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Insight into susceptibility genes associated with bipolar disorder: a systematic review

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Abstract. – OBJECTIVE: Bipolar disorder (BD) is a severe disorder, and it is associated with an increased risk of mortality. About 25% of patients with BD have attempted and 11% have died by suicide. All these characteristics suggest that the disorders within the bipolar spectrum are a crucial public health problem. With the development of molecular genetics in recent decades, it was possible to more easily detect risk genes associated with this disorder. This study aimed at summarizing the findings of systematic reviews and meta-analyses on the topic and assessing the quality of the available evidence.

MATERIALS AND METHODS: PubMed/Medline and Web of Science were searched to identify systematic reviews and meta-analyses published during 2013-2019. Standard methodology was applied to synthesize and assess the retrieved literature.

RESULTS: This systematic review identifies a number of potential risk genes associated with bipolar disorder whose mechanism of action has yet to be confirmed. They are divided into several groups: 1) a list of the most significant susceptibility genetic factors associated with BD; 2) the implication of the ZNF804A gene in BD; 3) the role of genes involved in calcium signaling in BD; 4) DNA methylation in BD; 5) BD and risk suicide genes; 6) susceptibility genes for early-onset BD; 7) candidate genes common to both BD and schizophrenia; 8) genes involved in cognitive status in BD cases; 9) genes involved in structural alteration in BD brain tissue; 10) genes involved in lithium response in BD.

CONCLUSIONS: Future research should concentrate on molecular mechanisms by which genetic variants play a major role in BD. Supplemental research is needed to replicate the applicable results.

Key Words:
Bipolar disorder, Genes, Gene regions, Genome-wide association, Genomic mutations, Chromosome.

Introduction

Bipolar disorder involves a very heavy burden of suffering for those who are affected by it, for its family members and the environment that surrounds it. BD causes unusual changes in the person's mood, energy and the capacity to function[1]. The clinical history of the disease may present episodes from mild depression and transitory hypomania to critical psychotic mania or depression. The elevated rates of delayed or mistaken diagnosis reported by bipolar patients imply that there is still a huge gap between the available knowledge of BD and its implementation in the clinical setting. There are still controversies related to the identification, classification and management of this condition[2]. It is widely accepted that bipolar disease is often misdiagnosed. An average of 8.9 years passed between the beginning of symptoms and the appropriate diagnosis of BD. One of the factors that contribute to this misdiagnosis is that patients believe their manic symptoms are normal and advantageous. The symptoms can also be very inconstant (starting from impulsivity behavior, fluctuations in the level of energy and substance abuse) and they can mask the BD[3]. The pathophysiology of BD has not been fully clarified because knowledge about the mechanisms that contribute to this disease is limited[4]. Bipolar disorder is related to an enhanced risk of mortality. About 25% of patients have attempted suicide and 11% have died by suicide. All these characteristics suggest that the bipolar spectrum disorder is a crucial public health problem[5].

The etiology of BD is complex, involving a number of independent and interlinked genetic factors. Even though the etiology has not yet been fully elucidated, a number of studies suggest that BD has a strong hereditary basis[6]. It is estimated that the risk of developing BD due to the influence

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of genetic factors is 60-85%[6]. Additional clinical data show that the risk of beginning and progressing BD in first-degree relatives of patients affected by this disease is 5-10 times higher than the prevalence in the general population[7]. With the development of molecular genetics in the recent decades, it was possible to more easily detect risk genes associated with BD. However, the method of inheritance has not been fully elucidated. For now, the disease is thought to be polygenic, inherited from a non-Mendelian inheritance model[7]. The use of hypothesis-free genome-wide association studies (GWAS) methodology has been on the rise in recent years. Thanks to this methodology, a number of risk genetic alleles have been identified in many genes associated with BD. Among them, CACNA1C and ANK3 have emerged as one of the most significant genetic risk factors involved in BD[7].

The purposes of the present systematic review are: a) to overview the findings of systematic reviews and meta-analyses on the association of bipolar disorder and potential risk genes; b) to summarize current and available evidence for genes and genetic alleles that play a role as a risk factor in the course and outcome of BD; c) to show which genes participate in pathological processes that are generated by the disease itself.

Materials and Methods

Recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used in the design, organization, and execution of the procedures to conduct the search strategy[8].

Search Strategy

To identify studies, we searched PubMed/Medline and Web of Science databases using the following keywords: "bipolar disorder and genes, or gene regions, or genome-wide association, or genomic mutations, or chromosome". We applied the following restrictions: latest 6 years; systematic review or meta-analysis; including data on humans. Furthermore, the references of all articles identified were carefully searched for additional studies. We reviewed all papers published in the English language from 31 December 2013 to 31 December 31, 2019, with an update on 30 May 2020.

Inclusion Criteria

Criteria for inclusion were:

- written in English;
- being a systematic review or a meta-analysis;
- should include studies with potential risk genes associated with bipolar disorder.

Scoping reviews and narrative reviews that were not systematic were excluded. Indeed, all studies that did not meet inclusion criteria were excluded. **Supplementary Table A** includes the titles of the excluded articles.

Data Extraction and Analysis

Two authors inspected the list of the retrieved articles. An evaluator inspected the title and abstract of the retrieved articles to establish whether they were congruent with the search criteria. A second, more experienced reviewer crosschecked this inspection. Duplicates were eliminated. Discrepancies were solved by discussion. Articles that passed the first check were thoroughly read to confirm they met the inclusion criteria. Again, a senior evaluator crosschecked again the first check by the junior evaluator. Collected articles were then thoroughly reexamined for content to confirm that they were congruent with the inclusion criteria, and their references section was scanned to identify missed systematic reviews or meta-analyses. The same procedure was applied to the scanning of the additional sources (Figure 1). The following data were extracted from the article: the name of the study, name of the author, publisher and year, in which country the systematic review/meta-analysis was done, which genes are analyzed, investigated genes mutations, how many studies are included, which databases are used, and what are the conclusions and recommendations.

Included Papers and Qualitative Assessment

We found 57 unduplicated studies (systematic review and meta-analysis). After this initial literature search, 19 meet criteria for inclusion and were selected for this systematic review. Table I sums up the details of the precise description and main findings of the included systematic reviews and meta-analysis. The critical qualitative appraisal of the systematic reviews and meta-analyses was done with the Scottish Intercollegiate Guidelines Network (SIGN) implementation of the assessment of multiple systematic reviews (AMSTAR)[9]. The SIGN implementation of the AMSTAR is rich in clarifications and notes to apply the scores[10]. Two evaluators independently assigned the rate to each item of the SIGN's AMSTAR. Rating

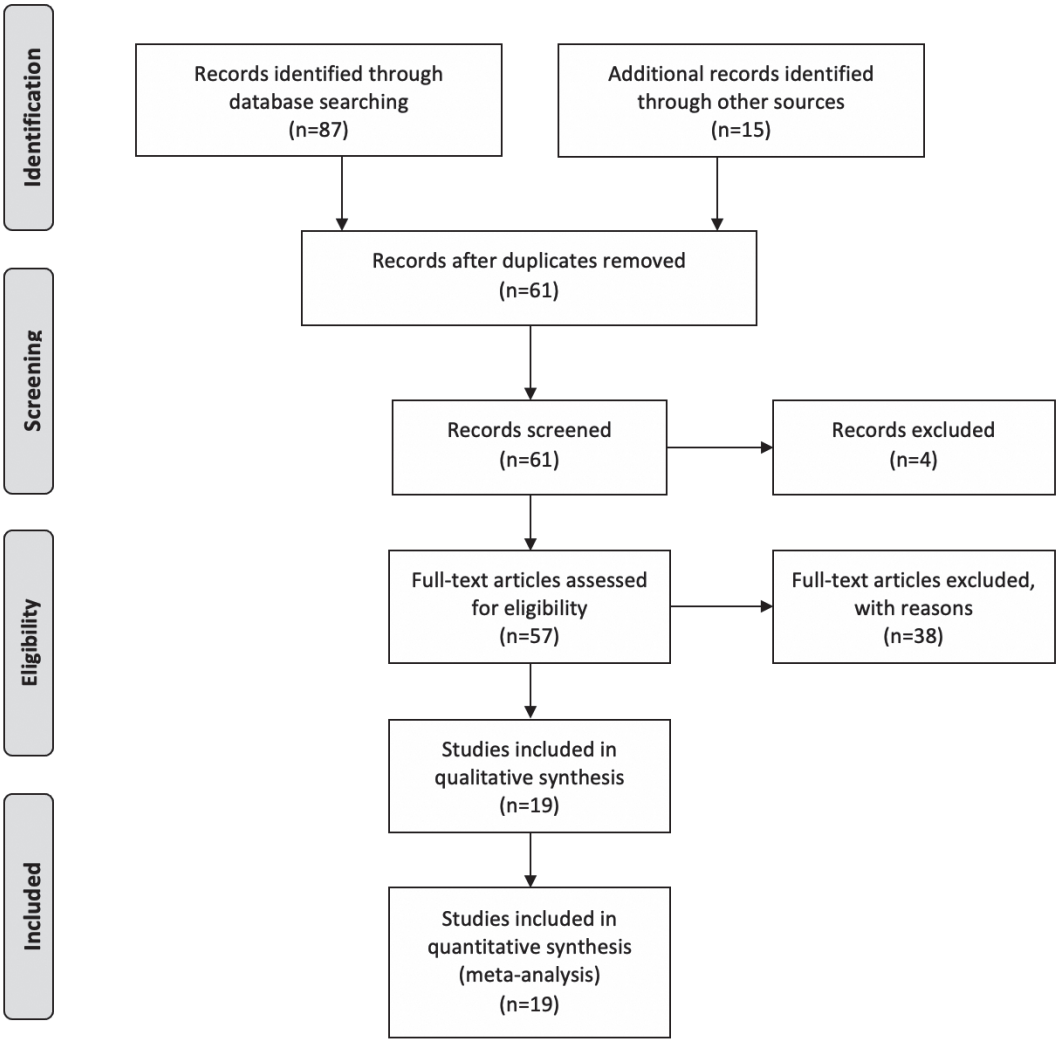

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Figure 1. Prisma Flow Diagram.

"yes" was assigned when the criterion was present. When the criterion was not met or it was uncertain whether it was met or not, the assigned rating was "no". A global score of "high quality", "acceptable quality", and "low quality" was assigned based on this detailed evaluation. **Supplementary Table B** summarizes the full evaluation of the included articles.

Data Synthesis and Presentation

We tabulated the main characteristics of the retrieved systematic reviews and meta-analyses. We also summarized the main findings with a focus on the outcome of interest. The qualitative assessment of the retrieved systematic reviews and meta-analyses was tabulated and discussed with reference to the main findings of each review.

Results

Out of 57 records that were identified after duplicates were removed, we identified 19 systematic reviews/meta-analyses that covered the investigated topic (Table I).

Table I. Summary description and main findings of the included systematic reviews and meta-analysis.

Systematic review Authors Year	Authors Year	Summary description	Searched databases	No. of studies included	Processed genes
Systematic review of genome-wide gene expression studies of bipolar disorder	Seifuddin, Fayaz et al[87] (2013)	Identification of genome-wide gene expression studies of bipolar disorder to synthesize the current findings	PubMed, Public microarray repositories including Gene Expression Omnibus, Array Express	10	FKBP5 WFS1 DUSP6 NPY GRIK2 S100B CACNA1C
TPH2 Gene Polymorphisms and Bipolar Disorder: A Meta-Analysis	Gao, Jin et al[93] (2015)	Systemically assess the association of different TPH2 variants with bipolar disorder	PubMed, Embase, HuGNet, and China National Knowledge Infrastructure (CNKI)	7	TPH2
The genetics of early-onset bipolar disorder: a systematic review	Kennedy, Kevin P et al[106] (2015)	Systemically assess the association between genes and early-onset bipolar disorder	PubMed	73	BDNF DAOA MTHFR DRD2 COMT 5-HTTLPR HTR2C TLR4 TLR2 CACNA1C TENM4 ANK3
Association between variants of zinc finger genes and psychiatric disorders: Systematic review and meta-analysis	Sun Y, Hu D, Liang J, et al[94] (2015)	ZNF804A as a susceptibility gene for multiple psychiatric disorders (especially schizophrenia and bipolar disorder)	PubMed, Embase, Proquest and Google Scholar	24	ZNF804A
Cellular models to study bipolar disorder: a systematic review	Viswanath, Biju et al[95] (2015)	Systematically reviewing current literature on the application of the above cellular models to understand the biology of bipolar disorder	Medline, PsychInfo and Scopus	85	HSPF1 NR1D1 GSK3B ANK3 RASGRP1 POLG1 CACNA1C
The HPA axis in bipolar disorder: systematic review and meta-analysis	Belvederi Murri, Martino et al[92] (2016)	Identification of the role of genes related to the HPA-axis in patients with bipolar disorder	PubMed, Psycinfo and Embase	41 (total) 15 (only for genes)	TSPO
Biological aspects and candidate biomarkers for psychotic bipolar disorder: a systematic review	Buoli, Massimiliano et al[96] (2016)	Update the available data about the potential biological markers of the psychotic dimension of bipolar disorder	PubMed, ISI Web of Knowledg and PsychInfo	145	S100B YWHAH NRG1 DAOA COMT
A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development	Cipriani, A et al[97] (2016)	Summarizing of LTCC antagonists in the treatment and prophylaxis of bipolar disorder and their implications for developing novel LTCC antagonists for use in bipolar disorder	Cochrane Library, Medline, PreMedline, PubMed, PsycInfo	23	CACNA1C CACNA1D CACNB2

Table continued

Table I. ***(Continued).*** Summary description and main findings of the included systematic reviews and meta-analysis.

Systematic review Authors Year	Authors Year	Summary description	Searched databases	No. of studies included	Processed genes
DNA methylation in peripheral tissue of schizophrenia and bipolar disorder: a systematic review	Teroganova, Nina et al[98] (2016)	Synthesize and evaluate the quality of available evidence for epigenetic modifications (specifically DNA methylation) in peripheral blood and saliva samples of schizophrenia and bipolar disorder patients in comparison to healthy controls	Medline, Embase, PsychInfo and PubMed	33	BDNF COMT HTR1A SLC6A4 GDNF 5-HTR1A
The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies	Amare, A T et al[99] (2017)	Analysis of cardiometabolic disease risk (CMD-R) genes that are also associated with mood disorders	National Human Genome Research Institute (NHGRI) GWAS catalog and Multiple Tissue Human Expression Resource (MuTHER)	153 (meta-GWA studies).	MTHFR CACNA1D CACNB2 GNAS TCF7L2 HTR1A CRY2 IGF1 ITIH1 ITIH3 ITIH4 BDNF CREB1 NCAN GSK3B SLC18A1
The Schizophrenia Susceptibility Gene ZNF804A Confers Risk of Major Mood Disorders	Ou, Jianjun et al[66] (2017)	Systematically collected data from the literature to perform meta-analyses of these SNPs from diverse ethnic groups	PubMed, Web of Science and Embase	7	CACNA1C ZNF804A
The relationship between genetic risk variants with brain structure and function in bipolar disorder: A systematic review of genetic-neuroimaging studies	Pereira, Licia P et al[100] (2017)	Providing a comprehensive and up-dated synthesis of all available 'imaging genetics' literature in bipolar disorder	Embase,PubMed/ Medline, and PsycInfo	44	CACNA1C ANK3 BDNF 5-HTTLPR, SREBF2 DAOA NRG1
ANK3 gene polymorphisms and bipolar disorder: a meta-analysis	Roby, Yang et al[101] (2017)	Evaluation of the main effects of ANK3 gene variants pertaining to bipolar disorder	PubMed, Medline, Embase, PsycInfo, and Scopus	14	ANK3
Genome-wide association studies of bipolar disorder: a systematic review of recent findings and their clinical implications	Ikeda M, et al[103] (2018)	Providing a brief summary of the susceptibility genes for bipolar disorder and discuss their clinical implications	GWAS Catalog. In addition bioRxiv	12	ANK3 CACNA1C TENM4 POU3F2 ERBB2 TRANK1 FADS1/2/3

Table continued

Table I. ***(Continued).*** Summary description and main findings of the included systematic reviews and meta-analysis.

Systematic review Authors Year	Authors Year	Summary description	Searched databases	No. of studies included	Processed genes
Interactions Between Variation in Candidate Genes and Environmental Factors in the Etiology of Schizophrenia and Bipolar Disorder: a Systematic Review	Misiak B, Stramecki F, Gawęda Ł, et al[67] (2018)	Performing an updated systematic and comprehensive review of studies investigating interactions between genetic variation in candidate genes and environmental factors in patients with schizophrenia spectrum phenotypes and bipolar disorder	PubMed, Medline, ERIC (Education Resource Information Center)	11 eligible studies performed on patients with BD and 50 studies on schizophrenia spectrum phenotypes as well as 1 study from both diagnostic groups	COMT BDNF FKBP5
Association between completed suicide and bipolar disorder: a systematic review of the literature	Plans, L et al[91] (2018)	An overall review of the existing literature of completed suicide in bipolar disorder patients, including clinical and genetic data	Medline/PubMed, PsycInfo and Cochrane database	61	TPH1 TPH2 5-HT1A 5-HTTLPR AKT1 GSK3B ADRA2 BDNF
The use of pharmacogenetic testing in patients with schizophrenia or bipolar disorder: a systematic review	Routhieaux, Melanie et al[105] (2018)	Description of the clinical value of pharmacogenetic testing in psychiatric pharmacy practice as it pertains to adult patients with schizophrenia or bipolar disorder	PubMed and EBSCOhost	18	BDNF SYN2 PDLIM5 COMT
Frequency and association of mitochondrial genetic variants with neurological disorders	Cruz, Ana Carolina P et al[102] (2019)	Identification and description in detail all genetic variants in mtDNA that were previously associated with neurodevelopmental syndromes, neurodegenerative diseases, and neuropsychiatric disorders	PubMed and Scopus	174	MT-ND1 MT-CYB
Associations of the serotonin transporter promoter polymorphism (5-HTTLPR) with bipolar disorder and treatment response: a systematic review and meta-analysis	Rao S, Han X, Shi M, et al[104] (2019)	Association between 5-HTTLPR and bipolar disorder	PubMed, Embase, and PsycInfo	38	5-HTTLPR

The Most Significant Susceptibility Genetic Factors Associated with BD

The most commonly associated genes to bipolar disorder up to date are: CACNA1C, ANK3, NCAN, BDNF, COMT, 5-HTTLPR, NRG1, and FADS1. CACNA1C (calcium voltage-gated channel subunit alpha1 c) gene is generally considered the cardinal one for BD so far according to the latest genome-wide association studies (GWAS)[11]. It is known that encodes the L-type voltage-dependent calcium channel 1C subunit. As claimed by two GWAS, its SNP rs1006737 is suggested as a risk variant for bipolar disorder[12]. An interesting fact is that the BD carriers of this risk genetic variant have a reduced volume of the left putamen[13] and increased activity of the amygdala in facial affect recognition task[14]. Modification of its expression has been observed in the frontal cortex in BD cases[15]. Next, the ANK3 (ankyrin 3) gene encodes a protein responsible for the stabilization and proper localization of ion channels, as well as for cell adhesion to Ranvier's nodes and initial axon segments[16]. Different genetic alleles from it may affect the white matter structure of the brain. A link between bipolar disorder and SNP rs10994336 has been shown. This genetic variant is involved in cognitive function, especially important in brain deficiency[17]. On the other hand, the risk C-allele of rs10761482 SNP is associated with impaired verbal expression, impaired speed of processing the information in the brain, and impaired logical memory. In patients with BD, more precisely in carriers of this genetic allele are found reduce in fractional anisotropy (FA) in the forceps minor[18]. A very important thing to note is that this gene potentially plays a major role in myelination in BD[19]. To sum up, different genetic alleles of the ANK3 gene mainly affect the white matter of the brain, which might lead to cognitive decline.

Besides, genetic risk factor SNP (rs1064395) in the NCAN (neurocan) gene has the potential to be a risk factor for bipolar disorder only in Europeans and Africans[20]. It is thought to play a function in structural changes in the cerebral cortex in individuals with BD[21]. This gene encodes a protein that balances cell adhesion, cell migration, and axon direction. The BNDF protein, which is encoded by the BNDF (brain-derived neurotropic factor) gene on chromosome 11p14.1, as a member of the superfamily of neurotrophins, participates in the differentiation of neurons, neuronal continuance, and the dependent plasticity of synapses in developed neurons[22]. The SNP rs6265 of it leads to a change in the nucleotide 196 (G/A), resulting in Val66Met substitution[23]. There is evidence[24] that patients with bipolar disorder and carriers of this risky allele have decreased hippocampal volume. This risk gene allele is also associated with an increased predisposition to suicide in BD[25]. On the other hand, there are also studies that show that there is no link between this risky genetic allele and bipolar disorder[26]. Many authors[27] think that BDNF gene has a central place in the pathophysiology of bipolar disorder. A recent meta-analysis[28] shows that the peripheral level of the protein encoded by this gene can be used as a potential biomarker to assess the activity of bipolar disorder. According to these authors[28], hypermethylation of the BDNF exon 1 promoter has also been reported in BD. COMT (catechol-o-methyltransferase) gene catalyzes the transfer of the methyl group to catecholamines, such as the neurotransmitters epinephrine, norepinephrine and dopamine. COMT 158Val allele has been linked to increased levels of schizotypy in patients with bipolar disorder who suffered trauma in childhood[29]. Furthermore, COMT 158Val/Val genotype is the main predictor of lower global cognitive presence in patients with bipolar disorder[30]. As far as for the 5-HTTLPR (serotonin-transporter-linked polymorphic region) gene, one study[31] found that the S allele of this gene might be affected by early life stress on the gray matter of the brain in the right prefrontal cortex in patients with BD. Moreover, this allele also was associated with an elevated volume of the right amygdala in the same group of patients[32]. The NRG (neuregulin 1) gene participates in the formation of myelin, synaptic transmission, and the survival of neurons and glial cells[33].

In patients with bipolar disorder, carriers of the NRG SNP (SNP8NRG221533) are associated with increased white matter mass in the cingulum, para-hippocampal gyrus, and the corpus callosum compared with non-carriers[34]. Table II includes the names, functions, and relations of the potential genes associated with bipolar disorder, according to the findings from included studies.

The Implication of the ZNF804A Gene in BD

The ZNF804A (zinc finger protein 804A) gene has been often related to bipolar disorder. ZNF804A gene is predominantly expressed in the brain. After birth, ZNF804A appearance is decreased suggesting that it probably performs a critical function in brain reorganization,

Table II. Potential risk genes for bipolar disorder.

Gene	Name	Function / Relation with Bipolar disorder
ZNF804A	Zinc Finger Protein 804A	Polymorphisms in this gene are thought to confer an increased predisposition to schizophrenia, bipolar disorder, and heroin addiction[86]. The rs1344706 SNP at chromosome 2q32.1 of ZNF804A is the first risk factor for bipolar disorder and was recognized by GWAS[42].
ANK3	Ankyrin 3	Ankyrins are a family of proteins that are believed to link the integral membrane proteins to the underlying spectrin-actin cytoskeleton. They play key roles in activities such as cell motility, activation, proliferation[86]. The C allele in rs10994415 of ANK3 is associated with bipolar disorder[77].
CAC NA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C	Encodes an alpha-1 subunit of a voltage-dependent calcium channel[86]. Rs1006737 and rs2159100 are the most studied SNP variations from this gene for in mood disorders, including and bipolar disorder[68].
TENM4	Teneurin Transmembrane Protein 4	The protein encoded by this gene plays a role in establishing proper neuronal connectivity during development[86]. The hot-spot mutations reported in this gene in patients with bipolar disorder are the variants rs12576775 and rs17138171[68].
POU3F2	POU Class 3 Homeobox 2	POU3F2 is a protein-coding gene. The POU3F2 protein is associates with bipolar disorder. It is involved in the neocortex development in mice and is linked to a single nucleotide polymorphism, Rs1906252, that is associated with a cognitive phenotype: speed of processing information in the brain[68].
ERBB2	Erb-B2 Receptor Tyrosine Kinase 2	Encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases[86]. The importance of ERBB2 in bipolar disorder is further supported by a genome-wide significant association finding and by the observation of dysregulated ERBB2 expression in the dorsolateral prefrontal cortex[70].
TRANK1	Tetratricopeptide Repeat and Ankyrin Repeat Containing 1	Protein coding gene. Diseases associated with TRANK1 include epileptic encephalopathy and bipolar disorder. The main studied SNP is rs9834970 which is about 12 kb at 3 'UTR of the TRANK1 gene[68].
FADS1	Fatty Acid Desaturase 1	Highly associated with the plasma levels of n-3/n-6 polyunsaturated fatty acids and other general lipids (i.e., HDL/LDL/TG/T-cholesterol). The susceptibility SNP for bipolar disorder is the quantitative trait loci SNP with such blood lipid traits[121].
MTHFR	Methylenetetrahydrofolate Reductase	The encoded MTHFR enzyme catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine[86]. The common MTHFR C677T was associated with depression and bipolar disorder[122].
CAC NA1D	Calcium Voltage-Gated Channel Subunit Alpha1 D	Mediates the entry of calcium ions into cells. Rare variants in the calcium channel genes (CACNA1B, CACNA1C, CACNA1D) are connected with bipolar disorder and may influence treatment response to lithium[40].
CACNB2	Calcium Voltage-Gated Channel Auxiliary Subunit Beta 2	CACNB2 gene polymorphisms were involved in mood disorders and bipolar disorder[123].
GNAS	BRCA2 DNA Repair Associated	Control the activity of endocrine glands through adenylate cyclase enzyme[86]. SNPs in the GNAS gene were associated with bipolar disorder (rs6064714, rs6026565, rs35113254)[124].
TCF7L2	Transcription Factor 7 Like 2	Regulate blood glucose and homeostasis[86]. Genome-wide association study of bipolar disorder in European Americans recognizes a new risk allele (rs12772424-A/T) within the TCF7L2 gene[125].
HTR1A	5-Hydroxytryptamine Receptor 1A	Encodes a G protein-coupled receptor for 5-hydroxytryptamine (serotonin) and belongs to the 5-hydroxytryptamine receptor subfamily[86]. A remarkable decline in HTR1A mRNA levels in the brain of patients with mood disorders and bipolar disorder was found[126].

Table continued

Table II. ***(Continued).*** Potential risk genes for bipolar disorder.

Gene	Name	Function / Relation with Bipolar disorder
CRY1	Cryptochrome Circadian Regulator 1	It regulates the circadian clock. Polymorphisms in CRY1 gene were notably related to bipolar disorder[127].
IGF1	Insulin Like Growth Factor 1	The protein encoded by this gene is similar to insulin in function and structure. An overexpression of IGF1 gene of bipolar disorder patients who react well for lithium treatment was also described[76].
ITIH1	Inter-Alpha-Trypsin Inhibitor Heavy Chain 1	Encodes a member of the inter-alpha-trypsin inhibitor family of proteins. Among its related pathways are cell adhesion and cell-matrix glycoconjugates[86].
ITIH3	Inter-Alpha-Trypsin Inhibitor Heavy Chain 3	Encodes the heavy chain subunit of the pre-alpha-trypsin inhibitor complex[86].
ITIH4	Inter-Alpha-Trypsin Inhibitor Heavy Chain 4	Genetic variants located in the regions of ITIH1, ITIH3, ITIH4 genes were associated with bipolar disorder and suicidal attempt in bipolar disorder patients[128].
BDNF	Brain Derived Neurotrophic Factor	Encodes a member of the nerve growth factor family of proteins. Expression of this gene is reduced in Alzheimer's, Parkinson's, and Huntington's disease patients[86]. The Val66Met polymorphism was connected with depressive disorder, bipolar disorder and also suicidal behavior in depressed and bipolar disorder patients[129].
CREB1	CAMP Responsive Element Binding Protein 1	Involved in different cellular processes including thesynchronization of circadian rhythmicity and the differentiation of adipose cells[86]. The CREB1 gene variants (rs6785, rs2709370) were associated with increased bipolar disorder vulnerability. Other SNPs on the CREB gene were proposed for bipolar disorder and lithium response[75].
NCAN	Neurocan	Modulation of cell adhesion and migration[86]. SNP (rs1064395) in NCAN gene was established to be a risk factor for bipolar disorder in the European population[20].
GSK3B	Glycogen Synthase Kinase 3 Beta	The protein encoded by this gene is a serine-threonine kinase belonging to the glycogen synthase kinase subfamily. Diseases associated with GSK3B include Alzheimer's Disease and Bipolar Disorder[86]. In addition, rare variants in the GSK3B gene showed the risen risk for bipolar disorder[130].
SLC18A1	Solute Carrier Family 18 Member A1	The vesicular monoamine transporter which accumulates cytosolic monoamines into vesicles, using the proton gradient maintained across the vesicular membrane[86]. Variations in the SLC18A1 (rs988713, rs2279709, Thr136Ser) gene show susceptibility to bipolar disorder[131].
COMT	Catechol-O-Methyltransferase	Catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine[86]. COMT 158Val/Val genotype is a bold predictor of lower global cognitive presentation in patients with bipolar disorder[30].
FKBP5	FKBP Prolyl Isomerase 5	The protein encoded by this gene is a member of the immunophilin protein family, which play a role in immunoregulation and basic cellular processes involving protein folding and trafficking[86]. FKBP5 does play a role in the predisposition for bipolar disorder as well as in repetition of depression and rapidity of response to antidepressant medication[62].
S100B	S100 Calcium Binding Protein B	S100B proteins are localized in the cytoplasm and/or nucleus of a broad range of cells involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation[86]. SNPs as an example rs2339350 and rs3788266 are strongly associated with bipolar disorder[132].
YWHAH	Tyrosin 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Eta	This gene product belongs to the 14-3-3 family of proteins which mediate signal transduction by binding to phosphoserine-containing proteins[86]. One SNP (rs2246704) is actively related to bipolar disorder[133].

Table continued

Table II. ***(Continued).*** Potential risk genes for bipolar disorder.

Gene	Name	Function / Relation with Bipolar disorder
NRG1	Neuregulin 1	The protein encoded by this gene is a membrane glycoprotein that mediates cell-cell signaling and plays a critical role in the growth and development of multiple organ systems[86]. Bipolar disorder was also noticed to be positively related to two polymorphisms (d2s436 and d13s785) of two loci (2p11q14 and 13q21-33,) in a family-based study. NRG1 plays a role in the pathophysiology of bipolar disorder and could be considered as a biomarker of the disorder[134].
DAOA	D-Amino Acid Oxidase Activator	This gene encodes a protein that may function as an activator of D-amino acid oxidase, which degrades the gliotransmitter D-serine, a potent activator of N-methyl-D-aspartate (NMDA) type glutamate receptors[86]. SNP (rs1935062) in this gene is significantly associated with bipolar disorder[135].
WFS1	Wolframin ER Transmembrane Glycoprotein	This gene encodes a transmembrane protein, which is located primarily in the endoplasmic reticulum and ubiquitously expressed with highest levels in the brain, pancreas, heart, and insulinoma beta-cell lines[86]. Several studies have directly involved WFS in the etiopathogenesis of bipolar disorder[136].
DUSP6	Dual specificity phosphatase 6	This gene is known to negatively regulate member of the MAP kinase superfamily, which play a role in neuronal differentiation, neuronal survival, and long term neuroplasticity[137]. Some studies suggest an association between DUSP6 and bipolar disorder[138].
NPY	Neuropeptide Y	This gene encodes a neuropeptide that is widely expressed in the central nervous system and influences many physiological processes, including cortical excitability, stress response, food intake, circadian rhythms, and cardiovascular function. It was found that NPY mRNA expression is remarkable declined in the prefrontal cortex of subjects affected by bipolar disorder[116].
GRIK2	Glutamate receptor ionotropic kainate 2 isoform precursor	Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated in a variety of normal neurophysiologic processes[86]. GRIK2 gene probably plays a role in suicidal ideation in patients with bipolar disorder[139].
SLC6A4	Solute Carrier Family 6 Member 4	This gene encodes an integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons[86]. Differential methylation of serotonin 2A receptor (SLC6A4) in patients with bipolar disorder is found[140].
GDNF	Glial Cell Derived Neurotrophic Factor	Encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins[86]. This gene also being indicated in studies with bipolar patients[141].
SYN2	Synapsin II	This gene is a member of the synapsin gene family. Synapsins encode neuronal phosphoproteins which associate with the cytoplasmic surface of synaptic vesicles[86]. Synapsin II is involved in the modulation of neurotransmitter release in patients with bipolar disorder[142].
PDLIM5	PDZ And LIM Domain 5	It is thought to function in cardiomyocyte expansion and in restraining postsynaptic growth of excitatory synapses[86]. There was, however, a major difference in the expression of PDLIM5 mRNA in BD patients compared to controls, which may show that it is a good marker for BD in general[143].
MT-ND1	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 1	In patients diagnosed with bipolar disorder, it was also found elevated levels of mutated mtDNA copies[144]. In patients with bipolar disorder, one of the variants was found in MT-ND1 protein coding gene[145].
MT-CYB	Mitochondrially Encoded Cytochrome B	In patients diagnosed with bipolar disorder, it was also found elevated levels of mutated mtDNA copies[144]. In patients with bipolar disorder one of the variants was found in MT-CYB protein-coding gene[145].

Table continued

Table II. *(Continued).* Potential risk genes for bipolar disorder.

Gene	Name	Function / Relation with Bipolar disorder
HSPF1 (DNAJB1)	DnaJ Heat Shock Protein Family (Hsp40) Member B1	Encodes a member of the DnaJ or Hsp40 (heat shock protein 40 kD) family of proteins[86]. The gene HSPF1 has been found to be up-regulated in post-mortem brain from patients diagnosed with bipolar disorder[146].
NR1D1	Nuclear Receptor Subfamily 1 Group D Member 1	Encodes a transcription factor that is a member of the nuclear receptor subfamily 1[86]. When the circadian clock genes were examined with respect to lithium response in bipolar disorder, using LCLs, it was shown that lithium response was best seen by the A allele of NR1D1 rs2071427[74].
RASGRP1	RAS Guanyl Releasing Protein 1	This gene is a member of a family of genes characterized by the presence of a Ras superfamily guanine nucleotide exchange factor (GEF) domain[86]. A very important finding was down-regulation of RASGRP1. RASGRP1 codes for a guanyl nucleotide exchange factor that activates ras, and has binding domains for Ca2+ and diacylglycerol[147].
POLG1	DNA Polymerase Gamma, Catalytic Subunit	The major finding was down-regulation of POLG1 gene in patients with bipolar disorder. POLG1 gene codes for the catalytic subunit of mitochondrial DNA polymerase[31].
5-HTTLPR	Serotonin-transporter-linked polymorphic region	In patients with bipolar disorder, it is found that carriers of the 5-HTTLPR S (i.e., short) allele had increased radial diffusivity in several brain white matter tracts, including the cingulum gyrus, corpus callosum (body and genum) and corona radiata compared to non-carriers[72].
SREBF2	Sterol Regulatory Element Binding Transcription Factor 2	This gene encodes a member of the ubiquitously expressed transcription factor that controls cholesterol homeostasis. In the patients with bipolar disorder, it is found that SREBF2 rs1052717 polymorphism A/A genotype leads to increased radial diffusivity and reduced FA (fractional anisotropy) in the cingulum, corpus callosum, superior and inferior longitudinal fasciculi, and anterior thalamic radiation[71].
TPH2	Tryptophan hydroxylase 2	This gene encodes a member of the pterin-dependent aromatic acid hydroxylase family. The encoded protein catalyzes the first and rate limiting step in the biosynthesis of serotonin, an important hormone and neurotransmitter[86]. Elevated levels of TPH2 expression have been found in the dorsolateral prefrontal cortex of patients with bipolar disorder[148].
TPH1	Tryptophan Hydroxylase 1	This gene encodes a member of the aromatic amino acid hydroxylase family. The encoded protein catalyzes the first and rate-limiting step in the biosynthesis of serotonin, an important hormone, and neurotransmitter[86]. Three polymorphisms of TPH1(A218C, A779C, and A6526G) have been examined, and some studies showed a remarkable relation of this gene with the risk of suicide in the patients of bipolar disorder[46].
AKT1	AKT Serine/Threonine Kinase 1	The serine-threonine protein kinase encoded by the AKT1 gene is catalytically inactive in serum-starved primary and immortalized fibroblasts[86]. This gene is associated with the risk of suicide and violent attack attempts in patients with bipolar disorder[49].
ADRA2	Adrenoceptor Alpha 2A	Alpha-2-adrenergic receptors are members of the G protein-coupled receptor superfamily. The alpha-2-adrenergic receptors are a type of adrenergic receptors (for adrenaline or epinephrine), which inhibit adenylate cyclase[86]. Some variants of this gene (including the promoter N521K, C1291G, rs11195419) have been associated with suicide in patients with bipolar disorder[52].

Table continued

Table II. ***(Continued).*** Potential risk genes for bipolar disorder.

Gene	Name	Function / Relation with Bipolar disorder
DRD2	Dopamine Receptor D2	Encodes the D2 subtype of the dopamine receptor. This G-protein coupled receptor inhibits adenylyl cyclase activity[86]. DRD2 is involved in the etiology and it is probably a general risk factor for bipolar disorder[149].
HTR2C	5-Hydroxytryptamine Receptor 2C	Encodes a seven-transmembrane G-protein-coupled receptor. The encoded protein responds to signaling through the neurotransmitter serotonin[86]. There is an association between early-onset bipolar disorder and Cys23Ser polymorphism of this gene[150].
TLR4	Toll Like Receptor 4	The protein encoded by this gene is a member of the Toll-like receptor (TLR) family which plays a fundamental role in pathogen recognition and activation of innate immunity[86]. Two SNPs in the TLR4 gene are associated with bipolar disorder and early-onset bipolar disorder (rs1927914 and rs11536891)[60].
TLR2	Toll Like Receptor 2	The protein encoded by this gene is a member of the Toll-like receptor (TLR) family which plays a fundamental role in pathogen recognition and activation of innate immunity[86]. Two SNPs in the TLR2 are related to early-onset bipolar disorder (rs3804099 TT and TLR2 rs4696480)[59].
TSPO	Translocator Protein	The protein encoded by this gene is a key factor in the flow of cholesterol into mitochondria to permit the initiation of steroid hormone synthesis[86]. It was found an association between bipolar disorder and the rs6971 polymorphism in the TSPO gene, which is possible to modify the process of synthesis of steroids or its regulation[151].

which might lead to BD[35]. Promising risk genetic variants of it is rs1344706 were assumed to be involved in suicide-attempt efforts in BD patients[36]. The rs1344706 SNP at chromosome 2q32.1 of the ZNF804A gene is the first risk factor for bipolar disorder identified by GWAS. Different studies[37] from different European populations show that rs1344706 is likely a risk SNP for bipolar disorder in Europeans.

BD and Genes Involved in Calcium Signaling

The effect of calcium signaling in bipolar disorder has been studied for a long time. Certain genetic findings have shown[38] that impaired calcium signaling is probably responsible for the pathophysiology of bipolar disorder. It has been found[39] that there are modifications in calcium levels in the cerebrospinal fluid observed in mania. One of the biggest culprits for impaired calcium signaling mediated by LTCCs (L-type calcium channels) is the abovementioned CACNA1C gene which encodes the LTCC Cav1.2 α1 subunit. Other genes included in this group are CACNA1D gene (calcium voltage-gated channel subunit alpha1 d) which encodes the Cav1.3 α1 subunit and CACNB2 gene (calcium voltage-gated channel auxiliary subunit beta 2), which encodes the β2 subunit[40]. The importance of LTCCs is reflected in the fact that they are involved in memory and circadian rhythm, which are of particular importance for BD. Hence, they are significant because of their use as a target for antagonists in the treatment of BD[41].

DNA Methylation in BD

DNA methylation of peripheral tissues is another phenomenon observed in bipolar disorder. Receptors, neurotransmitters, and transporters are most commonly methylated. In two studies, hypermethylation of the exon 1 promoter of the BNDF was observed[42,43]. As mentioned above, BDNF is a neurotrophin, and its levels in the peripheral blood are reduced in BD cases[44]. Moreover, hypermethylation of 5-HTR1A (hydroxytryptamine serotonin 1A receptor) gene has been reported in patients with BD[45].

BD and Risk Suicide Genes

Completed suicide is a crucial cause of death in patients with bipolar disorder. In the latest years several studies focused on the potential candidate genes associated with suicidal behavior in bipolar disorder. Candidate gene-based association

studies have given important evidence about the integration of genetic variation in suicidal presence. According to certain studies[46,47], polymorphisms from the TPH1 (tryptophan hydroxylase 1)[46] and TPH2 (tryptophan hydroxylase 2)[47] genes have been shown to be a risk factor for increased suicide attempts. This group also includes the gene responsible for transporting the serotonin, SLC6A4 (solute carrier family 6 member 4) gene, which is also the central gene for suicide-related research in BD cases[48]. Intriguingly, according to one study, an association was found between the AKT1 (AKT serine/threonine kinase 1) gene and suicide attempts and attempts with violence in BD[49]. As reported by another study[50], a link was found between the GSK3B (glycogen synthase kinase 3 beta) gene and an increased level of impulsivity, and thus an increased risk of suicide in BD individuals. The well-known BDNF gene is also known to be bound to suicide. A post-mortem study identified decreased levels of BDNF mRNA in the hippocampus and prefrontal cortex of suicide BD subjects[51]. In addition, ADRA2 (adrenoceptor alpha 2A)[52] and COMT[53] have been identified as potential risk suicide genes. Further research is definitely required, and other genes have to be taken into consideration. Other potential genes can be found listed in Table II.

Susceptibility Genes for Early-Onset BD

A specific feature of bipolar disorder is that early-onset has a significantly less favorable prognosis than late-onset. Therefore, it is important to identify potential genes associated with the etiology of early onset of bipolar disorder. There are several genes that have a potential impact on the onset of BD at an early age. One of those genes is the aforementioned BDNF gene. The BDNF Val allele was found more prevalent in patients with early-onset bipolar disorder than in those with late-onset BD[54]. Also, the DRD2 (dopamine receptor d2) gene has a significant association with the onset of BD at an early age[55]; however, some studies didn't find an association[56]. The role of COMT as a risk gene has been also evaluated. Several studies[57,58] have found an association between Val/Met SNP and early-onset BD. In recent years, the importance of the TLR2 (toll-like receptor 2)[59] and TLR4 (toll-like receptor 4)[60] genes as potential genes responsible for the pathogenesis of early BD has been emphasized. Two SNPs (rs3804099 TT and rs4696480 TT) from TLR2[59] and two SNPs from TLR4[60] (rs1927914 and rs11536891) are found as a strongly associated. Meanwhile, GWAS found that a small number of polymorphisms in the CACNA1C gene, as well as genes that encode proteins on the cell surface or make up the extracellular matrix, such as TENM4 (teneurin transmembrane protein 4), ANK3, and NCAN, can be considered genes involved in early-onset BD[61].

Candidate Genes for Both BD and Schizophrenia

Several studies pointed out that there is a genetic overlap between bipolar disorder and schizophrenia. One of the genes is the FKBP5 gene. Its carriers have a predisposition for developing bipolar disorder[62]. In the postmortem study of patients with schizophrenia, increased levels of FKBP5 (FKBP prolyl isomerase 5) gene mRNA were found[63]. Another interesting gene that is also linked to both psychiatric illnesses is MTHFR (methylenetetrahydrofolate reductase) gene. This gene is important for folate metabolism because it is involved in obtaining 5-MTHF or circulating folate form[64]. C677T polymorphism of this gene is expected as a risk for developing both BD and schizophrenia. However, this polymorphism has an impact on the age at onset of BD but not the age at onset of schizophrenia[65]. Other susceptibility genes in this group are ZNF804A[66], COMT[67], and BDNF[67]. Further research is definitely required, and other genes have to be taken into consideration. Other potential genes can be found listed in Table II.

Cognitive Status in BD Cases

The decline in cognitive status in patients with bipolar disorder is of great significance. Specific genes are thought to play a major role in this process. POU3F2 (POU class 3 homeobox 2) is considered to be one of the most essential risk genes for the cognitive status in BD patients. SNP from this gene (rs1906252) is associated with the speed of processing the information in the brain[68]. As already mentioned, COMT 158Val/Val genotype is the main predictor of lower global cognitive presence in patients with BD[30].

Structural Alteration in BD Brain Tissue

Structural changes in brain tissue are widely observed in BD. Some genes are thought to play a vital part in their formation. TPH2 gene is one of the most mentioned genes in this category. The protein encoded by this gene plays a role in catalyzing serotonin biosynthesis. Increased levels of expression of this gene in the dorsolateral prefron-

tal cortex have been reported in patients with BD[69]. Moreover, the expression of dysregulated ERBB2 (erb-b2 receptor tyrosine kinase 2) gene in the prefrontal dorsolateral cortex was found in patients with BD[70]. The SNP (rs1052717) of SREBF2 (sterol regulatory element binding transcription factor 2) gene responsible for homeostasis of cholesterol probably gives rise to increased radial diffusivity and reduced FA in the cingulum, corpus callosum, superior and inferior longitudinal fasciculi, and anterior thalamic radiation[71]. In patients with bipolar disorder, it is noticed that carriers of the 5-HTTLPR S (i.e., short) allele have growth of radial diffusivity in numerous brain white matter tracts, including the corpus callosum, cingulum gyrus, and corona radiate in comparison to non-carriers[72]. It is also shown that the mRNA expression of NPY (neuropeptide y) gene is remarkably declined in the prefrontal cortex of subjects affected by bipolar disorder[73].

Lithium Response and Genes in BD

Lithium (anti-manic agent) is one of the most frequently used and studied medications for treating bipolar disorder. Good responders of therapy with lithium usually have a family history of disorders, such as bipolar disorder, melancholic depression, and euphoric mania. This suggests that lithium-responsive BD cases might be a genetically visible phenotype[74]. When the circadian clock genes were examined with respect to lithium response in bipolar disorder, using LTCCs, it was shown that lithium response was best seen by the A allele of NR1D1 (nuclear receptor subfamily 1 group d member 1) gene (rs2071427)[74]. Also, SNPs on the CREB1 (CAMP responsive element binding protein 1) gene were proposed as responsible for bipolar disorder and lithium response[75]. Moreover, it was described an overexpression of the IGF1 (insulin like growth factor 1) gene in patients with bipolar disorder who react well for lithium treatment[76]. Because of these studies, the phenotype of people with BD who are good responders to lithium can be used to map their genetic risk. On the other side of the coin, FKBP5 gene is a susceptibility gene for the rapidity of response to antidepressant medication in BD[77].

Discussion

This systematic review highlights findings of the genetic background of bipolar disorder showing evidence of potential and promising risk genes that are linked with multiple facets of bipolar disorder, from a total of 19 reviewed studies (systematic reviews and meta-analysis). In the last 20 years, special attention has been paid to the genetic factors involved in various ways in the complex spectrum of BD. It is increasingly acknowledged that BD has a genetic basis with a heritability of up to 80%[78]. The sex of the transmitting parent seems to play a decisive role in the transmission of BD[79]. We divided our findings in: 1) a list of the most significant susceptibility genetic factors associated with BD; 2) the implication of the ZNF804A gene in BD; 3) the role of genes involved in calcium signaling in BD; 4) DNA methylation in BD; 5) BD and risk suicide genes; 6) susceptibility genes for early-onset BD; 7) candidate genes common to both BD and schizophrenia; 8) genes involved in cognitive status in BD cases; 9) genes involved in structural alteration in BD brain tissue; 10) genes involved in lithium response in BD.

The comprehensive number of risk alleles, their prevalence, and their effect proportion point to the genetic architecture of a certain phenotype or feature. However, although remarkable heritability indicates that genetics plays a key role in disease, the authentic genetic architecture underlying the heritability cannot be estimated and needs to be settled empirically. According to our evidence, the genes most commonly associated with bipolar disorder up to date are CACNA1C, ANK3, NCAN, BDNF, COMT, 5-HTTLPR, NRG1, and FADS1 genes.

Certain genes are known to be involved in the pathways of neurotransmission and neuroplasticity[80]. This group of genes includes BDNF, which is known to regulate synaptic function[81]. The ZNF804A gene might be involved in disorders of the dopaminergic system and neurotransmission, which in turn might lead to modifications in dopamine concentrations in the brain. Indeed, the main effect of this gene in BD is through the regulation of genes involved in dopaminergic pathways[82]. HTR2A[83] and COMT[84] are known as lead factors implicated in the neurotransmission metabolism. The CREB1 (cyclic AMP-responsive element-binding protein 1) gene might be also involved in neuronal activity and binding and in synaptic plasticity[85,86].

The CACNA1C gene appears to be the main carrier of modified calcium dynamic in BD, intermediated by LTCCs[37]. This evidence has been recently complemented by the presence of altered calcium channel expression and signaling in patients with BD. It is affected mainly by its

expression in the frontal cortex[15]. Although the mechanism is not yet known, it is considered that CACNA1C risk single nucleotide polymorphisms are associated with increased expression and action of LTCCs. In other words, activated neurons from subjects-carriers of the risk CACNA1C single nucleotide polymorphism demonstrate increased expression of calcium channel subunit mRNA, and expanded calcium signaling, contrasted with those who are not carriers of risk gene alleles[87,88].

Nevertheless, epigenetic genome alterations attribute to changes in the physical structure of the chromatin, without modification in the DNA construction[89]. The most widely studied epigenetic modification is DNA methylation, characterized by the covalent linking of a methyl (CH3) group to a cytosine residue[90]. Frequent locations of epigenetic modifications are in areas known to direct the accessibility of neurotrophins, dopamine, and serotonin. For instance, the BDNF gene is a neurotrophin whose peripheral blood levels in BD are reduced[91]. In fact, the use of peripheral tissue samples (blood or saliva) as research material for BD methylation models has increased[91]. Hypermethylation of the 5-HTR1A gene is also described in BD cases[45].

Above all, BD patients are exposed to a high risk of a suicide death. Identifying risk factors, including genetic ones, is imperative to intervene before it is too late. It is desirable to have genetic markers available, which in addition to medical history will serve to identify patients at increased risk of suicide. Family history in BD patients with suicide in first-generation relatives is the head risk factor for suicide. The genes associated with dopamine, serotonin, and norepinephrine have been investigated as genetic risk factors for this BD. In the last few years, GWAS are beginning to draw clearer conclusions about the genetic basis for suicide in the BD cases. In addition to the genetic background, other clinical factors associated with an increased risk of suicide in BD include a large number of depressive episodes, previous suicide attempts, substance, and drug abuse, the onset of the disease at an early age, and the presence of anxiety disorders[91]. Polymorphisms in TPH1[46] and TPH2[47] gene might be associated with this phenomenon which is common for BD. According to our data, other potential risk suicide genes in BD are BDNF[51], ADRA2[52], COMT[53] genes. The full description of the association of some genes and the risk of suicide in BD can be found listed in Table II[92-151].

Until now, little is known about the genetic structure differences of the early-onset and late-onset subtypes of BD. An increasing number of scientists are adhering to the thesis that the occurrence of BD at an early age is associated with thousands of ordinary SNPs with small effects and by a small number of rare variants with enormous effects[40]. Rare variants can be detected by using GWAS and using high-resolution techniques, such as whole-exome or whole-genome sequencing. It has been tried several times to replicate the previously indicated polymorphisms in larger populations, but as a result, now there is an increasing number of new genes associated with BD at an early age, but also certain genes whose previous association with BD-early onset is completely excluded. The most susceptibility genes associated with early-onset BD are BDNF[54], DRD2[55], COMT[57], and recent TLR2[59], TLR4[60], and CACNA1C[61] genes. The need for a standardized methodology for the genetic framework of early-onset BD is of great importance as one step closer to diagnostic reflections[106,109,111].

Bipolar disorder and schizophrenia have many features in common. Both disorders are characterized by abnormalities in behavior, cognitive status, thoughts, and mood[107]. The present evidence of the family impact for these two diseases is an indicator for the identification of genes that are a risk factor for their occurrence. Recent molecular genetic studies show that there is a genetic overlap between these disorders. Current data have found a genetic overlap of the regions on the chromosomes 1q, 13q, 22q, 6q, 8p, and 18[108]. The most investigated shared gene between schizophrenia and BD are the FKBP5[63], 5-MTHF[64], ZNF804A[65], COMT[67] and BDNF[67] genes.

The often-observed neurocognitive disability in patients with BD needs to be a therapeutic goal, in order to improve psychological functioning and quality of life in patients. The reasons for the cognitive decline in the patients, especially the genetic origin is one of the current topics to which is paid special attention. Several areas of human functioning in BD seem affected, such as memory, attention, and verbal learning[112,113]. As reported by some studies, the etiological heterogeneity of neurocognitive fluctuation involves several risk genes, such as POU3F2[114] and COMT[114]. Some authors[115] have suggested that neurocognitive deficits may be recognized as the underlying endophenotypes of BD.

Significantly reduced cortical thickness is found in patients with BD, with the greatest ef-

fects on the temporal, parietal, and frontal areas. It is a known fact that the genetic machinery of one BD individual has a leading role in their occurrence. Intriguing is the fact that the mRNA expression of the NPY gene is reduced in the prefrontal cortex in individuals with BD[116].

The most suitable application of genetics in patients with BD may originate from the purpose of pharmacogenetics, which looks over how genetic variation also influences the metabolism and success of therapeutic drugs. Genetic studies in the Asian population confirm the findings of previous studies in the Caucasian population that the CHL1 (cell adhesion molecule L1 like) gene, which is the neuronal recognition molecule, is associated with resistance to antidepressant treatment[117]. This confirmation is important because it is an overture to the development of methods and ways to plan treatment with antidepressants based on genetic background. Other genes thought to be involved in this resistance are BDNF, HTR2A, and RORA, but these findings are in need of independent confirmation[118].

Candidate gene association studies have been the cornerstone of the research about the lithium pharmacogenetic and lithium response so far. Although there have been a number of pre-confirmed associations, the response to lithium treatment based on genetic factors cannot yet be predicted with certainty. As supported by our data, CREB1[75] and the IGF1[76] are associated with the lithium response in BD. The principal reason for this might be pure that the biological basis and genetic transmission of BD continue to be mainly uncharacterized, thus studies established upon an insufficient conception of the disorder might not be targeting the crucial genes. GWAS concludes that the genetic base of BD is best considered as an oversized assembly of frequent alleles, each with minor effects that collectively report for disease risk[119]. Other current findings recommend that BD is also caused by a low number of rare mutations characterized with very high penetrance, best illustrated by copy number variants (CNM)[120].

Limitations and Strengths

The level and quality of each study included in this review are different. The global quality of each systematic review/meta-analysis included in our systematic review has been evaluated according to the SIGN implementation of the AMSTAR (quality assessment scale). In keeping with these criteria, ten of the included studies were rated with high quality, eight with acceptable quality, and only one paper was rated with low quality (Table B). It should be noted that a large number of individuals who carry the potential risk genetic alleles are healthy people, but this does not mean that they will develop the disease. Moreover, the genetic variants associated with BD are not only specific to bipolar disorder, but also to a wide range of other diseases. Therefore, recurrent variants are not suitable to prognoses the presence or nonappearance of clinical disease or the possibility of developing a disease (Table II).

Only for certain risk genes there are data about their impact on certain populations. The lack of evidence linking a particular gene to a larger population is a gap that needs to be filled in the future. It is well known that the genetic profile of a BD patient varies between populations.

We could not conduct on the data a meta-analysis, given the different methods used by the studies. This limitation should caution us to interpret the present results with some reservations. More studies of wider coverage are needed to assess the predominantly impact of the genes on BD, which in turn can probably aid in the development of possible therapeutic targets and advance of the treatment and outcome for BD. Another limitation is the complexities of genetics, particularly related to BD. Mutations are often found in the regulatory regions, not the "genes". But even when mutations are already known, we know that bipolar disorder has individual comportment of mutations. It would take tens of thousands of patients to likely recognize correlations, which is not currently achievable. The main strength of this review is its composition since it is systematic and includes the entire scientific evidence published so far on the main medical databases in the last 6 years. New content and new potential genes associated with BD have been described in this systematic review.

Conclusions

In summary, molecular genetic findings strongly endorse genetic factors conferring susceptibility across BD continuity. Results suggest that these polymorphisms may act as common vulnerability factors or as modifiers of the BD phenotype. Future research should concentrate on molecular mechanisms by which genetic variants play a major role in BD. Collected data about the identification of susceptibility genes for BD is interest-

ing and promising, but still insufficiently clarified. Supplemental research is needed to replicate the applicable results. In general, it is our recommendation that future studies should consider a panel of SNPs, probably covering the full length of the gene, to envelop as much as available all variations possibly changing the expression of the gene.

Conflict of Interest

The authors state they have no conflicts of interest.

Authors' Contributions

G. Kalcev and A. Preti searched the databases and evaluated the articles. G. Kalcev has prepared the first draft, all the authors have contributed to the improvement of the same. All authors approved the final content of the paper.

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