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Genetic Studies of Bipolar Disorder: A Review

Özden ARISOY[1], E. Timuçin ORAL[2]

Abstract

Bipolar disorder is a severe mental illness that afflicts approximately 1% of the world's population, and is characterized by mood swings from elation to depression. Although the etiology of bipolar disorder remains unclear, heritable factors have been shown to be involved. Family, twin, and adoption studies suggest a genetic etiology. Molecular genetic studies also support a genetic component. Many chromosomal regions have been implicated by these molecular genetic studies, but no single susceptibility gene has been identified. These findings show that bipolar disorder has a complex genetic etiology in which multiple unidentified genes and environmental factors play an important role in its pathogenesis. Herein, molecular genetic studies of bipolar disorder are reviewed based on a search of Medline using the key words, bipolar, genetic, and chromosome. Studies with positive results for bipolar disorder were selected first. The findings from these molecular genetic studies are reviewed systematically, chromosome by chromosome. Causes of the differences between the reported findings and of non-replication are discussed. Finally, important factors for designing a genetic study of bipolar disorder are examined.

Key words: *bipolar, genetic, linkage, association, chromosome*

INTRODUCTION

Bipolar disorder (BPD) is a severe mental disorder that afflicts approximately 1% of the world's population and is characterized by mood swings from elation to depression. Although the etiology of BPD remains unclear, heritable factors have been shown to be involved. Mitchell (1993) reported that Kraepelin was the first researcher that was adamant about the central role of genetic factors in BPD and demonstrated a hereditary link in about 80% of cases. Results of family, twin, and adoption studies also indicate the presence of a strong hereditary component, and advances in molecular genetics since the 1960s support these epidemiological findings. Since 2000, with the completion of the Human Genome Project, the number of molecular genetic studies have greatly increased and many chromosomal regions have been implicated in BPD, but no single susceptibility gene has been identified and findings have not be replicated.

Herein, molecular genetic studies of BPD are reviewed based on a search of Medline that used the key words, bipolar, genetic, and chromosome. Then, findings from these molecular studies are reviewed systematically, chromosome by chromosome. Finally, the causes of the difference between findings and of non-replication are discussed, and important factors for designing a genetic study of BPD are examined.

I) Genetic Epidemiology

Genetic epidemiology investigates the role of genetic and environmental factors in the etiology of a disorder. Family, twin, and adoption studies are important to this field.

a) Twin Studies

The most important findings about the genetic liability of BPD come from twin studies. If a disorder occurs

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[1]MD/Assistant Prof., Abant İzzet Baysal University, İzzet Baysal Faculty of Medicine, Psychiatry Dept., Bolu. [2]MD/Associate Prof., Bakırköy State Hospital for Mental and Neurological Diseases, 5th Psychiatry Clinic, İstanbul.
Özden Arısoy, e-mail: *ozdenarisoy@yahoo.com*

due to genetic factors, independent of environmental factors, the co-occurrence of the disorder in monozygotic twins (MZ) is expected to be 100%, as they are genetically identical. But if genetic and environmental factors both play a role in the etiology, this percentage is expected to be lower. The classical twin design relies on the comparison of MZ twins and dizygotic (DZ) twins raised together, and the comparison of MZ twins raised apart. Significantly higher concordance in MZ than in DZ twins is evidence of a genetic effect. Mitchell (1993) reported a concordance rate in MZ twins of 60%-70%, as compared to 20% in DZ twins. Bertelsen et al. (1977) observed greater heritability for BPD than unipolar disorder (UPD) in Danish twins. This supports the concept that BPD is a biological disorder, principally genetic in etiology, but it is not sufficient to prove that genetic factors are the only etiological factor in the pathogenesis of BPD. Factors other than genes can also play a part.

b) Adoption Studies

Studying adoptees seems to offer the opportunity to break the nexus between genetic and environmental transmission of disorders. Two major designs can be used: 1) The prevalence of the disorder in the biological and adoptive parents of affected adoptees can be compared; 2) The prevalence of the disorder in adoptees with affected and unaffected biological parents can be compared. If the disorder is genetic in nature, the risk will be greater in the biological parents of adoptees or in adoptees with affected biological parents.

Mendlewicz and Rainer (1977) carried out the first adoption study of BPD and reported an excess of psychopathology in the biological parents of affected adoptees, as compared to their adoptive parents (28% and 12%, respectively). Wender et al. (1986) carried out a study with 71 adoptees that had a history of affective disorder (AD) and observed in excess of 8 times more UPD and 15-fold greater risk of suicide among the biological relatives of affected adoptees than among those of control adoptees.

c) Family Studies

Family studies can also uncover the genetic liability of a disorder, as well as the genetic transmission mode. Detection of the transmission mode is the first step in discovering the gene responsible for the disorder (Akarsu, 1999). Family studies and pedigree analyses can also reveal the phenotypic characteristics of a disorder, such as age of onset, prevalence of other psychiatric disorders within the family, the phenomenon of anticipation (progressive increase in illness severity and decrease in age of onset from one generation to the next), and incomplete penetrance (no phenotypic expression of the disorder in a family member carrying the disease allele).

Andreasen et al. (1987) reported that the prevalence of UPD and BPD in the general population is 3% and 1%, respectively. They also observed that BPD clearly increases, with rates of 1.5%-14.5% in first degree relatives, as compared to 0.2%-1.3% in controls. UPD occurs more frequently in these pedigrees than in control pedigrees, and the risk of cyclothymia increased to 3%, as compared to 0.8% in controls. A small group of investigators have addressed the issue of the genetic relationship between bipolar I (BP-I) and bipolar II (BP-II) disorder. Coryell et al. (1984) reported that families of BP-I probands had an increased rate of both BP-I and BP-II, but families of BP-II probands had a higher risk of BP-II, while BP-I rates appeared to be similar to those in the general population. The results of such studies highlight the need to treat BP-II as a different threshold of AD; however, in general, most studies consider BP-I and BP-II to be in the same category. Overall, rates of AD clearly increase, by approximately 5-10-fold, in the families of bipolar (BP) probands.

Weismann et al. (1984) compared the parents of BP and UP probands to controls, and reported that the prevalence of BPD in the parents of BP probands was 6% versus 3% in the parents of UP probands and 0.6% in controls. Gershon et al. (1982) observed that offspring of a patient with AD have a 20%-30% risk of having AD and that the risk increases if the spouse also has AD, in which case the rate increases to 50%-75% if the disorder is BPD. If there is a history of AD in previous generations, the risk increases significantly. Taylor and Abrams (1981) reported that first degree relatives of BP probands with disease onset before 30 years of age had 3 times the risk of having AD than those of probands with disease onset after 30 years of age. Strober et al.'s (1988) report of higher familial aggregation rates in adolescent BP-I probands may indicate a greater likelihood of a genetic etiology.

In summary, results of genetic epidemiological studies indicate that rate of occurrence of AD in relatives of a patient with AD is about 60% in MZ twins, 20% in DZ twins, 15% in their off-spring, 5%-10% in their first degree relatives (mother, father, brother, sister), 5% in their second degree relatives, and 3.5% in their cousins (Gandini, 1992).

II) Molecular Genetic Studies

The study of molecular genetics includes gene mapping studies designed to locate the position of a locus responsible for a particular disorder. In a gene mapping study, a polymorphic marker whose location on a chromosome is known is used to find the chromosomal location of the susceptibility gene. Two methods are used to select the polymorphic markers to be used: A) The candidate gene approach; B) Whole-genome scan. With the candidate gene approach, candidate genes that may bear some a priori theoretical relevance to the etiology of a condition are selected. With a whole-genome scan, the entire genome is scanned, making no assumptions about candidate sites or genes. There are classically 2 kinds of molecular genetic studies: linkage and association.

a) Linkage Studies (parametric methods)

Linkage studies are based on the premise that a major single gene causes the disease being studied in the family; at least 3 multi-generational families in which more than 1 member is affected by the disease are needed in order to determine the mode of inheritance. This method requires no knowledge of disease pathophysiology and can be considered a purely genetic approach. This is obviously attractive to those studying psychiatric disorders for which the pathogenesis is poorly understood. Linkage is studied as the co-segregation of a specific form (allele) of a genetic marker,whose location on the chromosome is known,with the illness within a particular family. Due to the nature of meiosis, this co-segregation will occur only if the disease and marker genes are located close together on the same chromosome. As the distance between genes on a chromosome decreases, the probability that they will remain together after meiosis increases (that is, they are linked).

b) Association Studies (non-parametric methods)

Candidate genes are used in this approach, which presupposes that the researcher has a sufficient understanding of disease biology so as to be able to recognize genes that may be involved in the disorder. There is no need to find large families with a known mode of inheritance. Association studies compare the distribution of marker alleles in affected individuals with appropriate comparison individuals (cases and unrelated controls) matched for such potentially relevant variables as age, gender, and ethnicity. Sib-pairs, patients, and their healthy relatives or proband-parent trios can be compared in these studies.

Both methods have advantages and disadvantages. The selection of the method to be used depends on the possibility of finding a large family, contacting family members, and knowing the mode of inheritance.

Following are some molecular genetic studies of BPD. The results are reviewed systematically, chromosome by chromosome.

Chromosome 1: Several genome scans determined a linkage to this chromosome (Curtis et al., 2003; Macgregor et al., 2004; Savitz et al., 2007), but there is not enough knowledge about its pathophysiological connection with BPD and it requires confirmation in replication studies.

Chromosome 2: Goes et al. (2007) compared subjects with mood-incongruent (MIC) and mood-congruent (MC) psychotic features using genome-wide linkage scans, and observed that MIC psychotic features showed evidence of linkage to 2p11-q14 and 13 q21-33. The 13q21-33 finding supports prior evidence of a BPD/schizophrenia (SZ) overlap, while 2p11-q14 findings were the first to suggest that this SZ linkage region might also harbor a BPD susceptibility gene. Willour et al. (2007) analyzed genome-wide scan data of 162 BP pedigrees that had attempted suicide and detected a linkage to 2p12. This finding on 2p12 replicates results from 2 previous studies of attempted suicide in pedigrees with alcohol dependence and in pedigrees with recurrent early-onset depression.

Chromosome 3: 3q13.3 codes for dopamine receptor 3 (DRD3). Dopamine neurotransmission is implicated in the pathophysiology of SZ and more recently AD. Among the dopamine receptors, DRD3 can be considered as particularly related to AD due its neuroanatomical localization in the limbic region of the brain. The DRD3 gene is also of potential interest in the physiopathology of AD because of its expression patterns in brain structures that control various aspects of behaviour, cognition, and emotions. Moreover, it encodes a receptor protein that is the target of psychotropic drugs that are effective in the treatment of this disorder.

This region was investigated by numerous researchers and Dikeos et al. (1999) reported an association between DRD3 (Bal 1 polymorphism) and UPD. Chiaroni et al. (2000) observed that a subgroup of patients with BPD (homozygous for the Bal 1 polymorphism) exhibited a characteristic clinical pattern consisting of monopolar BPD, early onset, and initiation via an acute delusional episode. These results could involve the DRD3 locus as a gene of minor effect in BPD.

Chromosome 4: The 4pter-p12 region codes for

dopamine receptor type 5 (DRD5). DRD5 is a candidate gene for the psychopharmacological treatment of psychotic disorders and is considered in SZ research. The association between DRD5 and BPD was first reported by Ginns et al. (1998) in Old Order Amish families. Christoforu et al. (2007) later compared 368 BPD, 386 SZ, and 458 controls, and identified significant associations between BPD and SZ, and the 4p linkage region. Underwood et al. (2006) also observed an association between G protein-coupled receptor 78 (GPR78), which lies in the 4p region, and SZ and BPD in the Scottish population.

Chromosome 5: The telomeric region of 5p (5pter) codes for the dopamine transporter (DAT) gene, which plays a key role in the regulation of dopaminergic neurotransmission by mediating the active reuptake of synaptic dopamine. It is an important candidate gene for BPD, based on data implicating dopamine abnormalities in mania and because it is the site of action of amphetamine, which has psychomotor activating and psychotogenic properties. Kelsoe et al. (1996) reported an association between DAT and BPD. Another region, 5q32, which encodes the serotonin 4 receptor, was investigated by Ohtsuki et al. (2002), because possible irregularities in serotonergic neurotransmission may cause a variety of neuropsychiatric diseases and they observed an association with BPD, but not with SZ, even though this region was previously implicated in SZ. Kerner et al. (2007) analyzed BP-I patients with psychotic features as a homogenous population and reported an association with 5q33-34.

Chromosome 6: Abou Jamra et al. (2007) reported an association between 6q and 2q in 52 BP families of European descent. Schumacher et al. (2005) also noted an association between 6q24 in Romanian BP families. McQueen et al. (2005) analyzed data from 11 genome-wide linkage scans of 5179 individuals and reported a significant linkage to BPD on chromosomes 6q and 8q. Lambert et al. (2005) made a genome-wide scan of BP-affected sib-pairs and reported an association with 6q in male-male pairs. Schulze et al. (2004) studied 245 BP sib-pairs with BP-I disorder and observed a positive correlation with 6q. Affected siblings shared the maternal more often than the paternal chromosome, which would reflect a maternal parent-of-origin effect.

Chromosome 7: The 7p11 region codes for dopa decarboxylase (DDC), which is involved in the synthesis of both serotonin and dopamine, which makes it a potential susceptibility region for BPD. Borglum et al. (2003) investigated 1 base pair (bp) and 4 bp variants of DDC in a case-control group, and noted an increased segregation of 1 bp variant in familial cases and increased segregation of the 4 bp variants in proband-parent trios, with a paternal transmission. These results show that there is an association between the DDC gene and familial cases.

Chromosome 8: Chr 8 was implicated in several genome-wide scans (Cichon et al., 2001; McInnis et al., 2003). Lohoff et al. (2006) compared 585 BP patients with controls and reported an association with vesicular monoamine transporter 1 gene polymorphism located on 8p21, which is involved in the transport of neurotransmitters thought to play a relevant role in the etiology of BPD.

Chromosome 9: The 9q34.3 region codes for the N-methyl-D-aspartate 1 receptor gene (GRIN1). The role of abnormal glutamate neurotransmission and reduced GRIN1 expression has been proposed as a hypothesis for the pathogenesis of psychotic disorders such as SZ. Lithium and valproate also act on the NMDA receptor, which might indicate a role of the glutamatergic system in the pathophysiology of BPD as well. Itakowa et al. (2003) tested this hypothesis and reported that the low-activity allele of the GRIN1 receptor gene was actively segregated in BP families.

Chromosome 10: Two regions on the long and short arms of chromosome 10 were implicated in BPD. Savitz et al. (2007) observed a significant linkage to 10q25-q26 and that the 10p12-p13 region was linked to both BPD and SZ. Based on those results, Berrettini et al. (2001) indicated that SZ and BPD may have some common genetic susceptibility genes and that these 2 disorders may not be as distinct as current nosology suggests. In that sense, they recommend that susceptibility regions implicated in SZ also be investigated for a role in BPD.

Chromosome 11: The 11p15 region codes for tyrosine hydroxylase and the DRD4 receptor gene. The 11q22-23 region codes for the DRD2 receptor and the 11q14-q21 region codes for the enzyme tyrosinase. Tyrosine hydroxylase is the rate-limiting enzyme in noradrenaline and dopamine synthesis, and could be a candidate gene for BPD; however, there are conflicting results about its association with BPD (Turecki, 1998).

Chromosome 12: Avromopoulos et al. (2007) conducted a genome-wide linkage scan for BPD in a sample of Ashkenazi Jews and reported evidence for a linkage in the 12p region. This region harbors the gene encod-

ing for the ionotropic glutamate receptor subunit 2B (GRIN2B), which is a candidate gene for BPD. Van der Boagert et al. (2006) compared 135 UP, 182 BP, and 364 controls from Sweden and observed an association between UPD and BPD, and the chromosome 12 region, which codes for the enzyme tryptophan hydroxylase 2 (TPH2), a rate-limiting enzyme involved in serotonin synthesis. De Luca et al. (2005) also examined TPH2 mRNA levels in postmortem brains of 35 BP, 35 SZ, and 35 control subjects, and reported more TPH2 mRNA in the BP group. Because serotonergic neurotransmission has been implicated in suicidal behavior, Geijer et al. (2000) investigated polymorphisms in the genes coding for tryptophan hydroxylase, serotonin transporters, and the serotonin 2A (5HT2A) receptor in a sample that had attempted suicide and in controls, and noted a highly significant association between tryptophan hydroxylase and attempted suicide.

Chromosome 13: 13q14-q21 codes for the serotonin 2A receptor (5HT2A). Several antipsychotics and antidepressants have a high affinity for 5HT2A receptors and 5HT2A receptor density seems to be increased in depressive patients' platelets. These features make the 5HT2A receptor gene a candidate gene for BPD. Chee et al. (2001) observed that a polymorphism of the 5HT2A receptor gene might be related to the development of BPD in a Korean population. Bonnier et al. (2002) reported a higher frequency of the A allele of the 5HT2A receptor gene in a subgroup of patients with BP-I disorder without a personal and/or familial history of attempted suicide.

The 13q14 region is also implicated in SZ and BPD. Goes et al. (2007) performed a genome-wide scan of 708 BP families recruited from 10 academic centers. Subjects with MIC and MC psychotic features were compared, and they reported that MIC features were associated with a more severe course, and with increased rates of hospitalization and attempted suicide. They found evidence of linkage on 13q21-33 and 2p11-q14 in patients with MIC psychotic features. These results indicate that MIC psychotic features in BPD might represent phenotypic manifestations of susceptibility genes shared with SZ.

Chromosome 14: Segorado et al. (2003) observed an association between 14q21.1-32.12 and BPD in a meta-analysis of 18 BPD genome-scan data sets. This region codes for tetrahydrobiopterin (BH4), which is a cofactor of the enzymes tyrosine and tryptophan hydroxylase, which are involved in the synthesis of dopamine, noradrenaline, adrenaline, and serotonin. Dysregulation in this gene might cause a change in the synthesis of these neurotransmitters and might play a role in the etiopathogenesis of BPD. Cassidy et al. (2007) performed a genome-scan and reported that the quantity of the A allele of this gene is increased in Irish BP families.

Chromosome 15: Vazza et al. (2007) conducted a genome-scan of 16 families with SZ and BPD from northeastern Italy, and identified linkage on 15q26, concluding that this region influences susceptibility to both SZ and BPD, which is in agreement with the "continuum theory" that suggests an overlap between these disorders.

Chromosome 16: The 16p13.3 region codes for the somatostatin type 5 receptor (SSTR5). The dopamine D2 receptor (DRD2) and SSTR5 interact physically to form heterodimers with enhanced functional activity. Brain DRD2 receptors are among the major targets of the neuroleptic treatment of psychiatric disorders. Nyegaard et al. (2002) reported an association between the SSTR5 gene and BPD. Jones et al. (2007) observed linkage to 16p13 in bipolar affective puerperal psychosis.

Chromosome 17: The 17q11-q12 region codes for the serotonin transporter (5HTT) gene. Schumacher at al. (2002) reported positive results for the 5HTT gene in BPD. Lasky-Su et al. (2005) noted a significant association between the 5HTT gene and BPD in their meta-analysis. Tomas et al. (2006) reported linkage to 17q11 in BP families. Bellivier et al. (2002) tested the association between the variable number of tandem repeats (VNTR) polymorphism of the 5HTT gene in clinically and genetically more homogeneous sample of early-onset BPD patients, and observed that VNTR polymorphism significantly influenced age of onset. They observed that patients carrying at least 1 VNTR allele became ill later and that patients carrying the 'ss' genotype tended to become ill earlier. Savas and Yumru (2006) reported that there was no association between 5HTT gene polymorphism and BPD in Turkish patients.

Chromosome 18: The 18p11.2 region codes for the myo-inositol monophosphatase 2 (IMPA2) gene, which is found in the phospholipase C signaling pathway and has been shown to be inhibited by lithium. Yoshikawa et al. (2000) reported that silent mutations in this region tend to be associated with BPD. Ohnishi et al. (2007) performed a genetic association study with 496 Japanese BP patients and 543 controls, and observed an association with IMPA2 on the 18p11.2 region, whereas expression studies of postmortem brains showed increased transcription of the IMPA2 allele in the frontal cortex

of BP patients. Therefore, in contrast to a prior report, therapeutic concentrations of lithium could not suppress transcription of IMPA2 mRNA and the mood-stabilizing effect of lithium was, if IMPA2 was among the targets of lithium, generated via inhibition of the enzymatic reaction, rather than transcriptional suppression. Weller et al. (2006) also noted an association with the protein located on the 18p11 region, which was thought to play a role in the cellular processes required for neurotransmission in the central nervous system in BPD.

Chromosome 19: This chromosome was implicated in several genome-scans, but its etiopathological significance in BPD has not yet been determined (Detera-Wadleigh et al., 1997).

Chromosome 20: Radhakrishna et al. (2001) performed a genome-wide linkage analysis in a large Turkish pedigree and observed strong evidence for a BPD susceptibility locus on chromosome 20p11.2-q11.2. This region codes for 2 alpha adrenergic receptors, a G-protein subunit, and 2 enzymes involved in the phosphatidylinositol cycle, which have all been implicated in the action of lithium. One of these enzymes is phospholipase C-gamma-1 isoenzyme (PLCG1), located on 20q12-q13. Turecki et al. (1998) and Lovlie et al. (2001) reported a higher frequency of a PLCG1 polymorphism in BPD patients that responded well to lithium prophylaxis. Nonetheless, this polymorphism's role in the pathogenesis of BPD or in the mechanism of lithium response remains to be determined.

Chromosome 21: 21p22.3 codes for TRCP7 gene transcribed to the TRCP7 protein, which is a non-selective cation channel that works in conjunction with the inositol triphosphate system. It is highly expressed in the brain and is involved in regulating intracellular calcium (Ca) concentrations. Yoon et al. (2001) reported that TRPC7 mRNA levels were significantly lower in BP-I patients with high intracellular Ca levels and concluded that reduced TRPC7 gene expression may be a trait associated with pathophysiological disturbances to Ca homeostasis in a subgroup of BD-I patients. McQuillin et al. (2006) compared 600 BP patients to 450 controls and observed an association with a polymorphism in the TRPM2 gene that encodes for a Ca channel receptor in BP patients. This polymorphism is known to cause dysregulation in cellular Ca homeostasis in response to oxidative stress.

Chromosome 22: The 22q11 region codes for the catechol-o-methyltransferase (COMT) enzyme. COMT plays a major role in the breakdown of catecholamines, including the neurotransmitters dopamine and noradrenaline, in the synaptic cleft. Mynett-Johnson et al. (1998) observed that there was a tendency for the low-activity allele of COMT to be preferentially transmitted to female BP-I probands. Kirov et al. (1998) suggested that the low-activity COMT allele might be associated with rapid-cycling and Papolos et al. (1998) suggested that the low-activity allele was associated with ultra-ultra rapid cycling BPD. This finding is in line with the observation that antidepressants precipitate mania or rapid-cycling in BP patients by increasing the level of monoamines in the synaptic cleft and that individuals with the low-activity COMT allele would be expected to have higher levels of trans-synaptic catecholamines due to reduced COMT degradation of norepinephrine and dopamine, which places them at increased risk of rapid-cycling in response to antidepressant treatment.

Deletion on chromosome 22q11 causes velo-cardio-facial-syndrome (VCFS), a common congenital disorder associated with a variety of psychiatric illnesses, including SZ and BPD. The psychiatric manifestations of VCFS could be due to a polymorphism in the COMT gene within 22q11 (Lachmann et al. 1996).

The 22q11 region also harbors a gene coding for the G-protein receptor kinase 3 (GRK3) enzyme. GRK3 plays a key role in the homologous desensitization of G protein-coupled receptor signaling. Dysregulation in GRK3 expression might alter signaling desensitization and cause dopamine supersensitivity and, thereby, result in predisposition to the development of BPD. Barrett et al. (2003) reported that GRK3 protein levels were low in BPD patients with a severe disease course.

Chromosome X: The Xq24 region codes for the serotonin 2C receptor (5HT2C). Substantial evidence supports its role in the dysfunction of brain serotonergic (5-HT) systems involved in the pathogenesis of AD. Karkowski et al. (1997), in an epidemiologic sample of female-female twin pairs, observed that mania in 1 twin predicted major depression in her co-twin, suggesting a familial/genetic relationship between major depression and mania, which is consistent with the hypothesis that UPD and BPD are 2 points on a continuum of a single liability of illness. Lerer et al. (2001) examined a structural variant of the 5-HT2C receptor gene in UP and BP patients, and controls and reported a higher rate of 5HT2CR polymorphism in the patients than in the controls. Gutiérrez et al. (1996) also observed an excess of 5HT2CR polymorphism in female cases and indicated that this polymorphism might increase susceptibility to BPD in women.

TABLE. Chromosomal regions implicated in BPD.

Chromosome	Region	Candidate gene
Chromosome 1		
Chromosome 2	2p11-q14 2p12	
Chromosome 3	3q13.3 3p14	Dopamine receptor type 3 (DRD3)
Chromosome 4	4pter-p12 4p	DRD5 G protein related receptor 78 (GPR78)
Chromosome 5	5pter 5q32 5q33-34	Dopamine transporter Serotonin receptor type 4 (5HTR4)
Chromosome 6	6q24 6q12	
Chromosome 7	7p11	Dopa decarboxylase (DDC)
Chromosome 8	8p21	Vesicular monoamine transporter 1 gene
Chromosome 9	9q34.3	NMDA subunit 1 receptor gene (GRIN1)
Chromosome 10	10q25-q26 10p12-p13	
Chromosome 11	11p15 11q14-q21	Tyrosine hydroxylase (TH) gene and DRD4 Tyrosinase enzyme
Chromosome 12	12p	Glutamate receptor 2B and tryptophan hydroxylase 2 (TPH2) enzyme
Chromosome 13	13q14-q21	Serotonin 2A receptor (5HT2A)
Chromosome 14	14q24.1-32.12	GTP hydroxylase enzyme gene, the rate limiting enzyme in the synthesis of tetrahydrobiopterin (BP4)
Chromosome 15	15q26	
Chromosome 16	16p13.3	Somatostatin receptor type 5 (SSTR5)
Chromosome 17	17q11-q12	Serotonin transporter
Chromosome 18	18p11.2	Myo-inositol mono phosphatase 2 (IMPA2)
Chromosome 19		
Chromosome 20	20p11.2-q11.2	2 adrenergic receptors, G protein subunit and phospholipase C gamma 1 enzyme (PLCG1) in the phosphatidyl inositol cycles inhibited by lithium
Chromosome 21	21p22.3	TRPC7 (transient receptor potential cation 7) gene
Chromosome 22	22q11 22q11	Catechol-o-methyltransferase (COMT) G-protein receptor kinase 3 (GRK3)
Chromosome X	Xq24 Xq28	Serotonin 2C receptor (5HT2C) GABA receptor α3

The Xq28 region also contains the SYBL1 gene. SYBL1 encodes a member of the synaptobrevin family of proteins involved in synaptic vesicle docking, exocytosis, and membrane transport. Muller et al. (2002) reported that a polymorphism of this gene had a statistical trend to be more frequent in males with BPD than in male controls. The Xq28 region also codes for the GABA receptor α-3 subunit. GABAergic dysfunction also is thought to play a role in the pathogenesis of BPD. Masat et al al. (2002) reported that GABA 3 polymorphism increased significantly in BP patients.

DISCUSSION

As described above, many chromosomal regions are implicated in BPD (Table); however, many of the findings are conflicting and most could not be replicated in subsequent studies. The reasons that these findings are conflicting and non-replicated are discussed below.

1. The Ambiguity of the Pathogenesis of Mental Disorders

The American Psychiatric Association (DSM IV) points out the problematic nature of the term mental disorders. This term implies a distinction between mental and physical disorders, but this archaic notion is wrong because mental illnesses are as much disorders of the brain as those referred to as neurological. There is also dysfunction in the development and complex functioning of the systems of the brain that underlie cognition, emotion, and behavioral control in mental disorders. In

this regard, the identification of genes involved in the development, maintenance, and plasticity of the brain will provide essential tools for the elucidation of both normal function and of what goes awry in mental disorders. Otherwise, considerable progress cannot be made in the genetic analysis of mental disorders. Fortunately, considerable progress is being made due to the application of the new methods and tools of molecular, cognitive, and computational neuroscience. In particular, the application of molecular genetic methods to the study of the nervous system has led to the elucidation of fundamental mechanisms involved in propagation of nerve impulses, synaptic neurotransmission, and early neurodevelopment. This application also identified the underlying genetic mutations responsible for a number of neurological disorders; however, similar progress has not been made towards the elucidation of the genes involved in mental illness. There are several reasons why progress in understanding neurological disorders occured so rapidly: 1) Neurological disorders follow classical Mendelian patterns of inheritance; 2) The disorders involve only a single gene; 3) In the case of channelopathies, the genomic sequences and physiological functions of many ion channels involved in nerve signaling were known, so only a small additional step was necessary to identify the mutations responsible for the disorder. Yet, the situation is more difficult in the case of major psychiatric disorders, because as none follow a single Mendelian pattern of inheritance, they are likely to be polygenic and multifactorial, involving both environmental and genetic factors.

2. Difficulties in Phenotypic Modeling

The identification of genes associated with psychiatric disorders is made more difficult by the variability of disease phenotypes. DSM-IV lists operationalized diagnostic criteria for a large number of mental disorders based on a core of symptoms and signs that define those disorders. DSM-IV criteria have successfully elevated psychiatric diagnosis above its status of only 3 decades ago, but despite DSM's great success in improving the reliability of diagnosis, there's still a lack of validating criteria and laboratory gold-standards. Moreover, repeatedly changing the diagnostic criteria over time makes true phenotypic description much more difficult. Additionally, DSM-IV-defined signs and symptoms may not be specific to a disorder and this can lead to a situation in which many patients qualify for multiple diagnoses, leading to high rates of diagnosed co-morbidity. In addition, the changing course of psychiatric disorders can cause variation in age of onset and in some cases the disorder might begin later in life or the patient could die due to old age, and this can lead to false negative or false positive results. Therefore, researchers have great difficulty in selecting phenotypes for genetic analysis and cannot correlate genotypes and phenotypes, which makes the identification of genes very difficult.

3. Difficulties on the Pathway From Genotype to Phenotype

In many disorders, the phenotype is not a perfect indicator of the genotype. There may be many confounding factors on the path from genotype to phenotype. Even in disorders due to a single gene, 1) the same gene can lead to different phenotypes (pleiotropy), 2) different genes can lead to the same clinical phenotype in different pedigrees or populations (genetic heterogeneity) (for BPD this number is around 15-20 genes), 3) some members of the same family may not express the phenotype even though they carry the susceptibility gene (incomplete penetrance), and 4) non-genetic factors can cause similar phenotypes (phenocopies). All these factors can cause discrepancies between genotypes and phenotypes and in the case of BPD, in which a multitude of genes and environmental factors play a role in the etiology, making this correlation between the genotype and the phenotype may become more difficult.

4. A New phenotypic Model of BPD

In classical models, phenotypes are treated as a dichotomous trai t—affected vs. non-affected— but recent research suggests a new phenotypic model of BPD known as the multi-threshold model. According to this model, the phenotype occurs as a sum of the interaction of many genes of modest effect. But, in epistasis, the net effect of the interaction of a number of genes is greater than that of each gene alone. In polygenic disorders, different phenotypes occur on the same spectrum when different critical thresholds are exceeded. According to this hypothesis, in the case of AD, when different critical thresholds are exceeded, different phenotypes, such as SZ, BP-I, BP-II, and UPD appear.

The gene-environment interaction also plays a very important role in phenotypic appearance, as well as gene-gene interactions. A major effect gene can cause quantitatively different phenotypes in response to different environmental conditions, whereas interactions between a multitude of genes and environmental factors can cause qualitatively different phenotypes. An environmental

factor can influence the effect of a genetic risk factor by controlling the degree of gene expression, or, conversely, a gene could influence the sensitivity to an environmental risk factor. The first study to report a gene-environment interaction was published by Caspi et al. (2003), who observed that individuals with the short allele of the 5HTT gene exhibited more depressive symptoms in response to stressful life events than individuals with the long allele; the authors concluded that a functional polymorphism of the 5HTT gene moderates the influence of stressful life events on depression. As a result, in disorders with polygenic and multifactorial origins, like BPD, it is very difficult to establish a direct relationship between the genotype and the phenotype, indicating a need to use different phenotypic models.

5. Determination of the Parameters

To define the parameters to be used in statistical analysis, probands and their relatives first need to be classified as affected or non-affected. Statistical analysis depends on the probability assumption, so every phenotypic character can be given a probability value in order to define the parameters. For example, the probability of carrying the susceptibility gene without expressing the disorder will not be the same for normal siblings with an affected parent as for a married-in normal spouse. Again, the probability of carrying the susceptibility gene will not be the same for the normal siblings of a young or old affected parent. If the disorder is sexually transmitted, the probability of carrying the susceptibility gene, again, will not be the same for men and women. With so much variance among normal individuals the definition of parameters in affected individuals will also vary according to phenotypic modeling. As a result, true phenotypic modeling forms the basis of a gene mapping study designed to obtain valid results.

6. A New Approach to Defining the Parameters: Endophenotypes

Despite the progress in molecular genetics, the genes responsible for the development of BPD have not yet been identified. This failure can be attributed to the use of the classical nosological system, with an ambiguous phenotypic description. The classical system uses an affected-non-affected dichotomy, leaving out individuals with no clear and overt clinical phenotype even though they carry the susceptibility gene. These individuals, on the other hand, may express some other disorders on the same liability spectrum or may display some clinically unrecognized intermediate phenotypes. Those normal-appearing individuals can be said to not have the necessary specific combination of genes to express the disorder even though they carry some susceptibility genes. There is now a growing consensus that an endophenotype approach may be utilized to overcome the difficulties regarding phenotypic descriptions and facilitate the identification of susceptibility or protective genes. Endophenotypes can be defined as subclinical vulnerability markers, which may assist in the identification of the genetic underpinnings of psychiatric disorders, regardless of disease status (Ozer et al. 2004). Endophenotypes can be considered as intermediate phenotypes along the way from genotype to phenotype. In BPD with an oligogenic inheritance, different genes can cause a change in the function of the specific protein they code for. If we use that specific change in the physiological function instead of the disease phenotype, identification of the genes underlying BPD would be much more easier with molecular genetic studies. As a result, this approach may provide well-defined phenotypes that have a stronger relationship with the pathophysiology and genetic etiology than with the diagnostic categories themselves.

For a biological character to be an endophenotype it must 1) be associated with illness, 2) have a strong biological relationship to the disease, 3) be heritable, 3) easy to measure, 4) segregate with the disorder in the family, 4) present in non-affected family members at a higher rate than in the general population, 5) present within the normal population to a lesser extent, 6) present in patients before the onset of the disorder, 7) present both in the acute and remission phases of the illness (state-independent), 8) not be affected by treatment, and 9) not require treatment. An endophenotype may be an inherited neurophysiological, neuropsychological, cognitive, neuroanatomical, biochemical, or endocrinological trait. In most cases they cannot be recognized from the outside, as they manifest no clinical sign; therefore specific methods may be needed in order to define them.

To date, the endophenotypes studied in BPD are biological rhythms, sleep deprivation, p300 latency, white matter intensity, such structural changes as an increase in ventricle volume and cerebellar atrophy, and changes in levels of serotonin in the brain (Ozer et al. 2004).

7. Statistical Errors in Molecular Analysis

Parametric and non-parametric methods used in gene mapping analysis have advantages and disadvantages, and unavoidable statistical errors can be made when using them. The problem with linkage analysis is that

old individuals may have died in late-onset disorders and young individuals may not yet have expressed the disorder. In such cases, the definition of affected and non-affected individuals will be difficult. Additionally, the difficulties in phenotypic modeling can also complicate the distinction between affected and non-affected, causing mistakes in linkage analysis. In the case of association studies, the difficulty is in selecting the control group. The most important difficulty concerns assuming that the polymorphic changes specific to the ethnic origin are specific to the disorder. This assumption can mislead the statistical analysis and decrease the reliability of association studies.

CONCLUSION

Despite great advances in the molecular genetic study of BPD, psychiatric genetics has yet to identify the specific genetic mutations in this oligogenic/multifactorial disorder. The most important cause of this failure is the difficulty defining the phenotype and the inheritance mechanism. Epidemiological findings suggest that it would be better if the liability of BPD was defined on a continuum, rather than on a categorical basis (yes/no), and if the phenotype was defined quantitatively, rather than qualitatively. Nonetheless, the phenotypic classification currently used does not depend on criteria that can measure the genetic or neurobiological basis of the disorder. In addition to clinical features, homogeneous biological measurements strongly related to the pathophysiology and genetic etiology of the disorder should be used to define affected vs. non-affected status. The endophenotypic approach can narrow the identified linkage regions in BPD and can help researchers delineate which gene is related with which aspect of the disorder; however, the neurobiology of the disorder need to be understood well in order to identify these endophenotypes. The pathogenesis of the disorder would be elucidated with greater clarity if the interaction between the heritable genetic and neurobiological components of the disorder could be understood better. In order to improve our understanding of these interactions, neuroscientific, genetic, and behavioral research should be integrated (Ozer et al. 2004). Based on the endophenotypic approach, BPD can be considered a multidimensional structure composed of interactions between various endophenotypes, with different genetic backgrounds. In that sense, linkage to different chromosomal regions reviewed in this article may take on new meaning.

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