

Genetics of bipolar disorder: a review

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Summary

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The present review provides a brief overview of both genetic epidemiological and molecular genetic studies of bipolar disorder. Twin studies have consistently shown an increased risk of bipolar disorder in monozygotic (identical) co-twins as compared to dizygotic (fraternal) co-twins of a proband with bipolar-I disorder, which indicates that a substantial proportion of the variance in the aetiology of bipolar disorder is likely to be attributable to genetic factors. The involvement of genetic factors in the development of bipolar disorder is also supported by the results of two adoption studies. According to family studies that included direct interviews of relatives as well as of a control group the risk ratio for bipolar disorder among relatives of bipolar patients has been estimated at around ten. However, family studies have revealed that the relatives of bipolar probands are not only at an increased risk for bipolar disorder, but also for unipolar depression. Regarding the morbidity risk for offspring of parents suffering from bipolar disorder, a meta-analysis revealed a 2.5-fold increased risk of developing any psychiatric disorder in children of bipolars as compared to those of non-psychiatric controls.

Given the well-established familial aggregation of bipolar-I disorder as well as evidence that a substantial proportion of the variance in the aetiology of bipolar disorder is likely to be attributable to genetic factors, a series of linkage and association studies have attempted to identify the genes involved in the susceptibility to bipolar disorder. The findings of linkage studies are not consistent

with the existence of a gene of major effect for the vulnerability for bipolar disorder, but several chromosomal regions have repeatedly been shown to be implicated. Two meta-analyses found evidence for susceptibility genes on chromosomes 8p22, 9p22–21, 10q21–22, 13q32–34, 14q24–32 and 22q11–22, as well as on regions on chromosome 18. Other regions of interest, identified by recent linkage studies are 6q16–22 and 12q23–24. Regarding candidate genes, for each of them there were usually some positive studies and generally an even greater number of negative replications. Meta-analyses of studies on these polymorphisms have provided some support for the implication of MAOA, COMT and 5HTT metabolism, all with modest effect sizes though. However, the strongest evidence currently supports the DAOA/G30 and the BDNF genes.

The conflicting results obtained in psychiatry genetic research in the last decades are likely to be at least in part attributable to the heterogeneity of bipolar disorder. Therefore, the need to look for specific clinical indicators of bipolar disorder that could be used to identify more homogeneous subtypes of the disorder has frequently been highlighted. Recent studies that focused on early onset bipolar disorder or stratified the sample according to the age of onset have provided some interesting results.

It is of interest that some of the regions identified in linkage studies of bipolar disorder overlap with regions implicated in schizophrenia and variations at the DAOA/G30 and the BDNF genes could predispose to both schizophrenia and bipolar disorder. The overlap in the biological basis between the two disorders could have implications for the classification of these major psychiatric disorders, which have been classified as distinct entities over the last 100 years.

Keywords: bipolar disorder; molecular genetics; linkage; association studies

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Rapid advances in molecular genetics during the last decades entailed the development of tools to identify genes involved in the susceptibility to complex genetic diseases such as psychiatric disorders. The present review will provide a brief overview of both genetic epidemiological and molecular genetic studies of bipolar disorder.

Genetic epidemiological studies

The three basic designs of genetic epidemiology are family, twin and adoption studies. These studies focus on the fundamental questions of psychiatric genetics: does a disorder run in families and how can we disentangle the effects of genes from those of the environment [1]? Indeed, the fact that a disorder runs in families does not necessarily imply the involvement of genes as other factors such as cultural transmission or shared environmental adversity can account for similarity between family members.

Regarding narrowly defined bipolar disorder (i.e. bipolar-I disorder), the most widely established risk factor is a positive family history of mood disorders with sixty to sixty-five per cent of bipolar patients reporting a positive family history of unipolar depression or bipolar disorder [2]. A recent survey of a population-based cohort of over 2 million individuals assessed from the Danish Civil Registry showed that subjects with a first-degree relative with bipolar disorder had a more than 13-fold increased risk of developing bipolar disorder [3].

Twin and adoption studies

In contrast to family-genetic studies, twin and adoption studies can separately assess the effects of genetic and environmental factors and therefore disentangle the effects of genes from those of the environment. These studies have consistently shown an increased risk of bipolar disorder in monozygotic (identical) co-twins as compared to dizygotic (fraternal) co-twins of a proband with bipolar-I disorder, which indicates that a substantial proportion of the variance in the aetiology of bipolar disorder is likely to be attributable to genetic factors [4, 5; reviews: 6, 7]. Two recent twin studies estimated the heritability of bipolar-I disorder as high as 59 [4] and 85% [5]. Heritability estimates for bipolar disorder derived from twin studies tended to be higher than those for unipolar depression, which ranged between 45 and 75% [6, 8]. The only twin study of childhood bipolar dis-

order published in the literature showed genetic contributions of 54–68%, common environmental contributions of 18–30% and unique environmental contributions of 14–17% [9]. The evidence of a shared environmental component in juvenile bipolar disorder, as documented in this study, suggests that moderating shared environmental factors are involved in the expression of this phenotype, which may be more evident in early onset as compared to late-onset cases.

The involvement of genetic factors in the development of bipolar disorder is also supported by the results of two adoption studies that documented a threefold increased risk of bipolar disorder among biological compared to adopted relatives of bipolar patients [10, 11]. Moreover, patterns of concordance within monozygotic twin pairs suggest that there is a strong degree of specificity in the genetic aggregation of the polarity of mood disorders [5, 12]. However, the fact that the concordance rate for genetically identical monozygotic twins is substantially less than 100% demonstrates the involvement of non-genetic risk factors in the aetiology of bipolar disorder.

Family-genetic studies

According to family studies that included direct interviews of relatives as well as of a control group, the lifetime risk for bipolar disorder in first-degree relatives of bipolar patients is in the range of 5 to 10% compared to 0.5 to 1.5% in an unrelated person [13, review: 14]. Accordingly, the risk ratio for bipolar disorder among relatives of bipolar patients has been estimated to be at around ten [15]. An earlier age of onset of bipolar disorder in probands has been reported to further increase the risk of bipolar disorders in relatives [reviews: 7, 16, 17]. Studies on juvenile-onset bipolar disorder found relatives of these probands to be more than twice as likely to suffer from bipolar disorder as relatives of late-onset patients [18–20]. However, family studies also revealed that the relatives of bipolar probands are not only at an increased risk for bipolar disorder, but also for unipolar depression as compared to the relatives of controls [21–24]. The absolute risk of unipolar depression is even higher than that of bipolar disorder. This increase of the risk of unipolar depression in relatives of bipolar probands suggests that the two types of mood disorders have some shared underlying aetiologic factors [25]. Conversely, the fact that family studies on major depression have revealed an increased risk of major depression, but not of bipolar disorder among relatives of depres-

sive patients [21–23], supports at least some specificity of the polarity of mood disorders.

Regarding the morbidity risk for offspring of parents suffering from bipolar disorder, most of the studies that compared offspring of bipolar parents to those of parents without a major psychiatric disorder were based on small samples with generally less than 50 children, which limits the ability to accurately assess the risk of offspring to develop psychiatric disorders [reviews: 26–28]. In order to circumvent the problem of insufficient sample size in each singular study, Lapalme et al. [26] performed a meta-analysis including 795 children (aged 5 to 25) of bipolar parents. This analysis revealed a 2.5-fold increased risk of developing any psychiatric disorder for children of bipolars as compared to children of non-psychiatric controls. Fifty-two per cent of the offspring of bipolars met criteria for some type of psychiatric disorder. Moreover, the relative risk of developing a mood disorder was four times higher in children of bipolars with more than a fourth of these children suffering from mood disorders. Bipolar disorder was diagnosed in 5.4% of those with a bipolar parent as compared with none of the children of controls. A more recent review of studies on child and adolescent offspring of bipolar parents has reported rates of mood disorders in the offspring ranging from 5 to 67% compared to rates of 0 to 38% in the offspring of healthy controls [27]. Additionally, compared to the children of healthy controls, those of bipolar parents did not only exhibit mood disorders more frequently but also other psychopathology, including substance use, conduct, oppositional defiant and anxiety disorders.

Taken together, the results of epidemiological genetic studies support the important role that genes play in the susceptibility to bipolar disorder. However, they also underscore that factors other than genetics must play a part. The findings of epidemiological genetic studies are compatible with a complex mode of inheritance of bipolar disorder, which does not follow Mendelian patterns [6]. Moreover, analyses using mathematical modelling suggest that each of the numerous susceptibility genes for bipolar disorder is likely to have a modest effect size, which makes identification of these genes difficult as studies based on very large samples are required.

Molecular genetic studies

Given the well-established familial aggregation of bipolar-I disorder as well as evidence that a substantial proportion of the variance in the aetiology

of bipolar disorder is likely to be attributable to genetic factors, a series of linkage and association studies have attempted to identify the genes involved in the susceptibility to bipolar disorder.

Linkage studies

Linkage studies seek to find chromosomal regions within families that tend to be shared among diseased relatives and unshared among healthy individuals [29]. This type of research generally uses hundreds of known DNA markers across the whole genome in order to study the transmission of the marker and the disease within families. One advantage of this method is that it does not require any knowledge of disease pathophysiology.

Although bipolar disorder has been studied less than schizophrenia, several systematic genome screens have been conducted on a variety of samples ranging from large densely affected pedigrees to large numbers of affected sib pairs. This research has been reviewed extensively [30–36]. Craddock et al. [34] reached the conclusion that the results of linkage studies in bipolar disorder do not support the existence of a gene of major effect to explain the majority of cases. However, a number of chromosomal regions have repeatedly been shown to be implicated. One meta-analysis that included seven published genome scans found strong evidence for susceptibility genes on chromosomes 8p22, 13q31 and 22q11–13, with the 13q-linkage showing the strongest evidence [37]. In contrast, a more extensive and detailed meta-analysis did not find genome-wide significant linkage [38]. Nevertheless this second meta-analysis provided a more modest level of support for regions on chromosomes 9p22.3–21.1, 10q11.21–22.1, 14q24.1–32.12 as well as regions on chromosome 18. In addition, two genome scans, not included in the meta-analysis of Segurado et al. [38] because of their modest sample size of less than 20 genotyped affected individuals, provided evidence of significant linkage on chromosomes 4p16 [39] and 12q24 [40]. Similarly, among the genome-wide scans published after the meta-analysis of Segurado et al. [38] one found significant linkage on chromosome 6q22 [41], a region also supported by three genome-wide suggestive signals [40, 42, 43].

As family studies documented familial aggregation of early onset bipolar disorder at levels that may exceed those of late-onset forms, others have suggested a greater genetic role and less genetic heterogeneity in early onset forms of this disorder [14, 44]. Therefore, early onset forms should produce stronger genetic ‘signals’ in molecular genetic

studies. Accordingly, several linkage studies have recently focused either on early onset bipolar disorder or genes influencing the age of onset. One of these genome-wide scans based on 874 individuals in 150 pedigrees in the United States identified two loci with increased linkage on chromosomes 21q22.13 and 18p11.2 among bipolar patients who had early onset (≤ 21 years) and later onset (> 21 years), respectively [45]. In a second study, using partially the same sample, ordered-subset linkage analysis revealed the largest increase in LOD score on chromosome 9q34 in the subset of 58 families that had mania onset before the age of 20 [46]. Moreover, a European study using non-parametric linkage analysis in 87 sib pairs ascertained through an early onset bipolar-I proband (age of onset < 21 years) showed the most significant linkage to be at the 3p14 region [47]. Interestingly, the study of Faraone et al. [48] suggests that regions on chromosomes 12p, 14q and 15q may contain genes influencing the age of onset of mania in bipolar disorder.

It is also of particular interest that some of the candidate regions implicated in bipolar disorder have been found to converge or overlap with regions identified in linkage studies of schizophrenia. These common linkage regions are localised on chromosomes 6q, 8p, 13q, 14q, 18p and 22q [35].

Association studies

The original association study approach (population-based association study) seeks to identify susceptibility genes («candidate genes») using patients and ethnically matched controls [49]. Given the risk of spurious findings due to ethnic differences between patient and control groups (population stratification), the family-based association approach that seeks to identify susceptibility genes using triads which include patients and their parents [49] has become increasingly popular over the last decade. The family-based approach tests for linkage disequilibrium in the transmission of genes from the two parents to an affected child (TDT test). This TDT test compares the alleles transmitted by parents to those that were not transmitted which serve as the control group for the transmitted alleles. In contrast to linkage studies, association studies testing candidate genes depend on the level of understanding of disease pathophysiology, which is the rational basis for the choice of the tested candidate gene [30]. Such studies focusing on bipolar disorder have extensively been reviewed by Craddock et al. [50], and more recently by Craddock et al. [34] and Maier et al. [35]. Given

the relatively poor understanding of the pathophysiology of bipolar disorder, the bulk of these studies have initially focused on genes involved in neurotransmitter systems that are influenced by drugs used for the treatment of these disorders.

Polymorphisms involved in dopamine, serotonin and noradrenalin transmitter systems

These traditional candidates include genes encoding receptors or proteins and enzymes involved in metabolism, re-uptake or action of dopamine, serotonin and noradrenalin.

Monoamine oxidase A (MAOA)

The MAOA catalyses the oxydative degradation of biogenic amines including the neurotransmitters norepinephrine, epinephrine, dopamine and serotonin. The gene encoding for this enzyme is localised on the short arm of the X chromosome (Xp11.12–Xp11.4) [51, 52]. Association studies have focused on four MAOA marker genes: (1) a dinucleotide repeat polymorphism referred to as MAOA-CA [53], (2) a dinucleotide repeat directly adjacent to the imperfectly duplicated 23-bp variable number tandem repeat (VNTR) polymorphism [54], (3) a restriction fragment length polymorphism (RFLP) [55] and (4) more recently the MAOA promoter VNTR (MAOA-LPR) [56, 57]. These studies were extensively reviewed by Preisig et al. [58]. At least four out of nine studies using the case-control approach in different Caucasian populations reported an association between bipolar disorder and the MAOA-CA [59–61] or MAOA-LPR in females [62]. However, two studies using the family-based approach could not replicate these findings [63, 64].

Associations between bipolar disorder and polymorphisms of MAOA marker genes have also been tested in Asian populations. Kawada and colleagues [65] reported a significant association between bipolar disorder and MAOA-CA in a Japanese sample. However, two other Japanese studies [66, 67] and one Chinese study [68] did not find distribution differences of MAOA alleles between bipolars and controls.

Two recent meta-analyses have provided additional support for the association between MAOA-CA polymorphisms and bipolar disorder. Furlong et al. [69] reported a pooled OR of 1.55 (95% CI 1.06–2.28) in five studies employing Caucasian probands and an OR of 2.65 (1.29–5.45) in two studies from Japan. Interestingly, the effect size was greater in female Caucasians (OR 2.13, 95% CI 1.31–3.48) and the female probands also provided support for the association between bipolar disorder and the MAOA-RFLP marker gene (OR

0.70, 95% CI 0.49–0.99). A second meta-analysis [61] involving overlap in probands from the previous meta-analysis found an association between bipolar disorder and both the MAOA-CA (in the overall sample and in females) – even when the conservative Bonferroni correction for multiple testing was applied. The a6 (overall sample OR = 1.49, 99.17% CI 1.12–1.98; female OR = 1.49, 99.17% CI 1.06–2.01) and a5 alleles (female OR = 1.68, 99.17% CI 1.03–2.73) were more frequent, whereas the a2 allele was less frequent (overall sample OR = 0.63, 99.17% CI 0.42–0.94; female OR = 0.61, 99.17% CI 0.38–0.97) in bipolars than in healthy subjects. This meta-analysis also revealed an association between the r1 allele of the MAOA-RFLP and bipolar disorder in the overall sample (OR = 1.45, 99.17% CI 1.01–2.08).

Catechol-O-methyl transferase (COMT)

Similarly to MAOA, COMT is an enzyme involved in the degradation of monoamines. The gene encoding for this enzyme [70] is located at the 22q11 region, which is a candidate region implicated in bipolar disorder, schizoaffective disorder and schizophrenia [36]. The COMT gene carries multiple polymorphisms. Most studies have focused on a valin to methionine change (Val158Met) at codon 158 of the brain-predominant membrane-bound form of COMT and codon 108 of the soluble form of COMT [36]. The valin allele has been found to be associated with reduced performance in tests of frontal lobe function [71, 72]. Originally, an association was observed between this allele and velo-cardiofacial syndrome (VCFS). Many of the individuals with VCFS also revealed features of rapid cycling mood disorder [70]. Subsequently, an association was also found in a larger sample of bipolar adults without VCFS [73]. Although this polymorphism has been studied more frequently regarding vulnerability to schizophrenia, several case-control studies have also been carried out for bipolar disorder. A meta-analysis of 13 case-control samples including 910 bipolars and 1069 controls provided evidence that the methionine (low activity) allele may increase susceptibility to the illness, although the estimated effect size was very modest, with a pooled estimate OR of 1.18 (CI 1.02–1.35) [50]. Some additional support for an association with bipolar disorder comes from an Irish family-based [74] and an Italian association study [75]. However, two family-based association studies of adult patients in Italy [76] and of prepubertal children and early adolescents in the United States [77] could not support the involvement of the COMT Val158Met polymorphism in bipolar disorder. In the last years, three poly-

morphisms other than the Val158Met have been investigated. These polymorphisms may be more strongly associated with schizophrenia than bipolar disorder [78] but one haplotype was also found to be associated with bipolar disorder [79].

Some studies also suggest that the low activity allele at this common polymorphism may be a course modifier associated with increased susceptibility to rapid cycling within bipolar patients [70, 73, 80]. The possibility that low COMT activity is associated with rapid cycling has biological consistency with the observed tendency for antidepressants to induce rapid cycling in that both increase the availability of catecholamines at neuronal synapses [50]. However, as to susceptibility, existing studies suggest that COMT only makes a modest contribution to rapid cycling observed in bipolar samples.

Tyrosine hydroxylase

Tyrosine hydroxylase (TH), the rate limiting the enzyme that catalyses the first step in the synthesis of catecholamines, is another plausible functional candidate that has been subjected to considerable scrutiny over the last decade. The TH gene maps to 11p15, in the region implicated by the original Old Order Amish positive linkage report [81].

Initially, Leboyer et al. [82] documented a significant association with alleles at two RFLPs at tyrosine hydroxylase in a small French case-control sample. The same group later reported evidence of an association of one genotype at a tetranucleotide repeat polymorphism of the gene [83]. Several groups have examined these polymorphisms at tyrosine hydroxylase. However, a meta-analysis including 547 patients and 522 comparison individuals in six Caucasian and two Japanese samples revealed no evidence that variation at this locus influences susceptibility to bipolar disorder [84]. Moreover, two more recent family-based association studies [76, 85] did not support the involvement of tyrosine hydroxylase in bipolar disorder.

Tryptophan hydroxylase

Tryptophan hydroxylase (TPH), which catalyses the oxygenation of tryptophan to 5-hydroxytryptophan, is the rate-limiting enzyme of the serotonin (5-hydroxytryptamine) synthesis. Two functional TPH isoforms have been described: the TPH1 isoform, which is mainly expressed in peripheral tissues but also in the pineal gland [86], and the TPH2 isoform, which is more highly expressed in the brain [87]. The gene for TPH1 has been mapped on the short arm of chromosome 11 (11p14–p15.3) [88] and several polymorphisms have been identified and their influence on the susceptibility to

bipolar disorder has been tested in several association studies [review: 58].

First evidence of an association between the TPH polymorphism and psychiatric symptoms came from Nielsen et al. [89, 90], who reported the TPH polymorphism to be associated with suicidal behaviour in violent alcoholic offenders. Surprisingly, the allelic distribution of non-suicidal offenders differed from those of controls, whereas offenders with suicidal behaviour and controls had comparable allele frequencies at the TPH locus. Using a French sample, Bellivier et al. [91] found an association between bipolar disorder and the TPH A allele. Two studies carried out in Italy revealed a similar trend [75, 92]. However, the majority of studies, including the three studies using family-based controls [64, 93, 94], found no evidence of allelic association at this polymorphism [95–101].

Serotonin transporter (5-HTT)

The 5-HTT is an excellent functional candidate because it is the site of action of the selective serotonin re-uptake inhibitors (SSRI). The gene is located at chromosome 17q11.1–12 [102, 103]. Association studies focused on two polymorphisms, a VNTR polymorphism in intron 2 (5-HTTVNTR) and a 44-bp insertion/deletion polymorphism located in the promoter region (5-HTTLPR). An initial report suggested that a rare 9 repeat allele at the 5-HTTVNTR polymorphism may predispose to major depressive rather than bipolar disorder [104]. However, several further studies using both case-control and family-based approaches have produced modest evidence implicating this gene in the susceptibility to bipolar disorder [50]. At least five meta-analyses of case-control studies focusing on the 5-HTTVNTR or 5-HTTLPR polymorphism have been performed with considerable overlap in probands across these analyses [50, 105–108]. Four of these meta-analyses [105–108] have provided support for the association between 5-HTT polymorphisms and bipolar disorder although the effect sizes were consistently modest ($OR < 1.3$). Anguelova et al. [106] and Cho et al. [108] documented significant associations for both the promoter and VNTR locus, Furlong et al. [109] and Lasky-Sue et al. [107] only for the promoter locus. Two studies examined associations between early onset bipolar disorder and the HTTLPR polymorphism. Geller and Cook [110], using a sample of prepubertal and early onset adolescent bipolar probands, for whom trio blood collection was complete, did not find preferential transmission of the postulated high risk (short) allele. Similarly, a population-based

association study completed in a human population isolate from Colombia did not find an association between early onset bipolar disorder and the HTTLPR locus [111], although there was a non-significant over-representation of the short allele in younger patients.

Serotonin and dopamine receptors

Serotonin (5-HT) and dopamine receptors have been studied intensively in schizophrenia. Genes encoding for at least forty different serotonin receptor variants have also been studied regarding their implication in mood disorders [106]. Most of the studies focused on the T102C polymorphism of the 5-HT_{2A} receptor, which is located on chromosome 13q14–21 [112]. However, two meta-analyses, one of 8 (941 bipolars and 1306 controls), the other of 10 case-control studies (1095 bipolars and 1468 controls), did not provide evidence that variation at this polymorphism influences susceptibility to bipolar disorder [50, 106]. Similarly, the results of a collaborative study conducted in France and Switzerland did not support an association between two other polymorphisms (1438G/A, His452Tyr) of the 5-HT_{2A} and bipolar disorder [113].

Regarding dopamine receptors, associations between polymorphisms of all five receptors and susceptibility to bipolar disorder have been tested. However, the bulk of studies did not support such associations [114]. The D₃ receptor (DRD₃) is of particular interest because it is almost exclusively expressed in limbic regions of the brain – those areas thought to be most closely involved in the control of emotion [115]. The gene is located on chromosome 3q13.3. However, a meta-analysis of 11 case-control studies focusing on the Ball polymorphism of this receptor (nine of European Caucasian origin and two of oriental origin) found no evidence of allelic association or increased homozygosity at this polymorphism in bipolar disorder [116].

Other polymorphisms

In the last years association studies have increasingly focused on functional candidates other than those involved in the three main neurotransmitter systems. Among these new candidates the D-amino-acid oxidase activator (DAOA)/G30 locus and the brain-derived neurotrophic factor (BDNF) gene have attracted particular attention. Other new candidates included the Wolfram syndrome 1 polymorphism [85], the PIPK2A gene [35] as well as genes coding for proinflammatory factors, such as the interleukin-1 β or the tumour necrosis factor alpha gene [35].

DAOA/G30 locus

This locus, which was first implicated in studies of schizophrenia [117], is currently the best supported locus for bipolar disorder [36]. The D-amino-acid oxidase activator (initially referred to as G72 gene) and G30 genes are overlapping in the linkage region on chromosome 13q22–34, but transcribed in opposite directions. The DAOA gene is primate specific and expressed in the caudate and amygdala. DAOA enhances the activity of the D-amino-acid oxidase (DAO) in the human brain. This enzyme oxidises D-serine, a potent activator of the NMDA glutamate receptor.

At least six independent datasets support the influence of variations at the DAOA/G30 locus, including three US family samples [118, 119], a German [120], a Polish [121] and a large UK case-control sample [122]. The UK study that included 704 schizophrenic and 706 bipolar-I patients as well as 1416 ethnically-matched controls revealed a significant association of the DAOA/G30 locus with bipolar disorder, but no association in the schizophrenia sample. When the latter sample was dichotomised according to the occurrence of major mood episodes, an association was also found in the subsample of schizophrenia patients who reported depressive or manic mood episodes, but not in the other subsample. In contrast to these findings, the authors of the German study reported an association of the DAOA/G30 locus not only with bipolar-I disorder but also with schizophrenia. Moreover, additional analyses in the German and Polish samples also revealed that the association between the DAOA/G30 locus and bipolar-I disorder was restricted to patients with persecutory delusions [121].

BDNF gene

The gene of the BDNF, which lies on chromosome 11p13, has attracted growing interest in mood disorders. As a member of the neurotrophin superfamily, BDNF plays an important role in promoting and modifying growth, development and survival of neuronal populations [123]. In the mature nervous system BDNF is involved in activity-dependent neuronal plasticity. Such processes are prominent in the synaptic plasticity hypothesis of mood disorders, which focus on the functional and structural changes induced by stress and antidepressants at the synaptic level [36].

Only one frequent polymorphism has been identified in the human BDNF gene (a single nucleotide polymorphism), which causes an amino acid substitution of valine to methionine and may have a relevant effect on the functioning of BDNF [124]. This polymorphism has been found to be associated with bipolar disorder in three family-

based studies conducted in the United States using samples of Caucasians. Two association studies were based on adult samples [125, 126] and one on a child sample with a mean age of 10.7 years [127]. These studies have consistently shown over-transmission of the common Val allele. However, these findings could not be replicated in four case-control association studies conducted in Europe [128, 129], China [130] and Japan [131]. Similarly, in a recent case-control study conducted in the United Kingdom including more than 1000 bipolar cases no significant association between the Val allele and bipolar disorder has been found, but there was some evidence for association within the subset of cases in which rapid cycling had occurred at some time during the illness [132].

Conclusions

Although genetic epidemiological studies strongly support the implication of genetic factors in the vulnerability to bipolar disorder, the findings of linkage studies are not consistent with the existence of a gene of major effect, however, several chromosomal regions have repeatedly been shown to be implicated. Regarding candidate genes, for each of them there were usually some positive studies and generally an even greater number of negative replications. Meta-analyses of studies on these polymorphisms have provided some support for the implication of MAOA, COMT and 5-HTT metabolism, all with modest effect sizes though. However, these meta-analyses also had several limitations [58]. One limitation is the fact that the analyses only included studies with a case-comparison design that did not use family-based controls which increases the risk of spurious associations caused by unsuspected population stratification. A second problem is the appropriate adjustment of the significance level when several polymorphisms with multiple alleles are tested. Such an adjustment has rarely been done in these analyses. A third problem of meta-analysis is the risk of publication bias inducing an overly optimistic impression regarding positive findings since studies with negative data are more likely to remain unpublished.

The conflicting results obtained in psychiatry genetic research in the last decades are likely to be at least in part attributable to the heterogeneity of bipolar disorder. Therefore, the need to look for specific clinical indicators of bipolar disorder that could be used to identify more homogeneous subtypes of the disorder has frequently been highlighted. Efforts have been made to subtype

bipolar disorders according to course features (age of onset, bipolar-I versus bipolar-II type, rapid cycling), comorbidity patterns (anxiety disorders, suicidal behaviour, addiction or hyperactivity), temperamental features (presence of cyclothymic temperament), neurocognitive function or response to mood stabilisers. Recent studies that focused on early onset bipolar disorder or stratified the sample according to the age of onset have provided some interesting results.

It is also of interest that some of the regions identified in linkage studies of bipolar disorder overlap with regions implicated in schizophrenia and variations at several candidate loci, such as COMT, DAOA/G30 and BDNF, could predispose to both schizophrenia and bipolar disorder. Although genetic findings may be of limited value for the validation of psychiatric nosology as has recently been stressed by Kendler [133], the overlap in the biological basis between bipolar disorder and schizophrenia could have implications for the classification of these major psychiatric disorders, which have been classified as distinct entities over the last 100 years [30].

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Weiterbildung in Psychotherapie

zum Facharztstitel „FMH Psychiatrie und Psychotherapie“

Das C.G. Jung-Institut Zürich, Küsnacht, bietet den nächsten dreijährigen Weiterbildungskurs in Analytischer Psychotherapie nach C.G. Jung an.

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