Review

Associations between genetic polymorphisms and bipolar disorder

Associação entre polimorfismos genéticos e transtorno bipolar

Verônica de Medeiros Alves[1], Aline Cristine Pereira e Silva[2], Valfrido Leão de Melo Neto[3], Tiago Gomes de Andrade[4], Antonio Egidio Nardi[5]

[1] *Mestre em Ciências da Saúde pela Universidade Federal de Alagoas (UFAL), Maceió, AL, Brasil.*
[2] *Mestranda em Ciências da Saúde pela UFAL, Maceió, AL, Brasil.*
[3] *Mestre em Psiquiatria e Saúde Mental pelo Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brasil.*
[4] *Doutor em Fisiopatologia Médica pela Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brasil.*
[5] *Doutor em Psiquiatria e Saúde Mental pelo Instituto de Psiquiatria da UFRJ, Rio de Janeiro, RJ, Brasil.*

Received: 15/8/2011 – **Accepted:** 10/10/2011

Abstract

Bipolar disorder (BD) is a common disorder that affects approximately 1% of the population. It is associated with both chronic and acute severe features, such as low remission rates and a high prevalence of clinical and psychiatric comorbidities. The aim of the present article is to synthesize data from various articles that investigated genetic polymorphisms associated with BD. The 129 articles selected identified 79 (85.87%) genes associated with BD. This analysis identified the five genes that are the most cited in the literature: CANAC1C, DAOA, TPH2, ANK3 and DISC1. Of the 92 genes identified in these articles, 33 (35.87%) showed no association with BD. This analysis showed that, despite recent advances with respect to the role of genetic polymorphism in predisposition to BD, further research is still required to elucidate its influence on this disorder.

Alves VM, et al. / Rev Psiq Clín. 2012;39(1):34-9

Keywords: Bipolar disorder, genes, polymorphisms, heredity, gene ontology, association with bipolar disorder.

Resumo

Transtorno bipolar (TB) é uma doença comum que afeta aproximadamente 1% da população. Apresenta características crônicas e agudas graves, com índices de remissão de baixa e alta prevalência de comorbidades clínicas e psiquiátricas. O objetivo do presente artigo é sintetizar dados de vários artigos que investigaram polimorfismos genéticos associados com TB. Dentre os 129 artigos selecionados, identificaram-se 79 (85,87%) genes associados com TB. Essa análise identificou cinco genes que são os mais citados na literatura: CANAC1C, DAOA, TPH2, ANK3 e DISC1. Dos 92 genes identificados nesses artigos, 33 (35,87%) não mostraram associação com TB. Essa análise mostrou que, apesar dos avanços recentes com relação ao papel do polimorfismo genético na predisposição para TB, mais pesquisas ainda são necessárias para elucidar sua influência sobre esse transtorno.

Alves VM, et al. / Rev Psiq Clín. 2012;39(1):34-9

Palavras-chave: Transtorno bipolar, genes, polimorfismos, hereditariedade, ontologia genética, associação com transtorno bipolar.

Introduction

The evolution of the concept of bipolar disorder is ongoing. Its roots can be found in the work of Araeteus of Capadocia, who assumed that melancholia and mania were two forms of the same disease. The modern understanding of bipolar disorder began in France, through the work of Falret and Baillarger. The pivotal concepts of Emil Kraepelin changed the basis of psychiatric nosology, and Kraepelin's unitary concept of manic-depressive insanity was largely accepted. Kraepelin and Weigandt's ideas on mixed states were the cornerstone of this unitary concept. After Kraepelin, however, the theories of Kleist and Leonhard in Germany, as well as the work of Angst, Perris and Winokur, emphasized the distinction between unipolar and bipolar forms of depression. More recently, the emphasis has shifted again to the bipolar spectrum, which, in its mild forms, has been expanded to the limits of normal temperament[1,2]. Because the introduction of the concept of the bipolar spectrum broadened the boundaries of the disease, the estimated rates of BD have been found to be substantially higher. These estimates still need to be validated by population-based studies[3].

Bipolar disorder (BD) is a complex, multifactorial and polygenic condition characterized by episodes of mania/hypomania and depression[4,5]. Several genes potentially involved in the pathophysiology of BD have been studied relative to their association with severity, age at onset, number of hospitalizations, vulnerability to the disorder and other clinical aspects. The genetic characterization of BD will enable (A) the identification of parents that are especially predisposed to having bipolar descendants, (B) the early detection of individuals that are prone to developing BD, (C) the identification of bipolar patients that are likely to be non-responsive to lithium therapy and (D) the identification of patients that are likely to suffer severe episodes. There is currently only a preliminary knowledge of genes that are associated with BD. However, the increasing understanding of gene expression regulation by epigenetic mechanisms and the dimensional approach to mental disorders suggest new directions for further research in psychiatric genetics[6]. Because the complexity in mode of transmission of BD and its phenotypic heterogeneity many difficulties have emerged in the identification these genes[5].

In the recent years, advances on techniques of neuroimaging, molecular biology and genetics has provided new insights about the biology of bipolarity[7]. Several studies have identified genes that are associated with triggering BD. Work in molecular genetic epidemiology has shown the influence of inherited factors in mental disorders and begun to characterize their genetic interactions with environmental factors[8]. Research focused on major pathophysiological disorders has defined a number of candidate genes, focusing on functional polymorphisms and identified variant sequences that change relevant proteins or enzymes[8]. Despite numerous studies,

Address correspondence to: Verônica de Medeiros Alves. Travessa São José, 60, Jacintinho – 57040-515 – Maceió, AL, Brazil. Telephone: (+55) 3373-2535/(+55) 9994-7781.
E-mail: veronica.ufal.arapiraca@gmail.com

much of the genetic variation that may underlie the disease pathology is still unknown[9]. Analyses of changes in DNA and the molecular mechanisms by which environmental factors can act on the genome may lead to the identification of genes whose expression is involved in the etiology of mental disorders[10]. A large number of genes with small effects, combined with environmental factors, are responsible for the etiology of BD[11].

In pharmacogenomic analyses, the success of mood stabilizers is affected by genetic factors that may change the response phenotype; for most drugs, there is still insufficient information about the mechanism by which these effects occur[12]. Lithium is the most commonly used drug for BD treatment and has been the target of studies on genetic susceptibility to BD and subsequent therapeutic response[13]. Research on polymorphism and BD is relevant because the disease is heritable, as is resistance to treatment with lithium[14].

Given this context, the identification of genetic polymorphisms may provide evidence for the cause of BD and will also identify genes that are strong candidates for further study. Candidate genes are selected based on their linkage to a characteristic of interest (*e.g.*, circadian rhythm). The expression of these genes has also been studied and associated with BD; in this way, the presence of polymorphisms can be detected. Detection of polymorphism enables the identification of risk factors or protective factors that affect the development of BD.

A more successful approach would be to search for associations with more restricted phenomena, such as personality traits, symptoms or small groups of symptoms, and, preferentially, endophenotypes. The search for genetic susceptibility of mental disorders is warranted specially under new paradigms such as their interaction with the environment and other endophenotypic variables which have been investigated through neuropsychological and neuroimaging evaluations. Thus, this research seeks to identify articles that investigated the presence of genetic polymorphisms that are associated with BD[15].

Methods

Original articles published in the database PubMed/Medline were selected by means of the following associations: "bipolar disorder and SNP" and "bipolar disorder and polymorphism". A PubMed gene ontology search was used to determine the function of each gene identified. The references of the selected articles were not used as a source in this review.

The inclusion criteria were as follows:

- published between 2005 and 2011;
- written in English;
- included codes identifying the location of polymorphisms (e.g., rs 1006737 – Gene CACNA1C);
- described genes associated with bipolar disorder;
- no association with BD.

Results

We selected 129 original articles that identified genetic polymorphisms as associated or not associated with BD and were published between 2005 and 2011. We selected only those that included an identification code for the locations of the polymorphisms. Together, these articles identified 92 genes (Table 1).

Genes and polymorphisms associated with demonstration

The 129 articles selected, 79 (85.87%) genes associated with BD (Table 1). An analysis of these articles associated identified five genes as the most cited in the literature: CANAC1C[16-24], DAOA[25-32], TPH2[30,33-37], ANK3[21,38-39] and DISC1[40-43] (Table 2). These five genes account for 29 original articles that showed association with BD. The 29 articles represent research from several countries: United States[16,17,21,28,41], Germany[8,20,39], Australian[21], UK[19,23,24,32], Africa[25,26], Romania[23,33], Scotland[30], Finland[31,41], China[29,33,43], Sweden[34], Russia[8], France[37], Ireland[35], Canada[38], Japan[42], Italy[18] and the Netherlands[22]. Some articles related the genetic polymorphism specifying the classification of TBI[8,25,27,32,35,36,39,41] , in addition to TBI and II[37]. The population studied by the authors of the articles are mostly from ocidente[18,20,22,26,28,30,32,34-38] and a lower part are the oriente[25,27,33,43].

Among the 196 functions of these 92 polymorphic genes, according to gene ontology, the most common were the following: protein binding, appearing in 32.61% (30) of genes, metal ion binding (19.56%, 18), AT-binding (18.48%, 17), receptor activity (17.39%, 16) and nucleotide binding (16.3%, 15) (Table 2).

Among the five most cited genetic polymorphisms in the literature, it was possible to identify three genes, ANK3, CACNA1C and DISC1, with protein binding functions. TPH2 has metal ion binding activity. The DAOA gene was not associated with any function in the PubMed gene ontology database. None of these genes have a common gene ontology. The ANK3, CACNA1C and DISC1 genes were annotated as components of the cytoplasm, and the ANK3 and DISC1 genes encode components of the cytoskeleton.

The articles discussing the CACNA1C gene investigated BD patient sample populations that numbered between 282 and 2,021 individuals.

Table 1. Genetic polymorphisms associated with bipolar disorder, published between 2005 and 2011

GENES	GENES	GENES	GENES	GENES	GENES
ANK3*	G72/G30 DAOA*,a	GABRB2*	ADCY8*	hNP*	NCAM1*,a
Bcl-2*	NR1D1*	EGR3*	ST3GAL1*	QDPRa	PREPa
CACNA1C*	GPR50*,a	GRIA2*	PDLIM5*,a	CLOCK*	CHRNA2a
P2RX7*,a	GRM3*	GRIA1*,a	DGKH*	BHLHB2*	CHRNA5a
GSK3β*	LACE1*	AKT1*	PPARD*	CSNK1E*	CHRNB1a
AANAT*	CHRNA7*,a	SP4*	PALB2*	BDNF*,a	CHRNB4a
DOK5*	ITIH1*	PI4K2Ba	COMT*	SIAT4A*	TBX1a
CRY2*	RORB*,a	DFNB31*	TPH2*,a	TACR1*	IMPA2*
NR4A3*,a	PPARGC1B*	SORCS2*	PCDH□*	DISC1*	SST*
GRIN2B*,a	TEF*	SCL39A3*,a	PCNT*	TSNAX*	ARNTL*
HSP-70*	DHHCa	IGF1*	ATP1A3*	ATP1A1*	NOS1*
OTX2*,a	SLC6A3*	NAPG*	HTR2A*	ATP1A2*	KIAA0564*
SCN8A*	YWHAH*	ERG3a	DTNBP1*,a	PACAP/ADCYAP1*	NRG1*
5-HT1A*,a	TSPAN8*	NPAS2*,a	TRPM2*	VAPA*,a	CHMP1.5a
5-HT6a	DARPP-32a	NDUFV2*	RGS4*	MPPE1*,a	BRCA2*
VMAT1 (Thr136Ser)*	Per3*	MAOAa			

* Genes associated with BD.

a Genes not associated with BD.

Table 2. Study details for candidate bipolar disorder genes most often cited in the literature between 2005 and 2011

Genes	Designation	Function	Case/control	Authors	Polymorphism
CACNA1C	α-1C subunit calcium channel L – type voltage-dependent	Calmodulin Binding, protein binding, voltage-gated calcium, channel activity voltage-gated ion channel activity	90 cDNA	Quinn *et al.*, 2010	rs1006737
			585	Franke *et al.*, 2010	rs1006737
			1.868/2.938	Green *et al.*, 2010	rs1006737
			282/440	Bigos *et al.*, 2010	rs1006737
			110	Erk *et al.*, 2010	rs1006737
			2.021/1.840	Dao *et al.*, 2010	rs2370419 rs2470411
			1.213	Cassamassina *et al.*, 2010	rs10848635 rs1006737
			1.098/1.267	Ferreira *et al.*, 2009	rs1006737
			77	Kempton *et al.*, 2009	rs1006737
DAOA	D-amino acid oxidase	No description	191/188	Dalvie *et al.*, 2010	rs701567
			198/180	Grigoroiu-serbanescu *et al.*, 2010	rs3916965 rs1935057 rs3916967 rs2391191
			248/188	Gawlik *et al.*, 2010	rs2391191 rs1935062 rs3916966
			475/588	Zhang *et al.*, 2009	rs778293
			555/564	Maheshwari *et al.*, 2009	rs1935058
			706/1416	Soronen *et al.*, 2008	rs2391191 rs3916966
			723	Williams *et al.*, 2006	rs391695 rs1341402 rs1935058 rs2391191 rs778294 rs954581 rs1421292
			213/197	Prata *et al.*, 2008	rs2111902 rs3918346 rs746187 rs3916972
TPH2	Tryptophan hydroxylase 2	Function iron ion binding, metal ion binding, tryptophan 5-monooxygenase activity	151	Roche e Mckeon, 2009	rs1386482 rs1386486 rs4290270
			883/1.300	Cichon *et al.*, 2008	rs17110563 rs11178997 rs11178998 rs7954758
			198/180	Grigoroiu-Serbanescu *et al.*, 2008	rs17110563
			105/106	Lin *et al.*, 2007	rs4570625 rs11178997 rs11178998 rs11179003 rs171110747
			225/221	Harvey *et al.*, 2007	rs4290270
			182/364	Bogaert *et al.*, 2006	rs4131348
ANK3	Ankyrin G	Protein binding	47/67	Ruberto *et al.*, 2011	rs10994336
			90 cDNA	Quinn *et al.*, 2010	rs10994336
			1.098/1.267	Ferreira *et al.*, 2009	rs10994336
			923/774	Schulze *et al.*, 2009	rs10994336 rs9804190
DISC1	Disorder of schizophrenia 1	Protein binding	506/507	Xiao *et al.*, 2011	rs2738864 rs16841582
			379	Perlis *et al.*, 2008	rs10495308 rs2793091 rs2793085
			723 members of 179 families with BD	Palo *et al.*, 2007	rs821616
			373/717	Hashimoto *et al.*, 2006	rs821616

Control sample populations ranged in size between 440 and 2.938 healthy individuals. Four studies worked only with healthy people or with cDNAs (derived from lymphoblastic cells) from the HapMap database. Four codes describing the location of a polymorphic gene associated with BD were identified (Table 2). This gene is located on chromosome 12p13.3 (Figure 1).

Articles related to the DAOA gene sampled between 191 and 704 individuals with BD and between 180 and 1.416 healthy individuals. Only one study contained only healthy individuals. These studies identified 17 codes for the location of a genetic polymorphism associated with BD (Table 2). This gene is located on chromosome 13q34 (Figure 1).

Articles related to the TPH2 gene sampled between 105 and 883 individuals with BD and between 106 and 1.300 healthy controls. Only one study did not include control samples. These studies identified 11 codes for the locations of polymorphisms associated with BD (Table 2). This gene is located on chromosome 12q21.1 (Figure 1).

Articles related to the ANK3 gene sampled between 47 and 1.098 individuals with BD and between 67 and 1.267 control individuals. One article studied cDNAs (derived from lymphoblastic cells) from the HapMap database. These studies reported four codes representing the location of the polymorphism associated with BD (Table 2). This gene is located on chromosome 10q21 (Figure 1).

Articles related to the DISC1 gene sampled between 373 and 506 patients with BD. One article did not include control samples, and another studied members of families affected with BD. These studies identified six codes indicating the location of the polymorphism associated with BD (Table 2). This gene is located on chromosome 1q42.1 (Figure 1).

The functionality of the polymorphisms identified was observed made to analyze the variation in the expression of genetic polymorphism in association with some variables: cognitive assessment[39], memory[39,41], making decision[39]. Psychotic illness after the use of alcohol, drug dependence, intravenous drug abuse, psychotic illness secondary to medicamentos[20]. Emotional memory, emotion on the face, the work memory[17]. Episodes of hospitalization disease[25,27]. Age of first hospitalization[26,34]. First age[36], number of episodes, family history of disease psyquiatric[8,36] on first and second grau[25]. Attention[41]. These variables have been showing greater respect of the polymorphisms and episodes of TB, which when studied polymorphism with TB diagnosis.

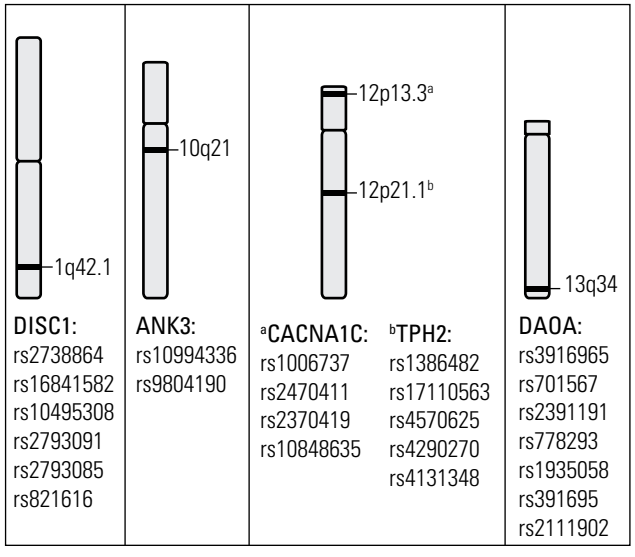

Figure 1. Chromosomal locations of the five genes most commonly associated with BD and their polymorphisms.

Genes/polymorphisms lacking association with BD

Of the 92 genes identified, 33 (35.87%) specifically showed no association with BD (Table 1). DAOA, TPH2, P2RX7, NR4A3, GPR50, CHRNA7, RORB, GRIA1, PDLIM5, BDNF, NCAM1, VAPA, DTNBP1, SLC6A3, 5-HT1 and OTX2 were described both as associated with BD and not associated with BD by different studies (Table 1).

Discussion

The study of genetic polymorphism associated with TB raises the possibility that mental illness is mainly associated with common genetic variants is outdated. Is now plausible that multiple rare variants each have a potent effect on disease risk and that they could accumulate to become a substantial component of mental disease risk[44]. The search for genetic information that are associated with the outbreak of TB involves structural and environmental factors. Among the genes associated with BD, those with protein binding activity may be especially relevant. Because the biological properties of a cell are determined by the active proteins expressed, these genes may be involved in BD through changes in protein structure, thereby increasing or decreasing some feature/function that can cause major cellular changes. Alternatively, these genes may still be active, along with other proteins, but with changes in their functions that trigger BD.

Adenosine triphosphate (ATP) is a key energy-transferring molecule that is used in many biological processes. It is involved in the active transport of molecules, the synthesis and secretion of substances, locomotion and cell division. Genes involved in ATP synthesis may therefore interfere in one or more of these biological processes, promoting the onset of BD. Genes involved in receptor function may increase or decrease the receptor activities and thereby modify some function/action that may then contribute to the onset of BD. Changes in nucleotide (adenine, guanine, cytosine, thymine and uracil) synthesis may result in mutations or polymorphism, depending on the effect of the structural change. This may contribute to BD.

Studies of the five most cited genes show their influence in the etiology of BD. Several articles confirmed the association of polymorphisms in CACNA1C with BD. The strong expression of CACNA1C in BD patients suggests an increased activity of calcium channels. Thus, calcium channel inhibitors may have clinical value for the treatment of BD. One of these studies further identified a potential mechanism for bipolar disorder risk[16]. A decrease in CACNA1C expression can protect against the development of mood disorders[17]. Two polymorphisms in the CACNA1C gene (rs10848635, rs1006737) had a protective effect on BD episodes. The polymorphism rs1006737 was also correlated with reduced severity of depression and insomnia. However, both alleles were associated with an increased risk of suicide during treatment for depression[18]. This is a clear demonstration that there is an overlap between genes in the biological basis of susceptibility to mental illness across the clinical spectrum[19].

Research conducted by Erk *et al.*[20] suggests a gene-environment interaction mechanism for BD, i.e., a dysfunctional adaptation to stress. CANAC1C has been established as a drug target because of its binding site for calcium channel blockers (verapamil); these drugs have shown some evidence of effectiveness in mood stabilization of BD patients. Calcium channel subunit expression is decreased in the mouse brain in response to lithium, one of the most effective bipolar therapies[21]. Genetic variation in CACNA1C is associated with the volume of the brainstem that modulates central control over the motor, cognitive, affective and arousal, providing a psychiatric risk factor[22]. Magnetic resonance imaging showed that there was significant correlation between CACNA1C mutation and the total volume of gray matter, but not in regional grey matter volume, white matter volume, or cerebrospinal fluid or volume[23].

Several highly cited articles regarding the DAOA gene confirm its association with BD. An initial study by Dalvie *et al.*[25] provided preliminary evidence that ancestral DAOA gene alleles (rs701567) have a protective effect, lessening the chances of having severe BD

(psychosis and repeated hospitalizations). Haplotypes of DAOA/G30 are associated with affective psychoses, but do not contribute to the pathogenesis of affective disorders[26]. Different SNPs that potentially indicate membership in the DAOA/G30 haplotype were found to be correlated with psychotic episodes and mood changes with delusions in Romanian BD patients[27]. Other studies suggest that DAOA does not have a major effect on susceptibility to BD, but can contribute to susceptibility in some families[28]. In contrast, multiple sensitizing (and perhaps protective) variants of the DAOA/G30 gene are present in different populations[29]. Additional evidence supports the involvement of DAOA/G30 and DAO in the etiology of bipolar disorder, but none indicated any interaction between these genes[30]. DAOA thus may play an important role in the predisposition of individuals with a mixed phenotype of psychosis and mania and lead to changes in the expressed characteristics of these psychological illnesses[31]. Williams *et al.*[32] suggested that depression is associated with greater glutamatergic function. Patients with mutations in the DAOA gene, which is associated with affective disorders, have symptoms that should be associated with reduced activity and/or frontal activation of DAO.

An analysis of the articles related to TPH2 shows that this gene may influence the risk of BD[33]. A study performed in a population of Swedish descent provides preliminary evidence for the association of the TPH2 gene with protection against the pathogenesis of affective disorders[34]. An examination of the functional effects of TPH2 provided evidence for the lower thermal stability and solubility of the mutant enzyme, suggesting that the reduced production of 5-HT in the brain may serve as a pathophysiological mechanism of BD[35]. Studies carried out by Grigoroiu-Serbanescu *et al.*[36] also support the involvement of TPH2 variability in the etiology of BD. The polymorphism rs17110563, which lies in the TPH2 protein coding region, was detected in a Romanian patient but not in control individuals, supporting the hypothesis that it represents a risk factor for a rare form of BD. The BD susceptibility locus in TPH2 shows a statistically significant association with BD at both a locus-specific SNP and haplotype marker SNPs[37].

The ANK3 protein is found in the initial segment of the axon and governs the localization of voltage-dependent sodium channels. The mRNA expression levels of ANK3 and CACNA1C are affected by local genetic variation[24]. ANK3 is reduced in the mouse brain in response to lithium, one of the most effective bipolar therapies. Significant literature suggests that bipolar disorder is an illness of ion channels[21]. The ANK3 gene has a selective effect on sensitivity to signals that affect an individual's sustained attention and thus can eventually contribute to the risk of BD[38]. Regions close to the rs9804190 and rs10994336 polymorphisms will be jumping off points for future studies that aim to define functional variants that are responsible for susceptibility to BD[39]. A small sample of article related to the ANK3 gene may show little significance of its association with TB[38].

The involvement of DISC1 in the etiology of BD was first suggested by Palo *et al.*[40]. These authors suggested that polymorphisms in DISC1 contribute to variations in the psychotic features of bipolar spectrum disorder. DISC1 may represent a new target for the development treatments and diagnostic tools for bipolar disorder[41]. DISC1 is associated with lowered biological activity of ERK (extracellular regulated kinase), reduced grey matter volume in the brain and increased risk for major depressive disorder[43]. A haplotype [rs2738864 (C)-rs16841582 (C)] was associated with BD. This discovery provides of the role of DISC1 in BD[43].

Conclusion

This study shows that, despite advances with respect to the role of genetic polymorphisms in predisposition to BD, significant research must still be performed to elucidate the roles of specific genes and their variants in this disorder.

References

1. Del Porto JA. Evolução do conceito e controvérsias atuais sobre o transtorno bipolar do humor. Rev Bras Psiquiatr. 2004;26(III):3-6.
2. Del-Porto JA, Del-Porto KO. História da caracterização nosológica do transtorno bipolar. Rev Psiq Clín. 2005;32(1):7-14.
3. Lima MS, Tassi J, Novo IP, Mari JJ. Epidemiologia do transtorno bipolar. Rev Psiq Clín. 2005;32(1):15-20.
4. Souza FGM. Tratamento do transtorno bipolar – Eutimia. Rev Psiq Clín. 2005;32(1):63-70.
5. Michelon L, Vallada H. Fatores genéticos e ambientais na manifestação do transtorno bipolar. Rev Psiq Clín. 2005;32(1):21-7.
6. Machado-Vieira R, Bressan RA, Frey B, Soares JC. As bases neurobiológicas do transtorno bipolar. Rev Psiq Clín. 2005;32(1):28-33.
7. Michelon L, Vallada H. Genética do transtorno bipolar. Rev Bras Psiquiatr. 2004;26(III):12-6.
8. Cichon S, Winge I, Mattheisen M, Georgi A, Karpushova A, Freudenberg J, et al. Brain-specific tryptophan hydroxylase 2 (TPH2): a functional Pro206Ser substitution and variation in the 50-region are associated with bipolar affective disorder. Hum Mol Gen. 2008;17(1):87-97.
9. Emily M, Mailund T, Hein J, Schauser L, Schierup MH. Using biological networks to search for interacting loci in genome-wide association studies. Eur J Hum Gen. 2009;17:1231-40.
10. Rutten BPF, Mill J. Epigenetic mediation of environmental influences in major psychotic disorders. Schizophr Bull. 2009;35(6):1045-56.
11. Klar AJS. A proposal for re-defining the way the aetiology of schizophrenia and bipolar human psychiatric diseases is investigated. J Biosci. 2010;35(1):11-5.
12. Squassina A, Manchia M, Zompo MD. Pharmacogenomics of mood stabilizers in the treatment of bipolar disorder. Hum Genomics Proteomics. 2010:1-19.
13. King J, Keim M, Teo R, Weening KE, Kapur M, McQuillan K, et al. Genetic control of lithium sensitivity and regulation of inositol biosynthetic genes. PLoS ONE. 2010;5(6):e11151.
14. Tang B, Thornton-Wells T, Askland KD. Comparative linkage meta-analysis reveals regionally-distinct, disparate genetic architectures: application to bipolar disorder and schizophrenia. PLoS ONE. 2011;6(4):e19073.
15. Nishioka SA, Perin EA, Sampaio AS, Cordeiro C, Cappi C, Mastrorosa RS, et al. The role of the VNTR functional polymorphism of the promoter region of the MAOA gene on psychiatric disorders. Rev Psiq Clín. 2011;38(1):34-42.
16. Bigos KL, Mattay VS, Callicott JH, Straub RE, Vakkalanka R, Kolachana B, et al. Genetic variation in CACNA1C affects brain circuitries related to mental illness. Arch Gen Psychiatry. 2010;67(9):939-45.
17. Dao DT, Mahon PB, Cai X, Kovacsics CE, Blackwell RA, Arad M, et al. Mood disorder susceptibility gene CACNA1C modifies mood-related behaviors in mice and interacts with sex to influence behavior in mice and diagnosis in humans. Biol Psychiatry. 2010;68:801-10.
18. Casamassima F, Huang J, Fava M, Sachs GS, Smoller JW, Cassano GB, et al. Phenotypic effects of a bipolar liability gene among individuals with major depressive disorder. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(1):303-9.
19. Green EK, Grozeva D, Jones I, Jones L, Kirov G, Caesar S, et al. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry. 2010;15:1016-22.
20. Erk S, Meyer-Lindenberg As, Schnell K, Boberfeld CO, Esslinger C, Kirsch P, et al. Brain function in carriers of a genome-wide supported bipolar disorder variant. Arch Gen Psychiatry. 2010;67(8):803-11.
21. Ferreira MAR, Donovan MCO, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genetics. 2008;40(9):1056-8.
22. Franke B, Vasquez AA, Veltman JA, Brunner HG, Rijpkema M, Fernández G. Genetic variation in CACNA1C, a gene associated with bipolar disorder, influences brainstem rather than gray matter volume in healthy individuals. Biol Psychiatry. 2010;68:586-8.
23. Kempton MJ, Ruberto G, Vassos E, Tatarelli R, Girardi P, Collier D, et al. Effects of the CACNA1C risk allele for bipolar disorder on cerebral gray matter volume in healthy individuals London, United Kingdom. Am J Psychiatry. 2009;166(12):1413-4.
24. Quinn EM, Hill M, Anney R, Gill M, Corvin AP, Morris DW. Evidence for cis-acting regulation of ANK3 and CACNA1C gene expression. Bipolar Dis. 2010;12:440-5.
25. Dalvie S, Horn N, Nossek C, Merwe L, Stein DJ, Ramesar R. Psychosis and relapse in bipolar disorder are related to GRM3, DAOA, and GRIN2B genotype. Afr J Psychiatry. 2010;13:297-301.

26. Gawlik M, Wehner I, Mende M, Jung S, Pfuhlmann B, Knapp M, et al. The DAOA/G30 locus and affective disorders: haplotype based association study in a polydiagnostic approach. BMC Psychiatry. 2010;10(59):1-7.
27. Grigoroiu-Serbanescu M, Herms S, Diaconu CC, Jamra RA, Meier S, Bleotu C, et al. Possible association of different G72/G30 SNPs with mood episodes and persecutory delusions in bipolar I Romanian patients. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:657-63.
28. Maheshwari M, Shi J, Badner JA, Skol A, Willour VL, Muzni DM, et al. Common and rare variants of DAOA in bipolar disorder. Am J Med Genet B Neuropsychiatr. 2009;150B(7):960-6.
29. Zhang Z, Li Y, Zhao Q, Huang K, Wang P, Yang P, et al. First evidence of association between G72 and bipolar disorder in the Chinese Han population. Psychiatr Genet. 2009;19:151-3.
30. Prata D, Breen G, Osborne S, Munro J, St. Clair D, Collier D. Association of DAO and G72(DAOA)/G30 genes with bipolar affective disorder. Am J Med Genet B Neuropsychiatric Genet. 2008;147B:914-7.
31. Soronen P, Silander K, Antila M, Palo OM, Tuulio-Henriksson A, Kieseppa T, et al. Association of a nonsynonymous variant of DAOA with visuospatial ability in a bipolar family sample. Biol Psychiatry. 2008;64(5-3):438-42.
32. Williams NM, Green EK, Macgregor S, Dwyer S, Norton N, Williams H, et al. Variation at the DAOA/G30 locus influences susceptibility to major mood episodes but not psychosis in schizophrenia and bipolar disorder. Arch Gen Psychiatry. 2006;63:366-73.
33. Lin Yi-Mei J, Chao Shin-Chih, Chen Tsung-Ming, Lai Te-Jen, Chen Jia--Shing, Sun HS. Association of functional polymorphisms of the human tryptophan hydroxylase 2 gene with risk for bipolar disorder in Han Chinese. Arch Gen Psychiatry. 2007;64(9):1015-102.
34. Bogaert AVD, Sleegers K, Zutter S, Heyrman L, Norrback KF, Adolfsson R, et al. Association of brain-specific tryptophan hydroxylase, TPH2, with unipolar and bipolar disorder in a Northern Swedish, isolated population. Arch Gen Psychiatry. 2006;63:1103-10.
35. Roche S, McKeon P. Support for tryptophan hydroxylase-2 as a susceptibility gene for bipolar affective disorder. Psychiatric Genetics. 2009;19:142-6.
36. Grigoroiu-Serbanescu M, Diaconu CC, Herms S, Bleotu C, Vollmer J, Muhleisen TW, et al. Investigation of the tryptophan hydroxylase 2 gene in bipolar I disorder in the Romanian population. Psychiatric Genetics. 2008;18:240-7.
37. Harvey M, Gagne B, Labbe M, Barden N. Polymorphisms in the neuronal isoform of tryptophan hydroxylase 2 are associated with bipolar disorder in French Canadian pedigrees. Psychiatric Genetics. 2007;17:17-22.
38. Ruberto G, Vassos E, Lewis CM, Tatarelli R, Girardi P, Collier D, et al. The cognitive impact of the ANK3 risk variant for bipolar disorder: initial evidence of selectivity to signal detection during sustained attention. PLoS ONE. 2011;6(1):e16671.
39. Schulze TG, Detera-Wadleigh SD, Akula N, Gupta A, Kassem L, Steele J, et al. Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder. Mol Psychiatry. 2009;14(5):487-91.
40. Palo OM, Antila M, Silander K, Hennah W, Kilpinen H, Soronen P, et al. Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. Hum Mol Genetics. 2007;16(20):2517-28.
41. Perlis RH, Purcell S, Fagerness J, Kirby A, Petryshen TL, Fan J, et al. Family-based association study of lithium-related and other candidate genes in bipolar disorder. Arch Gen Psychiatry. 2008;65(1):53-61.
42. Hashimoto R, Numakawa T, Ohnishi T, Kumamaru E, Yagasaki Y, Ishimoto T, et al. Impact of the DISC1 Ser704Cys polymorphism on risk for major depression, brain morphology and ERK signaling. Hum Mol Genetics. 2006;15(20):3024-33.
43. Xiao Y, Zhang J, Wang Y, Wang P, Li X, Ji J, et al. Limited association between Disrupted in Schizophrenia 1 (DISC1) gene and bipolar disorder in the Chinese population. Psychiatric Genetics. 2011;21:42-6.
44. Gershon ES, Alliey-Rodriguez N, Liu C. After GWAS: searching for genetic risk for schizophrenia and bipolar disorder. Am J Psychiatry. 2011;168:253-6.