Genetics of bipolar disorder

Genética do transtorno bipolar

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Abstract

Bipolar disorder (BD) is a worldwide highly prevalent mental disease. This disorder has a genetic inheritance characterized by complex transmission mechanisms involving multiple genes. Many investigation strategies have been put forward in order to identify BD susceptibility genes. Linkage studies reveal markers and candidate genes for the association studies. Monoaminergic system genes and intracellular signaling pathway genes are also important candidates to be investigated in the etiology of this disorder. Recent techniques of gene expression mapping suggest novel genes whose mutations may be responsible for BD. Due to the complexity of the transmission pattern for BD and its phenotypic heterogeneity many difficulties have emerged to exactly define bipolar susceptibility genes. There is currently only preliminary results of genes associated with BD. However, the increasing understanding of gene expression regulation by epigenetic mechanisms and the dimensional approach to mental disorders can give directions for further research in psychiatric genetics.

Keywords: *Bipolar disorder/genetics; Genetic makers; Gene expression*

Resumo

O transtorno bipolar (TB) possui alta prevalência na população mundial e causa perdas significativas na vida dos portadores. É uma doença cuja herança genética se caracteriza por mecanismos complexos de transmissão envolvendo múltiplos genes. Na tentativa de identificar genes de vulnerabilidade para o TB, várias estratégias de investigação genética têm sido utilizadas. Estudos de ligação apontam diversas regiões cromossômicas potencialmente associadas ao TB, cujos marcadores ou genes podem ser candidatos para os estudos de associação. Genes associados aos sistemas monoaminérgicos e vias de sinalização intracelulares são candidatos para investigação da etiologia genética do TB. Novas técnicas de mapeamento de expressão gênica em tecidos especializados apontam para novos genes cujas mutações possam ser responsáveis pelo aparecimento da doença. Em virtude da complexidade do modo de transmissão do TB e de sua heterogeneidade fenotípica, muitas dificuldades são encontradas na determinação desses genes de vulnerabilidade. Até o momento, há apenas resultados preliminares identificando alguns genes associados à vulnerabilidade para desenvolver o TB. Entretanto, a compreensão crescente dos mecanismos epigenéticos de controle da expressão gênica e a abordagem dimensional dos transtornos mentais podem colaborar nas investigações futuras em genética psiquiátrica.

Descritores: *Transtorno bipolar/genética; Marcadores genéticos; Expressão gênica*

Introduction

Bipolar disorder (BD) is characterized by mood alterations, with recurrent depressive and manic episodes in lifetime. The estimations regarding its prevalence in the population are generally conservative, due to the use of narrow diagnostic criteria proposed by the categorical classifications currently used. Therefore, lifetime prevalence found in the US for bipolar I disorder reaches 1.6%.[1] In the city of São Paulo there is 1% prevalence.[2] Recent studies with more comprehensive criteria, which allow the inclusion of less intense, but not less severe mood alterations, have shown a 4 to 8% lifetime prevalence for the bipolar *continuum.*[3]

The understanding of the etiology and pathophysiology of this disorder in all its heterogeneity is extremely important to define treatment and prevention strategies. Twin, adoption and family studies with multiple affected subjects show the influence of multiple environmental and genetic factors in its etiology. The concordance between identical twins (monozygotic) varies from 61 to 75% and the morbid risk of first-degree relatives ranges between 1.5 and 15.5%.[4] These data suggest that BD has a high heritability, but in a non-Mendelian inheritance mode. Therefore, BD is a complex disease, whose appearance depends on the presence of vulnerability genes and their interaction with the environmental influence.

Pharmacological and molecular studies allow to select genes and genomic regions potentially implied in the susceptibility to BD. Receptor codifying genes and enzymes of the monoaminergic system are natural candidates for association studies, as they correspond to binding sites of drugs used in the treatment of mood alterations. Linkage studies allow to situate chromosomal regions potentially associated with the occurrence of BD and to identify genes present in these regions. Post-mortem studies assessing the profile of genic expression in brains of BD subjects raise new possibilities of susceptibility genes. Pharmacogenetic studies may establish a set of variants or genic expression profile characteristic of etiological subtypes due to the pharmacological response.

Different genetic mechanisms may be involved in the etiopathogenesis of BD such as the heterogeneity of alleles, of genes (loci), epistasis, dynamic mutation leading to the phenomenon of anticipation, 'imprinting', and mutation of mytochondrial genes. All these mechanisms have been assessed as potentially involved in the vulnerability to BD. We will describe below some of these studies.

Cytogenetic studies

Some genomic regions potentially associated with BD were identified from the observation of co-segregation of chromosomal alterations and this disorder in families with multiple affected members. Balanced translocation is the main alteration found in these cases.

Several regions were identified as candidate loci in the genetic susceptibility to BD. Craddock and Owen,[5] assessing previous reports of chromosomal abnormalities associated with BD, identified four regions of interest: 11q21-25, 15q11-13, chromosome 21 and Xq28. Other reports of chromosomal abnormalities in affected families suggest other sites potentially associated with BD: 8p21 and 15q22-24,[6] 18q23,[7] 18p11.3 and 18q21.1,[8] 9p24 and 11q23.1,[9] 1q42.1 and 11q14.3.[10]

Chromosomal abnormalities found in subjects with mental disorders can be generally considered as significant if the alteration is rare, with independent reports of their segregation with behavioral alterations or when the alteration occurs in regions also pointed by linkage studies as associated with the studied disease. Therefore, it is suggested that subjects with strong family history, cognitive alterations and/or congenital abnormalities should be submitted to investigation of their cariotypes.[11]

The repercussion of structural genomic alterations in the development of diseases depends on the locus in which they occur. When the disruption occurs in one genic sequence, the transcription product of the genes involved is impaired, as well as all cellular processes dependent on this product. However, the physiological repercussion depends on the importance or exclusiveness of the genic product in the cellular metabolism and signaling pathways. If the region involved has not a genetic sequence, the expected repercussion is less intense, although the segments free of codifying sequences may influence the expression and transcription processes in the neighboring segments.

Linkage studies

One of the strategies to locate a gene with great effect in the susceptibility to a disorder is based on the concept of genetic linkage. This concept refers to the fact that two genic loci which are situated very close in the same chromosome tend to be inherited together (linked). Therefore, if a determined genetic marker, whose location is already known, is always inherited with the disease by the affected members of one family, the disease's gene will be much probably situated near to this marker. This type of investigation generally needs large multiplex families and was originally developed to assess the transmission of only one major effect gene . This is the main limitation of this strategy.

Linkage studies use LOD score analysis, which requires the specification of genic frequencies, mode of transmission and penetrance. As mental disorders do not have a known mode of transmission, a variety of models must be tested, incurring in type I and I errors. Besides, the phenotype considered is wide and the genetic heterogeneity present between affected subjects in one family impairs the specificity of the findings and reduces the chance of replicating the data. Even though, linkage studies allow to focus the investigation on more limited regions of the genome, whose markers or genes can be assessed in association studies in large samples of patients.

Early studies showed promising results, but which have not been confirmed. Similarly, several subsequent studies found a great number of chromosomal regions with significant association with BD. The variety of loci potentially related to BD partially reflects the phenotypic heterogeneity and complexity of the genic interaction in the determination of the susceptibility to mental disorders. Among the regions identified up to now, chromosomes 4, 12, 13, 18, 20 21 and 22[12-15] are promising and have the highest LOD scores (Table 1).

Table1 – Chromosomal loci reported by linkage studies for bipolar disorder

Location	LOD score	Reference
1q31-q32	2,6	Detera-Wadleigh et al, 1999[16]
4p16	4,8	Blackwood et al, 1996[17]
12q23-24	3,4	Ewald et al, 1998[18]
13q32	3,5	Detera-Wadleigh et al, 1999[16]
18q22	4,0	McInnes et al, 1996[19]
20p11.2-q11.2	4,3	Radhakrishna et al, 2001[20]
21q22	3,4	Vallada et al, 1996[21]
22q11-q13	3,8	Kelsoe et al, 2001[22]

Modified from Tsuang et al[15]

Association studies with candidate genes

Association studies are one alternative for the study of genes involved in complex diseases with unknown mode of transmission. The association with the marker investigated occurs when the gene or locus with linkage disequilibrium with the marker are involved in the pathophysiology of the disease. The greatest advantage of association studies is that they may detect genes with modest effects. Besides, very large samples are needed to obtain statistical significance. Spurious associations may occur in case of population stratification. This kind of bias may be reduced using parents as controls. In case of positive associations, it should be established if the allele associated with the disease causes functional alterations responsible for its pathophysiology.

Natural candidate genes initially used in association studies were those related to the monoaminergic system, due to theories involving these pathways in the pathophysiology of affective disorders. These studies, however, have not been conclusive, providing many conflicting results for the several investigated genes.[23-24]

More recently, association studies have been concentrated in the investigation of codifying genes of proteins involved in the intracellular signaling transduction systems. The discovery of these pathways is due to the increasing understanding of the mechanism of action of the drugs used in the treatment of BD and of their repercussion in the metabolic activity and in the regulation of the genic expression.[25] The identification of genes associated with the signaling pathways in chromosomal regions linked with BD provides interesting candidates for association studies. For instance, the GRK3 (G protein receptor kinase 3), situated in the chromosome 22q12.[26]

Glycogen synthase kinase 3 beta (GSK3â) is an enzyme which performs an important role in the control of tissue development and cell life. Lithium binds directly to it and inhibits it, blocking apoptotic processes.[27] One recent study has found positive association between the polymorphism –50T/C of the GSK3â allele T gene with early onset of BD.[28]

The G allele of the polymorphism A196G of the BDNF (brain-derived neurotrophic factor) showed preferential transmission in bipolar patients, representing important risk locus for BD.[29]

Association studies with genes of diseases which represent a risk factor for BD

Some hereditary diseases are generally accompanied by mental disorders. Patients with Wolfram Syndrome and Darier's Disease usually show affective disorders.

Wolfram Syndrome has a recessive autossomic inheritance and is characterized by the presence of diabetes mellitus and optical atrophy. The WFS1 gene, whose mutations are responsible for the syndrome, is situated in the chromosome 4p16.[30] Linkage studies in BD also point to this region.[17] Consequently, mutations

in the gene WFS1 were examined in BD subjects. Furlong et al[31] noted a higher frequency in the mutation Ala559Thr in affective disorders. Other groups were not able to identify any association with the mutations studied.[32-33] As the possible mutations identified are multiple, and one proband may show innumerous ones, it is difficult to assess associations with BD. Besides, the protein codified by this gene seems to interact with mitochondrial DNA, which is other genomic region potentially associated with BD.

Darier's disease has a dominant autossomic inheritance and is characterized by dermatological alterations (acantholysis and abnormal queratinization) and mental disorders are commonly associated with it. The gene, whose mutations leads to the appearance of this disease, is situated in the chromosome 12q23-24.1 and codifies the enzyme Ca-ATPase of the endoplasmatic reticule. Considering the report of co-segregation with family BD and the calcium-dependent alterations found in BD, it is suggested that the mutations in this gene may have pleiotropic effects on the skin and the brain. Jacobsen et al[34] studied the association of the mutations observed in this gene on BD patients which were part of multiple pedigrees that showed linkage with markers in the same chromosomal region with no positive results.

The presence of BD in a significantly higher frequency than in the general population occurs also in the velo-cardio-facial syndrome, caused by a microdeletion in chromosome 22q11, resulting in several somatic, learning and behavioral disturbances. The finding that 64% of these patients meet criteria for bipolar spectrum[35] suggests this locus as being possibly involved in the susceptibility to BD.

Anyway, diseases with Mendelian inheritances which show high rates of associations with mental disorders may function as paradigms for the search of regions linked to the genetic susceptibility for the development of BD.

Repetitions of trinucleotides

Anticipation, a phenomenon in which a disease appears in a progressively earlier age in successive generations, may explain deviations in Mendelian inheritance models observed in some hereditary diseases. Repetitions in the sequence of trinucleotides are correlated with anticipation. These sequences are unstable, and may expand in size between generations and thus lead to a worsening of the disease's symptoms. These mutations may explain the discordance of affective disorders between monozigotic twins. Although the phenomenon of anticipation may be caused by environmental factors, the observation of its occurrence among BD patients led to the investigation of the expansion of CAG/CTG repetitions in affective disorders. Among the expansions investigated, large CTG/GAC repeat alleles, situated in the chromosome 18q21.1, and ERDA1 alleles, in the chromosome 17q21.3, were more frequent in bipolar patients in the studies by Lindblad et al[36] and Verheyen et al,[37] respectively. However, other studies have not observed such an association, including samples of Brazilian patients.[38]

Imprinting

Epigenetic factors refer to the modifications in the DNA which regulate the genomic activity. The understanding of these mechanisms allows a better assessment of inheritance patterns, such as the phenotypic discordance between monozigotic twins, the risk age for the appearance of the disease, the clinical differences between genders, and the floating course of the disease. One of the mechanisms used in this control is the imprinting.

Imprinting refers to a non-Mendelian inheritance pattern in which the phenotypic transmission depends on the parental origin of the allele associated with the disease. It is noted that bipolar patients have higher frequency of affected mothers than fathers, and more maternal than paternal affected ancestors.[39]

Some aspects of genetic inheritance may determine this pattern. Mitochondrial inheritance may explain the maternal transmission of the phenotype.[40] Mitochondrial dysfunction in BD has been suggested by several studies.[41-42] Linkage studies show the locus 18p11 associated with BD in pedigrees with paternal transmission of the disease,[43] suggesting the mechanism of methylation of DNA as a mediator of imprinting in these cases.

Other findings suggest a preferentially paternal transmission of Dopa Decarboxilase alleles in BD,[44] for the loci in 18q22, 13q12 and 1q41.[45]

Genic expression profile

The new technologies in molecular genetics have enabled the characterization of the genic expression profiles of each organ. The application of these techniques on post-mortem brain tissue of individuals with BD and other psychiatric diseases became an important tool for the identification of the genes involved in the etiology and pathophysiology of the disease.

The comparison between the brain tissue of BD and controls can be used to identify reduction in the TGF-beta 1 and increase in the precursor of caspase-8 and erbB-2 in the pre-frontal cortex of bipolar patients.[46] Post-mortem studies also consistently reveal alterations in the levels of several intracellular messengers, such as PKA and PKC, ERK/MAPK.[47] Trying to determine specific genes of BD regarding the other common mental disorders, such as schizophrenia and major depression, Iwamoto et al[48] observed in bipolar subjects a trend to downregulation in the expression of membrane, ionic and transporting codifying genes, and upregulation in the expression of genes related to stress-response, such as HSPF1 (heat shock protein 40). It is not clear, however, if those alterations are due to variations in the codifying genes or are secondary to other molecular causes and interactions.

Other molecular alterations were identified for the neuropeptide Y, whose mRNA levels are reduced in the frontal cortex of bipolar subjects,[49] for the G protein receptor kinase 3 (GRK3), whose levels are decreased in one subgroup of patients.[50]

The advantage of these techniques is being capable of identifying thousands of genes expressed in the brain tissue which may have their transcription regulated by patterns that identify the disease. Therefore, the investigation of new genes potentially involved in the determination of the disease can be more rapidly and comprehensively conducted. These studies have increasingly evidenced the participation of genes which codify proteins that are part of important intracellular signaling pathways, transcription factors, and factors that regulate cellular apoptosis or protection.[51]

Other variant of studies which have contributed for the recognition of genes involved in the pathophysiology of mood is based on pharmacogenomic, which may help in the characterization of the genetic subtypes of the disease through the assessment of the genic expression profile associated with the therapeutical response to a determined psychopharmac. Regarding BD, the understanding of the genic expression pattern stemming from the exposition to lithium or to anticonvulsants allows distinguishing subgroups of genes modulated by the action of lithium which may mark a good response or also define genetic subtypes of BD responsive or non-responsive to mood stabilizers. This pharmacological distinction may imply a pathophysiological distinction.

Discussion

In complex diseases there is no direct correspondence between genotype and phenotype. The same genotype may determine a range of phenotypes depending on the interaction with other

genes or environmental factors. On the other hand, distinct genotypes can lead to a single phenotype. These aspects widens the possibilities of clinical presentation, reinforcing the idea of a *continuum,* implying in turn the existence of multiple genes and mechanisms by which these genes interact between them and with the environment in the determination of the disease.

The proliferation of studies showing apparently inconsistent and frequently non-replicated results may reflect this lack of homogeneity in the delimitation of the phenotype. Interferences by the comorbidity or phenocopies (similar manifestations to the studied disease but with non-genetic origin) and from the ethnical difference of the samples assessed can lead to false results. Biased results may also stem from the ethiological complexity of the disease proper which would have a genetic heterogeneity, i.e., the same phenotype would result from different affected genes in different families. The difficulty in establishing the inheritance mode of BD and the genes involved stems partially from these aspects.

All findings, however, are important to direct the genetic investigation on complex diseases such as BD. These studies indicate regions and genes potentially associated with the behavioral phenotype, which when analyzed enhance the knowledge of the genome and its interaction with the environment. Other evaluation strategies arose from the difficulties found and the findings obtained. The investigation of endophenotypes, for example, can reduce the difficulties originated from disease heterogeneity. The utilization of the concept of *continuum*, not considering only affective disorders, but also comprising the group of schizophrenias, can help in the identification of genes with more robust effects on shared symptoms. The widening of the investigation strategy of candidate genes for second messengers and components of the signaling and regulation pathways of genic expression has shown promising and has more consistent results. In this perspective are situated the obtainment of genic expression profiles characteristic of BD patients and the use of the pharmacogenomic in the definition of more homogeneous clinical subtypes.

In the next years the result of the application of these strategies will be seen. New chromosomal regions and genes will be highlighted and their relationship with susceptibility to BD will be consistently established.

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