hypoexpressed). Authors presented the following genes as those with most prominent decreased expression in MDD: PCDH10, TNXB, PPL, and MET. Considering the effects on brain development and function of MET, the researchers also assessed expression of genes belonging to the MET intracellular cascade. They were PIK3R1, HGF, GAB1, SOS1, RAPGEF1, STAT3, PTPN11, PAK1, MAPK1, CRKL, JUN, PTEN, RAP1A, MAP2K1, HRAS, ErbB2. In the end, they validated 14 differentially expressed mRNA by qPCR. Of these, 12 presented differences between MDD and HC, with a strong correlation between the microarray and qPCR analysis.

Frodl et al. [31] and Teyssier et al. [41] did not find differences in gene expressions in between MDD and HC groups. Frodl et al. [31] assessed glucocorticoid receptor (GR) mRNA expression and glucocorticoid-inducible genes (GILZ and SGK-1) expression, and Teyssier et al. [28] assessed ring finger protein 123 (RNF123) gene expression.

3.4.2.2 miRNA Expression in MDD

Garbett et al. [32] also detected 38 miRNAs different expressed in MDD samples. Of these, 17 miRNAs presented downregulation (hsa-miR-377, hsa-miR-122, hsa-miR-32, hsa-miR-196b, hsa-miR-193a-3p, hsa-miR-337-5p, hsa-miR-675, hsa-miR-3176, hsa-miR-21, hsa-miR-22, hsa-miR-425, hsa-miR-185, hsa-miR-296-5p, hsa-miR-103a, hsa-miR-107, hsa-miR-186, and hsa-miR-887), and 21 presented upregulation (hsa-miR-132, hsa-miR-421, hsa-miR-542-3p, hsa-miR-450a, hsa-miR-16-2, hsa-miR-424, hsa-miR-628-3p, hsa-miR-629, hsa-miR-4293, hsa-miR-661, hsa-miR-3909, hsa-miR-33a, hsa-miR-135b, hsa-miR-7, hsa-miR-4267, hsa-miR-548aa, hsa-miR-548d-3p, hsa-miR-613, hsa-miR-3714, hsa-miR-1294, and hsa-miR-429) compared to HC.

3.4.2.3 lncRNA Expression in MDD

Long non-coding RNAs (lncRNAs) are noncoding RNA with a length longer than 200 bases highly expressed in mammalian genomes. They play key roles as epigenetic and transcription modulators [30,56]. Cui et al. [29] found that eight lncRNA (TCONS_L2_00001212, NONHSAT102891, TCONS_00019174, NST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707) were downregulated in MDD (non-medicated, with severe symptoms) compared to HC. Cui et al. [30] used the findings of MDD lncRNA expression of Cui et al. [29]. They found six downregulated lncRNA expressions (TCONS_00019174, ENST00000566208, NONHSAG045500, NST0000051757, NONHSAT034045, and NONHSAT142707) in MDD group.

3.4.2.4 Protein Expression in MDD

Xu et al. [37] performed isobaric tags for relative and absolute quantitation - liquid chromatography–tandem mass spectrometry (iTRAQ-LC-MS/MS) - based comparative proteomic approach to identify proteins differentially expressed in treatment-naive MDD and HC plasma samples. Five proteins were overexpressed in MDD sample: Apolipoprotein D (Apo-D), Afamin (AFM), Apolipoprotein B-100, a-1B-glycoprotein (A1BG), Isoform 1 of vitamin D-binding protein (VDP); and four were hypoexpressed: ceruloplasmin (Cp), histidine-rich glycoprotein (HRG), Semaphorin-3F, a-2-macroglobulin. Then, they selected Apo-D, Cp, HRG and VDP for analysis in n=42 individuals samples (21 per group), observing trends in the expression of Apo-D, Cp, HRG and VDP that were consistent with iTRAQ results, but they were not significant in the validation result.

3.4.2.5 Methylation in MDD

Numata et al. [49] searched for DNA methylation in two set of samples: discovery and replication. They selected and validated biomarker with 100% accuracy, suggesting multiplex DNA methylation markers may be useful for discrimination between MDD and HC. Among 313 differentially methylated CpG sites in the CGIs in the gene promoter regions, they observed that DGKH (cg00109274), GSK3B (cg14472315), and SGK1 (cg06642177) were related to MDD, confirmed later by the independent replication cohort. Most of all hypomethylated loci (85.7%) were located in the CGIs in the gene promoter regions. According to authors, GSK3B is one of the most interesting genes among CpG sites that demonstrated significant diagnostic differences in DNA methylation.

Both in a discovery and in the replication set, there was significantly lower DNA methylation in MDD patients than HC at the CpG site (cg14472315) in the CGI in the promoter region of the GSK3B gene. They found a significant weakness to a moderate inverse correlation between GSK3B gene expression and promoter methylation.

Fuchikami et al. [39] assessed methylation profile of 2 CpG islands - I and IV - in promoters of the brain-derived neurotrophic factor (BDNF) gene and observed different rates of methylation of 29 CpG units out of 35 CpG units in BDNF CpG I in MDD compared to HC. In MDD patients, In CpG I, subunits 1, 9, 15, 18, 23, 24, 37, 52, 61, 63, 71, 77, 78 and 79 were hypomethylated; and subunits 19, 20, 21, 22, 28, 32, 36, 47, 48, 80 and 81 were hypermethylated.

3.4.2.6 Polymorphisms in MDD

Kreining et al. [48] and Ho et al. [44] found no differences in the frequency of polymorphisms between MDD and HC. Kreining et al. [48] evaluated the polymorphism rs6265 (Val66met) and Ho et al. [44] genotyped three genetic variants (rs25531, rs6354 and STin2) of the serotonin transporter gene (SLC6A4). Tian et al. [26] genotyped eight SNPs within the epidermal growth factor (EGF) gene in MDD (first episode) and HC. They observed that the frequency of the rs11569017 (T)-rs11569126 (G) haplotype was significantly higher in MDD patients.

3.4.3 Biomarkers for BPD and MDD

Of N=27 articles selected, n=3 (11.11%) assessed genetic biomarkers candidates for BPD and/or MDD. Of those 3 studies, n=2 applied gene expression [22,34]; and n=1, protein expression [54]. All these n=3 studies validated their results. The total sample in those studies was n= 554 subjects (n=88 BPD, n= 224 MDD, and n= 242 HC). Table 3 summarizes those studies (n=3), showing the genetic analysis that was applied. The subjects and the severity of symptoms (in the case of MDD patients) and/or their mood state (in the case of BPD patients), the results (candidates that found difference between or among groups), if the results were validated or not, and the bias.

INSERT Table 3

3.4.3.1. Gene Expression in BPD and MDD

Powell et al. [22] assessed expression 87 inflammation-related genes for distinction among MDD, BPD, and HC. Authors found a higher transcription of CCL24 in MDD group, significantly differentiating from BPD and HC groups, in the discovery and validation cohort. Also, they found a lower transcription of CCR6 and NR3C1 that differentiated MDD patients from HC in discovery and validation cohort. Li et al. [34] studied BDNF gene expression and plasma levels in MDD and BPD patients in their first depression episode comparing to HC. BPD group presented the lowest BDNF gene expression levels than MDD and HC groups, and MDD patients presented lower BDNF expression when compared to HC.

3.4.3.2 Protein Expression in BPD and MDD

Maccarrone et al. [55] assessed disease-specific protein biosignatures in cerebrospinal fluid of MDD, BPD and schizophrenia (SCZ) patients comparing them to HC group and the patients' groups against each other, using the Reverse Phase Protein Microarray (RPPM) technology. The proteins that could differ MDD from HC subjects with relative frequencies over 75% were GNAI2, CAPZA2, STXBP1, ATP2B1, FAM159B. Those proteins that could that differentiate BPD from HC were NEGR1, SPTBN1, OMG, SCG5, PTPRZ1, ATP6V0D1, CAPZA2, CRTAC1, NPDC1, NAPG, CNDP1, CADM2, ATP2B1, SEZ6, GPX3, CHGA. All of the proteins cited above were upregulated in patients' sample.

4. Discussion

It is ascending the number of studies on the topic "biomarker". About fifty thousand new articles have been published per year in recent years [57]. A good biomarker is one that has a good sensitivity and specificity, affordable cost, which provides reproducible experiments and results, available in organic samples that require less invasive methods for collection, and that is reliable to be used in clinical practice [57].

Most of the available articles about genetic biomarkers for affective disorders assessed only MDD or only BPD. The articles that aimed to explore genetic biomarker for MDD and BPD distinction are still rare in literature, and they are very relevant to improve the differential diagnosis. Besides detecting a difference between or among groups, to be considered a reliable biomarker, the studies

investigating them must present an adequate study design, accurate methods, subjects' assessment and selection, process of validation, and other factors that may avoid bias.

BDNF was the noteworthy genetic biomarker found among all the selected potential biomarker presented by this systematic review. Starting from n=27 articles final selected, which only n=6 presented quality to indicate reliable biomarkers considering the capacity of distinguishing groups, adequate methodological care, and validation, n=2 articles presented BDNF as a good biomarker. BDNF expression [34] and BDNF CpG I methylation patterns subunits differentiated MDD from HC [39]. As well, BDNF distinguished BD from HC and MDD [34]. BDNF, according to literature, is involved in synaptic plasticity, neurogenesis, learning, memory, cognition, mood control and other critical processes [58-61]. The reduction of BDNF levels is associated with an ageing process, some psychiatric disorders, and exposure to excessive stress [58,62,63]. The data found in this systematic review corroborate literature information and enforces BDNF as a good genetic biomarker.

About the other potential genetic biomarkers found PDE4B are major cyclic AMP metabolizing isoenzymes found in inflammatory and immune cells [64]. PDE4B may be a key molecule in the proinflammatory state of PBD [36], and literature data corroborate showing that BPD patients present HPA axis immune-inflammatory dysfunctions [65-67]. The lncRNAs expression (TCONS_00019174, ENST00000566208, NONHSAG045500, NST00000517573, NONHSAT034045, and NONHSAT142707) may also be interesting genetic biomarkers for MDD. Depression, like BPD, is a disorder that predisposes the patient to accelerate

ageing [61,68], and lncRNAs are involved in various biological processes of the central nervous system, such as hippocampal development, oligodendrocyte myelination, and brain ageing [30]. Currently, there are few studies about lncRNAs as genetic biomarkers. COX5B and GRK6 gene expressions may be considered, as well as BDNF, good biomarkers. COX5B participates of mitochondrial respiratory chain. There is an animal model of depression involving inhibition of mitochondrial respiratory chain (Razin et al., 2008) and studies of antidepressants and their effect on mitochondrial respiratory chain activity [69]. GRK6 is a member of G protein-coupled receptor kinases (GRK) family [70]. GRK6 may be predominantly involved in regulation of postsynaptic D2 dopaminergic receptors [71,72]. Literature data show the role of dopamine in the pathophysiology of depression [73].

Despite some of the selected studies were very careful about methodology [27,29,31,34,36,38,39,42] and validation [25,29,30,32,36-40,43,49,52] for obtaining a more reliable biomarker, still there were cases that bias was present because of the lack of investigation symptoms severity in MDD or mood states in BPD sample [26,32, 33, 35,40,45,54], gathering in a same BPD sample people in different mood states [22,36,43,54] or severity of symptoms [22,30,36], presenting difference between or among groups age [22, 41, 45, 48] or sex [44], not considering body index mass or the smoking habit [52, 49, 45, 50], or not controlling for drug use [45], or having a very small sample size [28,44,45,48]. It is known that heterogeneity of mood states or intensity of depressive symptoms may alter gene [36] and protein [74] expressions and methylation patterns [75]. Also, BMI and

smoking habit play a major role in inflammatory status [76-79] and gene expression [80-83].

Some primordial cares are required during the investigation of genetic biomarkers, as replicating the data present in literature and validating the new findings, applying adequate study designs, subjects' assessment and selection. Those procedures are the basis for finding reliable genetic biomarkers, which may contribute considerably to clinical practice.

5. CONCLUSION

As well as there is a lack of genetic biomarkers studies investigating differences between BPD and MDD, there are many studies in the literature that do not take all the methodological care necessary to avoid bias, making it harder finding reliable biomarkers that could help in clinical practice. More than finding new genetic biomarkers, it is essential to validate the existing data in the literature. BDNF gene expression was outstanding among all others selected genetic biomarkers because it distinguished MDD and BPD groups and the finding could be reproduced in more than one study.

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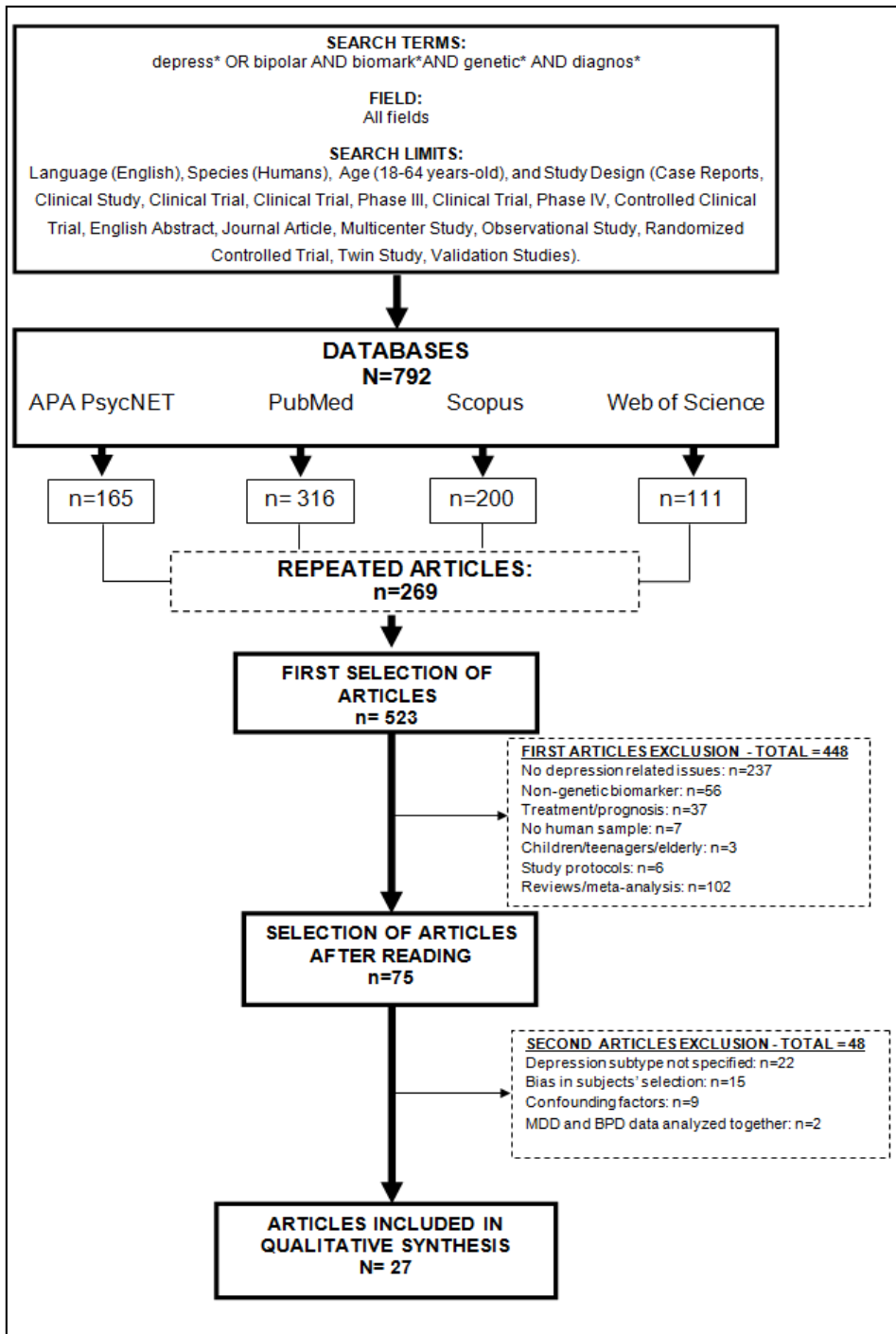


Figure 1. Articles search and selection criteria flowchart

Table 1. Characteristics and results of selected studies that assessed genetic biomarker candidates for BPD.

GENETIC ANALYSIS	AUTHORS, YEAR	GROUP (mood state)	RESULT BIOMARKER CANDIDATE	VALIDATION	BIAS
Gene expression	Akarsu et al. (2015)	BPD (man) vs. HC	↑NDUFV1, ↑NDUFV2, ↑NDUFS1	no	n/a
Gene expression	Munkholm et al. (2015)	BPD (dep, man, eut) vs. HC	↓TOGG1, ↑POLG	yes	Different mood states between BPD
Gene expression	Kato et al. (2011)	BPD (unknown) vs. HC	↑ANK3, ↓RASGRP1, ↓POLG1	yes	No evaluation of mood states or symptoms severity
Gene expression	Zhang et al. (2011)	BPD (eut) vs. HC	↑P11	no	n/a
Gene expression	Padmos et al. (2008)	BPD (dep, man, eut) vs. HC	↑PDE4B, ↑IL1B, ↑IL6, ↑TNF, ↑TNFAIP3, ↑PTGS2, ↑PTX3, ↑MAPK6, ↑DUSP2, ↑NAB2, ↑ATF3, ↑BCL2A1, ↑EMP1, ↑CCL7, ↑CCL20, ↑CXCL2, ↑CCR2, ↑CDC42, ↓CCL2,	yes	Different mood states between BPD
Gene expression	Padmos et al. (2008)	BPD (eut) vs. HC	↑PDE4B, ↑IL1B, ↑IL6, ↑TNF, ↑TNFAIP3, ↑PTGS2, ↑PTX3, ↑MAPK6, ↑DUSP2, ↑NAB2, ↑ATF3, ↑BCL2A1, ↑CCL7, ↑CCL20, ↑CXCL2, ↑CCR2, ↑CDC42, ↓CCL2, ↓EMP1	yes	n/a
Gene expression	Kittel-Schneider et al. (2015)	BPD (unknown) vs. HC	n.s.	no	Small sample size, difference in age between groups, no evaluation of mood states or symptoms severity, some subjects with substance abuse disorder and smokers
Protein Expression	Kazuno et al. (2013)	BPD (unknown) vs. HC	↑PGAM-1	yes	No evaluation of mood states or symptoms severity

Methylation	Nohesara et al. (2011)	BPD (unknown) vs. HC	↓MB-COMT promoter	no	No evaluation of mood states or symptoms severity
Methylation	Ghadirivasfi et al. (2011)	BPD (unknown) vs. HC	↓HTR2A - T102C	no	No evaluation of mood states or symptoms severity
Polymorphisms	Kittel-Schneider et al. (2015)	BPD (unknown) vs. HC	n.s.	no	Small sample size, difference in age between groups, no evaluation of mood states or symptoms severity, some subjects with substance abuse disorder and smokers

BPD: bipolar disorder; HC: healthy controls; dep: depressive state; eut: euthymic state; man: manic state; n/a: not applied; n.s.: no significant difference; ↑: upregulation (or polymorphism more frequent) in patients when compared to HC; ↓dowregulation (or polymorphism less frequent) in patients when compared to HC.

Table 2. Characteristics and results of selected studies that assessed genetic biomarker candidates for MDD.

GENECTIC ANALYSIS	AUTHORS, YEAR	GROUP (severity of symptoms)	RESULT BIOMARKER CANDIDATE	VALIDATION	BIAS
Gene Expression	Rizavi et al. (2016)	MDD (severe) vs. HC	↑IL1β, ↑IL6, ↑TNFα, ↑IL1R1, ↑IL1RA, ↑TNFR1, ↑TNFR2	no	No body max index or smoking habit data
Gene Expression	Watanabe et al. (2015)	MDD (moderate) vs. HC	↑PDGFC, ↑SLC6A4, ↑ARHGAP24, ↑HDAC5, ↓PRNP	yes	The influence physical of body max index, smoking, infection, and inflammation on leukocyte gene expression was not examined.
Gene Expression	Numata et al. (2015)	MDD (severe) vs. HC	↑GSK3B	yes	No body max index or smoking habit data
Gene Expression	Garbett et al. (2015)	MDD (unknown severity) vs. HC	↓PCDH10, ↓TNXB, ↓PPL, ↓MET	yes	No evaluation of symptoms severity
Gene Expression	Teyssier et al. (2013)	MDD (severe) vs. HC	n.s.	no	Small sample size
Gene Expression	Milanesi et al. (2012)	MDD (at least moderate) vs. HC	↓ErbB3	no	Difference in age between groups
Gene Expression	Frodl et al. (2012)	MDD (severe) vs. HC	n.s.	no	n/a
Gene Expression	Yi et al. (2012)	MDD (at least moderate) vs. HC	Δ ABL1, Δ AP3B1, Δ C19orf6, ΔCAPRIN1, ΔFGD3, ΔNRAS, ΔPA2G4, ΔPIK3AP1, ΔPRKCB, ΔPURA, ΔSLC16A3, ΔSTRN, ΔTERF2, ΔTM6SF2, ΔZCCHC3	yes	n/a

miRNA Expression	Garbett et al. (2015)	MDD (unknown severity) vs. HC	<p>↑hsa-miR-132, ↑hsa-miR-421, ↑hsa-miR-542-3p, ↑hsa-miR-450a, ↑hsa-miR-16-2, ↑hsa-miR-424, ↑hsa-miR-628-3p, ↑hsa-miR-629, ↑hsa-miR-4293, ↑hsa-miR-661, ↑hsa-miR-3909, ↑hsa-miR-33a, ↑hsa-miR-135b, ↑hsa-miR-7, ↑hsa-miR-4267, ↑hsa-miR-548aa, ↑hsa-miR-548d-3p, ↑hsa-miR-613, ↑hsa-miR-3714, ↑hsa-miR-1294, ↑hsa-miR-429, ↓hsa-miR-377, ↓hsa-miR-122, ↓hsa-miR-32, ↓hsa-miR-196b, ↓hsa-miR-193a-3p, ↓hsa-miR-337-5p, ↓hsa-miR-675, ↓hsa-miR-3176, ↓hsa-miR-21, ↓hsa-miR-22, ↓hsa-miR-425, ↓hsa-miR-185, ↓hsa-miR-296-5p, ↓hsa-miR-103a, ↓hsa-miR-107, ↓hsa-miR-186, ↓hsa-miR-887</p>	yes	No evaluation of symptoms severity
lncRNA Expression	Cui et al. (2017)	MDD (moderate and euthymics) vs. HC	<p>↓TCONS_00019174, ↓ENST000005662, ↓NONHSAG045500, ↓NST0000051757, ↓NONHSAT03404, ↓NONHSAT142707</p>	yes	Different levels of depressive symptoms in MDD sample
lncRNA Expression	Cui et al. (2016)	MDD (severe) vs. HC	<p>↓TCONS_L2_00001212, ↓NONHSAT10289, ↓TCONS_00019174, ↓ENST00000566208, ↓NONHSAG045500, ↓ENST00000517573, ↓NONHSAT03404, ↓NONHSAT142707</p>	yes	n/a
Protein Expression	Xu et al. (2012)	MDD (at least moderate) vs. HC	n.s.	yes	n/a
Methylation	Numata et al. (2015)	MDD (at least moderate) vs. HC	<p>↓GSK3B (cg14472315), ↓DGKH (cg00109274), ↓SGK1 (cg06642177)</p>	yes	No body mass index or smoking habit data

Methylation	Fuchikami et al. (2011)	MDD (at least moderate) vs. HC	BDNF CpG I subunits ↓1, ↓9, ↓5, ↓18, ↑19, ↑20, ↑21, ↑22, ↓23, ↓24, ↑28, ↑32, ↑36, ↓37, ↑47, ↑48, ↓52, ↓61, ↓63, ↓71, ↓77, ↓78, ↓79, ↑80, ↑81	yes	n/a
Polymorphism	Kreinin et al. (2015)	MDD (at least moderate) vs. HC	n.s	no	Difference in age between groups; small sample size
Polymorphism	Ho et al. (2013)	MDD(at least moderate) vs. HC	n.s	no	Difference in proportion of sexes between groups; small sample size
Polymorphism	Tian et al. (2012)	MDD (unknown severity) vs. HC	↑ rs11569017 (T)–rs11569126 (G) haplotype (EGF gene)	no	No evaluation of symptoms severity

HC: healthy controls; MDD: major depressive disorder; n/a: not applied; n.s.: no significant difference; ↑: upregulation (or polymorphism more frequent) in patients when compared to HC; ↓dowregulation (or polymorphism less frequent) in patients when compared to HC; Δ: difference (study did not specify if there was up or downregulation) in expression between MDD and HC samples.

Table 3. Characteristics and results of selected studies that assessed genetic biomarker candidates for BPD and/or MDD.

GENECTIC ANALYSIS	AUTHORS, YEAR	GROUPS (mood state and/or severity of symptoms)	RESULT BIOMARKER CANDIDATE	VALIDATION	BIAS
Gene Expression	Powell et al. (2014)	BPD (eut) vs. MDD (eut and moderate-severe)	CCL24 (BPD <MDD)	yes	Different mood states between BPD and MDD samples; MDD sample younger than other groups; less clinical problems in MDD sample than other groups
Gene Expression	Powell et al. (2014)	MDD (eut and moderate-severe) vs. HC	↑CCL24, ↓CCR6, ↓NR3C1	yes	Different mood states between BPD and MDD samples; MDD sample younger than other groups; less clinical problems in MDD sample than other groups
Gene Expression	Li et al. (2014)	BPD (severe depression) vs. MDD (severe) vs. HC	BDNF (BPD<MDD<HC)	yes	n/a
Protein Expression	Maccarrone et al. (2013)	BPD (man and dep) vs. HC	↑NEGR1, ↑SPTBN1, ↑OMG, ↑SCG5, ↑PTPRZ1, ↑ATP6V0D1, ↑CAPZA2, ↑CRTAC1, ↑NPDC1, ↑NAPG, ↑CNDP1, ↑CADM2, ↑ATP2B1, ↑SEZ6, ↑GPX3, ↑CHGA	yes	Different moods in BPD samples

Protein Expression	Maccarrone et al. (2013)	MDD (unknown severity) vs. HC	↑GNAI2, ↑CAPZA2, ↑STXBP1, ↑ATP2B1, ↑FAM159B	yes	Unknown level of depressive symptoms in MDD sample
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BPD: bipolar disorder; HC: healthy controls; dep: depressive state; eut: euthymic state; man: manic state; MDD: major depressive disorder; n/a: not applied; n.s.: no significant difference; ↑: upregulation (or polymorphism more frequent) in patients when compared to HC; ↓: downregulation (or polymorphism less frequent) in patients when compared to HC; >: upregulation (or polymorphism more frequent); <: downregulation (or polymorphism less frequent).
