

## INVOLVEMENT OF GENETIC FACTORS IN BIPOLAR DISORDERS: CURRENT STATUS

Giada Juli, Maria-Rosaria Juli & Luigi Juli

Centro Studi Psichiatrici Provaglio D'Iseo, Italy

### SUMMARY

*Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. The involvement of genetic factors has been evaluated through twin, family, linkage and association studies but specific genes that contribute to the illness remain unclear. This study gives an overview of available literature.*

**Key words:** bipolar disorder - genetic factors - candidate genes

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### INTRODUCTION

In the past 30 years, human genetic studies have identified more than 1000 genes responsible for human diseases. These successes have largely been for uncommon diseases whose inheritance follows a classical pattern (e.g. Huntington's disease or cystic fibrosis) or traits for which a more genetically homogeneous subgroup can be isolated for a more common disease (familial breast and ovarian cancer or sub-forms of type 2 diabetes mellitus). The picture for complex traits more generally has been mixed: Despite an enormous effort to identify genes responsible for numerous critically important human diseases (cancer, metabolic diseases, neuropsychiatric disorders, etc.), a surfeit of reproducible findings is still lacking.

Although it has already been known since ancient times, Jean-Pierre Falret (1794-1870), Marseilles psychiatrist, and Jules Gabriel Francois Baillarger (1809-1890), French neurologist, gave the first description of what is known today as bipolar affective disorder. They called it, in an independent way, "folie circulaire and folie à double forme", an autonomous disease that is characterized by alternating moods and manic depressive episodes. They concluded that these were not two separate diseases, but two different expressions of the same disease. Later, Kraepelin gathered in the diagnosis of "psychosis manic-depressive" traces of more clinical features such as depression, mania, mixed states, and fluctuation of periodic and circular insanity. In 1957 Karl Leonhard concluded the separation of depressive unipolar forms characterized by repeated episodes of depression and bipolar forms, those in which there is a fluctuation of depressive moods, mania, hypomania and also mixed states. Jules Angst and Carlo Perris also drew this same conclusion in 1966. Today, the most commonly used methods of international classification of mental illnesses are: the DSM IV-TR (APA) and the ICD-10 (WHO). These systems are based on axial and categorial criteria which do not fully meet the wide variety of the clinically painted pictures that each mental disorder is said to represent. More recently, it

has been suggested that a unitary model of the "spectrum" better describes the clinical course; it is one that takes into consideration the familiar studies and environmental factors; it considers the selection of homogeneous groups in the investigation of genetic inheritance; and encourages research into biological markers.

Recently, the international research community focused on the possibility that genetics also plays a critical role in vulnerability to this perplexing disorder (bipolar disorder). In this review, we evaluate the current state of research into molecular genetic studies of bipolar disorder which will be beneficial for future research.

### MOLECULAR GENETIC STUDIES

Two major study designs are generally employed to identify genes responsible for complex traits like bipolar disorder: linkage and association studies.

The purpose of a genome wide linkage study is to identify the genomic regions that might harbor predisposing or protective genes. In essence, linkage is a "discovery science" tool that does not require a prior assumption about the nature and locations of genes involved in the etiology of bipolar disorder (Sham 1998). Linkage analysis for complex traits requires a large sample of pedigrees with multiply affected individuals (Allison et al. 1998). Anonymous genetic markers across the genome are genotyped and used to identify chromosomal regions that may contain etiological genes. Linkage approaches effectively narrow the search space from the entire genome to one or several chromosomal regions. Genes located in these chromosomal regions become positional candidate genes.

Association studies contrast cases with bipolar disorder to appropriate controls without the disorder. The usual approach has been to select a set of specific candidate genes thought by the investigator to be involved in the pathophysiology of bipolar disorder. Historically, unlike linkage studies, prior knowledge has been required in order to conduct an association study-

to select candidate genes, to genotype a set of genetic markers, and to compare genotype and haplotype frequencies between cases and controls.

## LINKAGE STUDIES OF BIPOLAR DISORDER

Linkage studies for bipolar disorder have showed significant results concluding that the regions with the best evidence for linkage include areas on chromosomes 1q, 2p, 4p, 4q, 6q, 8q, 11p, 12q, 13q, 16p, 16 q, 18p, 18q, 21q, 22q, and Xq.

In particular, a probable linkage was found to 1q31-32 in a genome-wide scan of 22 pedigrees (Detera-Wadleigh et al. 1999). Linkage of multiple psychiatric diagnoses, including bipolar disorder, to 1q42 has been shown in a family with a translocation (Millar et al. 2004).

A study of an Israeli and American sample of 57 extended families (1508 Caucasian individuals) with bipolar disorder showed a parametric linkage for the region 2p13-16 using an intermediate disease phenotype and a dominant model of transmission (Liu et al. 2003).

The first significant linkage to chromosome 4p was reported in a Scottish pedigree (Blackwood et al. 1996) and it was also reported a linkage to 4p16-p14 (Detera-Wadleigh et al. 1999). An analysis of a 55-pedigree sample comprised of 674 individuals found a parametric linkage on chromosome 4q35 (Badenhop et al. 2003). Another linkage was found on chromosome 4q31 under a dominant model and a broad disease phenotype (Liu et al. 2003).

A genome-wide linkage analysis conducted on 1152 individuals from 250 families in the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Survey, reported that chromosome 6 yielded a suggestive linkage under a broad disease model (Dick et al. 2003).

Using meta-analytic techniques to 18 bipolar genome scans, chromosome 8q appeared to be linked to bipolar disorder under narrow and broad disease models (Segurado et al. 2003). It was also reported to be another piece of evidence for linkage to 8q under a narrowly defined disease phenotype (Dick et al. 2003).

Chromosome 11 has been of keen interest to investigators since the first indication of linkage in Old Order Amish kindred (Egeland et al. 1987). Parametric analysis revealed a heterogeneity linkage on this chromosome under a dominant, intermediate disease model (Zandi et al. 2003).

Evidence for linkage to 12q24 chromosome has been shown in large French Canadian families (Morissette et al. 1999).

A sufficient amount of evidence of linkage to chromosome 13q32 was shown in the NIMH Genetics Initiative pedigrees (Stine et al. 1997) and further support for this finding was reported in the neurogenetics sample (Detera-Wadleigh et al. 1999). Suggestive findings of linkage on chromosome 13q have also been reported (Kelsoe et al. 2001). A meta-analysis of published whole-genome scans of bipolar

disorder and schizophrenia, reported that 13q show significant evidence for linkage to both disorders (Badner & Gershon 2002).

There is evidence that suggests linkage signals on chromosome 16 in both the original and the replication samples from the NIMH Genetics Initiative. Further analysis of combined samples has been conducted using non-parametric affected relative pair analysis that identifies a region containing four markers that all yield a significant result (Dick et al. 2002).

Convincing and significant linkage are reported to the pericentromeric region of chromosome 18 (Berrettini et al. 1994). In addition, Costa Rican pedigrees supported linkage to the tip of 18p and 18q22-23 (Garner et al. 2001).

Linkage studies have also been performed on chromosome 21 reporting a large result on 21q22 (Straub et al., 1994) and additional evidence for linkage to this region was observed in two independent samples (Detera-Wadleigh et al. 1996). Another study also reported the evidence of linkage in 56 families to chromosome 21 (Liu et al. 2001).

Several groups have reported linkage to chromosome 22 in bipolar samples (Kelsoe et al. 2001). Evidence of linkage in families with psychotic mood disorder to 22q12 have been found (Potash et al. 2003).

The analysis of the NIMH Genetics Initiative pedigrees showed linkage to the X chromosome on Xp22.1 (McInnis et al. 1999). The relationship between the X chromosome and bipolar disorder in a sample of 341 Finnish individuals affected from 41 families, using a dominant model of inheritance, showed a suggestive linkage under a narrow disease model (Ekholm et al. 2002).

## ASSOCIATION STUDIES TO IDENTIFY CANDIDATE GENES IN BIPOLAR DISORDER

The volume of genetic association studies along with their specialized terminology can be dizzying to the reader unfamiliar with genetic research. Several research groups have focused their attention on association studies to identify candidate genes involved in bipolar disorder. There are many candidate genes that have been investigated such as genes involved in serotonin, dopamine and norepinephrine/noradrenaline pathways.

**Serotonin transporter.** Much interest has been shown in the relationship between an insertion/deletion polymorphism in the promoter region of the gene encoding the serotonin transporter and the development of depressive symptoms following adversity (Zammit et al. 2006). However, no significant associations were detected in association studies on two moderate-sized data sets (135 nuclear families with a bipolar proband and a separate sample of 545 cases and 58 controls) by examining polymorphisms across the gene as well as in the promoter (Mansour et al. 2005).

**Catechol-o-methyl transferase** is an enzyme involved in the degradation of monoamines and its gene is a reasonable candidate for bipolar disorder (Craddock et al. 2006). The gene contains a much studied polymorphism, Val108/158Met, which influences catechol-o-methyl transferase (COMT) activity levels. Some evidence shows that this polymorphism (Lachman et al. 1996, Kirlov et al. 1999) influences clinical features of bipolar disorder, such as rapid cycling, and that a separate single nucleotide polymorphism (SNP) elsewhere in the gene is associated with both schizophrenia and bipolar disorder (Shifman et al. 2004).

**Brain-derived neurotrophic factor (BDNF)**, which has also been implicated in unipolar depression, encodes a nerve growth factor protein and its transcription is highly susceptible to modulation by antidepressants (Ivy et al. 2003). Two polymorphisms of this candidate gene have been examined in bipolar disorder: a single nucleotide variation that causes a switch in amino acid from valine to methionine (Val66Met polymorphism) and a varying length microsatellite that was originally reported as a GT repeat, 1 kb upstream of the translation initiation site, in the BDNF-linked complex polymorphic region (BDNF-LCPR).

The Val66Met polymorphism has been reported to have a small but significant effect on bipolar disorder (Sklar et al. 2002, Neves-Pereira et al. 2005). BDNF-LCPR is a complex polymorphism, and to date, two studies have found association with bipolar disorder (Okada et al. 2006, Kremeyer et al. 2006).

**Tyrosine hydroxylase** is one of the rate-limiting enzymes in catecholamine synthesis. Association studies suggested some association between the tyrosine hydroxylase polymorphisms and manic-depressive illness (Leboyer et al. 1990). However, a subsequent meta-analysis revealed no evidence of variation in this gene associated with bipolar disorder (Turecki et al. 1997).

**G72/G30**, known as D-amino acid oxidase activator (DAOA), is associated with both schizophrenia and bipolar disorder (Hattori et al. 2003, Schumacher et al. 2004). In a study of more than 1400 patients with schizophrenia and bipolar disorder and more than 1400 ethnically matched controls, nine polymorphisms have been genotyped that tag the common genetic variations at DAOA/G30. It has been shown that DAOA/G30 does not increase susceptibility to prototypic schizophrenia or psychosis, but variations in this gene complex do influence susceptibility to episodes of mood disorder across the traditional bipolar disorder/schizophrenia boundaries (Williams et al. 2006).

**Neuregulin (NRG1)** was one of the first confirmed genes conferring susceptibility to schizophrenia (Stefansson et al. 2002). An association study has shown a similar effect size for NRG1 in bipolar disorder as for schizophrenia, and this was even greater in those patients who experienced mood incongruent psychotic symptoms (Green et al. 2005). However, another study was not able to replicate these findings in a small sample of 92 bipolar disorder type I Irish trios (Cassidy et al. 2006).

**Disrupted in schizophrenia genes DSC1 and DSC2** were the first discovered in a large Scottish family in which a balanced translocation between chromosome 1 and 11 was found to be strongly associated with mental illness (Blackwood et al. 2001). The phenotype had complicated features and consisted of schizophrenia, bipolar disorder and mild mental retardation. An association between DSC1, a gene at 1q42 coding for a neural structural protein, and bipolar disorder was found in the Scottish population (Millar et al. 2004).

## FAMILY AND TWIN STUDIES

It has been recognized that bipolar disorder tends to run in families (Kraepelin 1919). Around 20 studies have confirmed that first-degree relatives of bipolar patients have a 5-10 times greater risk of developing the illness than the general population (Jones et al. 2004) and are also twice as likely to develop unipolar disorder. Even more strikingly, the monozygotic cotwins of bipolar probands are at a 45-75 times greater risk of developing the disorder than the general population (McGuffin et al. 2003). These studies also demonstrate that, as with most common diseases, bipolar disorder does not show a Mendelian pattern of inheritance. Even after allowing for the possibility of incomplete penetrance, the available data is incompatible with single locus inheritance (Jones et al. 2004). In a study of monozygotic and dizygotic twins, there is a very high concordance for bipolar disorder in monozygotic twins (75%), and a lower concordance for dizygotic twins (10.5%) (Kieseppa et al. 2004). This compares with an earlier study showing 67% concordance in monozygotic twins and 19% in dizygotic twins (McGuffin et al. 2003) and both of these studies looked at a relatively small number of patients. That the concordance between monozygotic twins is not a 100% is an indication that the phenotype of bipolar disease is not exclusively determined genetically. The disease has components which are not dependent on the genetic makeup of the individual patient, but is also contributed to by other factors such as environment (Boomsma et al. 2002).

## FUTURE DIRECTIONS AND RESEARCH NEEDS

Genetic studies of bipolar disorder surely are in an early phase and the needs for the future are clear: The genetics of bipolar disorder has a need for greater and larger studies. A combination of linkage, association and other approaches will probably be necessary to clarify the genetic mechanisms of bipolar disorder. Genetic research on bipolar disorder may also benefit from the increased use of endophenotypes (i.e. traits associated with the disease that are heritable and possibly precede disease onset and are present in unaffected relatives). In schizophrenia research, endophenotypes have received much attention but are less widely used in bipolar disorder research. Candidate

endophenotypes include circadian rhythm disruption, response to sleep deprivation, psychostimulants, tryptophan depletion (Lenox et al. 2002) and melatonin levels (Nurnberger et al. 2000). Further research is needed to establish whether these markers validly reflect underlying genetic vulnerability. Although the influence of genes in bipolar disorder is clearly critical, evidence suggests that environmental factors play a significant role in the course of the illness. For example, several studies have provided evidence that life events may precipitate episodes (Johnson et al. 2000, Mortensen et al. 2003). It may be necessary to consider other factors, such as gene-environment and gene-gene interactions, in order to definitely demonstrate the role of genetic factors in the susceptibility to bipolar disorder.

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Correspondence:

Giada Juli  
Centro Studi Psichiatrici  
Provaglio D'Iseo, Italy  
E-mail: giadajuli@libero.it