Chapter 4

Comorbid Mental Disorders in Anxiety Disorders: Genetic Aspects of Bipolar Disorders and of Ethnicity

Yun-Hsuan Chang, Sheng-Yu Lee and Ru-Band Lu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66117

Abstract

Anxiety disorder (AD) is commonly comorbid with other mental illness. It could be a state or trait, controversially. Evidence for an association between alcoholism and anxiety has emerged from clinical studies of patients with alcoholism, and those of patients with anxiety disorders. Alcohol dependence (or abuse) as well as bipolar disorder (BP) is usually comorbid with anxiety disorder and/or depressive disorder, which often coexist and are difficult to distinguish from one another. However, in Han Chinese population, the comorbidity rate either with alcoholism or bipolar disorder was not reported as much high as reported in Caucasians, this finding of comorbidity between anxiety/depressive disorders and alcohol dependence (or abuse) or/and bipolar disorders, possibly at the genetic level, makes the differentiation of their categorical diagnoses in the association study vitally important.

Keywords: comorbidity, ethnics, genetics, mental illness

1. Introduction

Feinstein [1] started to draw attention on patients with one or more than one diagnosable disease and defined "Comorbidity" as "*any distinct additional clinical entity that has coexisted or that may occur during the clinical course of a patient who has the index disease under study*." In the majority of studies, comorbidity refers to the co-occurrence of at least two different disorders in the same individual. Although the majority of comorbidity research has been at the diagnostic (or syndrome) level (i.e., the presence of co-occurring DSM-IV disorders); another approach is to study the extent to which certain symptoms or symptom patterns tend to co-occur [2–5].

Regardless of types of anxiety disorder (AD), anxiety is one of the most prevalent of all psychiatric disorders in other mental illnesses, such as mood disorders and alcoholism. Different types of mental illnesses commonly comorbid with AD as well as the ethnic role will be reviewed. The comorbidity has gained increasing prominence in psychiatry and psychology in the past few decades [6]. A distinction between two types of comorbidity has been drawn a decade ago by Angold et al. [7].

Reiger et al. [8] reported that approximately 15% of people suffered from AD, according to Diagnostic and Statistical Manual-3rd edition (DSM-III) during their lifetime. Keith et al. (1991) compared the prevalence of AD, including subtypes between community and the institute prevalence rates, and found the lifetime rate of AD was 15% overall, 16% in nursing home residents, 28% in prisoners, and 51% in patients in mental hospitals. Further, Robins et al. [9] studied the prevalence of AD and found that phobia is the most common AD (**Figure 1**).

As the more specific and classified the AD was studied, simple phobia was reported as the most common comorbidity, up to nearly 50%. Approximately 13% of people reported symptoms matching the DSM criteria, and social anxiety disorder was in the second place of highest reported disorder of anxiety. Post-traumatic stress disorder (PTSD), often goes unrecognized, but its prevalence reached 20% in victims of war trauma.

However, the more commonly recognized disorders, such as generalized anxiety disorder (GAD) and panic disorder (PD), have the lower lifetime prevalence rates of approximately 5 and 3.5%, respectively. Another often underdiagnosed disorder, obsession-compulsive disorder (OCD), is found in 2.5% of the population. Interestingly, a recent study found very little change in the prevalence of mental disorders, including specific anxiety disorders, since 1990 [10].

Because of high recognition and high prevalence rate, researchers started to explore whether AD is a genetic-related psychiatric disorder. Therefore, genetic risk factors are being studied; researchers have found genetic predisposition for two broad groups of anxiety disorders: a panic-generalized anxiety-agoraphobia group and a specific phobia group [11]. More clinically important risk factors include comorbid substance abuse and family history. Weissman et al. [12] conducted a 20-year study in the offspring of depressed parents and found a threefold increase in ADs, including greater substance abuse, younger onset, and more significant physical health concerns.

Although a genetic predisposition for developing an AD is likely [11], environmental stressors clearly play a role in varying degrees. All of the disorders are affected in some way by

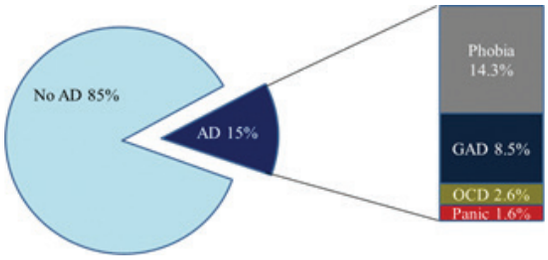

Figure 1. Robins et al. [9] studied in the prevalence of subtypes of AD.

http://dx.doi.org/10.5772/66117

external cues and how they are proceeded and reacted to. Research has also shown that patients suffering from anxiety are generally more sensitive to physiologic changes than nonanxious patients, and panic disorder sufferers are even more sensitive to these than the GAD patients. Objective testing, however, reveals that physiologic changes between anxious and nonanxious patients are comparable. This heightened sensitivity leads to diminished autonomic flexibility, which may be the result of faulty central information processing in anxiety-prone persons [13].

The neuroanatomical foundation of anxiety may be related to the influence of the septohippocampal system in the brain on learning and memory [14]. Patients with AD manifest impaired divided attention [15], verbal learning, verbal recall [16], visual learning and memory [17], episodic memory and executive function [18], and cognitive information processing [19].

2. Anxiety disorder as comorbidity

2.1. Anxiety disorder as comorbidity in bipolar disorders

Prior to year 2000, there were few studies on bipolar disorder II (BPII) and little research into the differences between BPI and BPII patients. More and more studies have been conducted to distinguish between the subdivisions of bipolar disorders (BPI and BPII). Genetically, there was an association with the interaction between *COMT* and *DRD3* gene in BPI [20] as well as the interaction between *DRD2*/*ANKK1* and the *ALDH2* gene in BPII patients [21]. A statistically significant, main effect for the Met/Met genotype of the *COMT* Val158Met polymorphism and a significant interaction effect for the Met/Met genotype of the *COMT* Val158Met and Ser/Ser genotypes of the *DRD3* Ser9Gly polymorphism could predict BPI, but not BPII compared to normal subjects [20]. Moreover, Lee et al. [22] provided evidence that the *ALDH2* and *5-HT2A* genes interact in BPI but not in BPII. A series of studies have been conducted to prove that BPI and BPII are different from genetic aspect.

Anxiety disorders have been reported as a common comorbidity in BP [23–28], the life time prevalence was reported by National Institute of Mental Health (NIMH) as 51.2% [29, 30], and current anxiety disorders in 31% of the first 500 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) [30]. The National Comorbidity Survey reports that approximately 90% (BPI: 86–92%; BPII: 89%) of bipolar patients comorbid with AD [31–33]. More often, comorbid with panic disorder (PD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) either in the community or in primary care and psychiatric settings has been reported [30, 32, 34, 35]. There is a growing body of research evidence that bipolar depressives have comparable if not higher rates of comorbid anxiety disorders than unipolar depressives [23, 24, 26–28, 36]. Accordingly, anxiety comorbidity could be a fundamental feature of bipolar disorder [37]. Recent studies reported that among all bipolar disorders, BPII has higher comorbidity with AD than does BPI [23, 25, 26, 28, 38].

Other important aspects to be borne in mind are recognition and prognosis. Compared to noncomorbid BP, BP patients with AD are susceptible to a higher risk of suicidal behavior [39], substance abuse [30, 40, 41], lower psychosocial performance [29] and has a more

frequent family history of mental illness [42]. Moreover, the AD comorbidity can complicate the course of illness and pharmacological treatment strategies [43]. Not only the high comorbidity between BP and AD has been noticed, but the types of AD comorbidity in BP could also complicate the recognition of BPI and BPII and predict the prognosis. Patients with BP and AD are susceptible to higher risk of suicidal behaviour [39], substance abuse [30, 40, 41], lower psychosocial performance [29], and a more frequent family history of mental illness than BP patients without AD [42]. Moreover, the AD comorbidity would complicate the course of illness and pharmacological treatment strategies [43].

A number of studies [23–26, 44] have shown bipolar disorder to be highly comorbid with anxiety disorder; a prevalent rate of 51.2% was reported by the National Institute of Mental Health (NIMH) [30, 45]. BP is most frequently associated with panic disorder (PD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD), whether in the community, in primary care, or in psychiatric settings [30, 32, 34, 35]. The National Comorbidity Survey reports that approximately 90% of BP patients (BP-I: 86–92%; BP-II: 89%) have at least one comorbid AD [31–33].

There is a growing body of research evidence that individuals with bipolar depression have comparable if not higher rates of comorbid ADs than do individuals with unipolar depression [23, 24, 26, 27, 36, 44]. Anxiety comorbidity is, then, a fundamental feature of BP [37]. Moreover, established studies [23, 25, 26, 38, 44] show that BP-II is more often comorbid with AD than is BPI. The BP patients with AD comorbidity have been pointed out to have worse prognosis, such as shortened euthymia, delayed remission, and rapid cycling. The AD comorbidity worsens BP patients' episode and their response to treatment, and increases their suicidal behavior. Previous researchers have also pointed out a higher possibility of comorbidity with substance use disorder in BP patient comorbid with AD (BP+*AD*) than in BP without AD (BP^{-AD}) [30, 34, 46–54]. Consequently, the comorbidity with AD receives more attention clinically [55, 56].

2.2. Anxiety disorder as comorbidity in bipolar disorders of ethnics

Chang et al. [57] found that the anxiety disorder comorbidity rate in both BPI (26.7%) and BPII (39.0%) were lower in Han Chinese in Taiwan than in Western populations (more than 50% in BPI and BPII) [26, 30]. There was no significant difference in the gender-based distribution of anxiety disorder in our patients, which agrees with one study [58] but disagrees with others [34, 59, 60] that report a higher prevalence in women than in men. One reason may be that lower prevalence of a disease shows a greater statistical meaning for fixed heritability and a fixed number of trait loci [61]. Therefore, the lower anxiety disorder comorbidity rate not only is more easy for researchers to look at the genetic factor of AD high comorbid with BP but also may decrease psychosocial, cultural, and other confounding factors. Those factors and their interaction might increase the prevalence rate of mental illness, especially anxiety disorder. In addition, a higher comorbidity rate with BPII than with BPI was found which agreed with most of large-sample epidemiological studies [23, 25, 26, 28, 38]. Patients with BP and co-occurring anxiety symptoms or anxiety disorders are susceptible to higher rates of depressive episodes [29], which may explain the higher comorbidity rate in patients with BPII than with BPI.

http://dx.doi.org/10.5772/66117

For further investigation of the AD subtypes with BP, Chang et al. [57] found that the highest AD comorbidity in both subtypes of BP patients was GAD instead of PD or OCD, the major AD comorbidities in the western BP populations. Wittchen et al. [62] reported that the highest rate of comorbidity of GAD was associated with major depressive disorder (62.4%) and the lowest with BP (10.5%). One of the possible reasons may be due to ethnic differences or the genetic heterogeneity of anxiety disorder and depressive disorder like BPII. A higher occurrence of GAD with BPII was found in Chang et al. (2012)'s study, which is similar to previous studies showing higher occurrence of GAD with MDD [63, 64]. This gender difference in BPII could be derived from the high GAD-associated depression. However, the causal relationship should be further investigated. The other reason could be that the same diagnostic criteria of BPI and BPII except the duration might not be appropriate, the redefinition of the diagnostic criteria after more different ethnic BP subtype studies are suggested.

Chang et al. [57] have reported a relatively low rate of anxiety-disorder comorbidity in both BP subtypes in Han Chinese population in Taiwan, implying an ethnic possibility. Because of this low anxiety-disorder comorbidity in BP population in Taiwan, it was easier to identify BP patients with/without comorbidities to study the influence of anxiety-disorder comorbidity on neuropsychiatric performance. Although causal relationship between the comorbid anxiety disorders in BPI and BPII is not yet clear, additional studies are required, and the ethnic differences are suggested to be taken into account.

BPII patients with anxiety-disorder comorbidity also showed more substance abuse and dependence, suicide attempts, and personality disorders than did BPI patients [23, 25, 26, 28, 30, 57, 65]. After excluding the comorbidity of anxiety disorder, BPI and BPII patients have similar suicide rates, suggesting that AD comorbidity increases the risk of suicide in BPII [66]. The risk of suicide in Han Chinese BP patients in Taiwan may be lower than western BP populations, but it needs further study to confirm.

Anxiety disorders occur most frequently during depressive episodes in patients with BP [67], except for those in the depressive state, anxiety disorder would often present during subsyndromal states [68]. Boylan et al. [49] reported that about 32% of their BP patients had more than two comorbid anxiety disorders. The lower incidence in BPI patients (21.9%) and a similar incidence in BPII patients (33.8%) were found. This finding implies that BP patients with multiple anxiety-disorder comorbidities may have a more severe psychopathology and a worse prognosis, even with what is currently considered as appropriate treatment [69]. In addition, anxiety disorder may be a predisposing factor for BP. Long-term follow-up studies are needed to confirm whether some anxiety-disorder comorbidities are in remission during the inter-episode stage or increase in intensity as symptoms of depression worsen.

2.3 Genetic aspect in comorbidity with anxiety disorder in bipolar disorders

Relative genetic factor between BP and AD was proposed [70], but no definite susceptibility gene for BP has been identified. One possible explanation could be neither subtypes of BP nor comorbidities were differentiated in most studies [71–73]. The contribution of genetic factors to the etiology of BP has also been reported from studies on family, twin, and adoption [72, 74]. From the twin studies, the inheritance for bipolar disorder overall is around 85% [75, 76].

The distinction between BPI and BPII may be associated with different genetic categories [21, 77–79]. Knowing the association between AD comorbidity and BP at the genetic level may improve our understanding more in this mental illness.

Dopaminergic dysfunction has been implicated in the pathogenesis of bipolar disorder, especially the dopamine D2 receptor gene (*DRD2*) on chromosome 11q22.3, and dopamine D3 receptor gene (*DRD3*) on chromosome 3q13.3, expressed exclusively in the limbic regions of the brain responsible for controlling emotions and behavior as well as cognition [80, 81]. The DRD2 Taq-IA (rs1800497) restriction in fragment length of polymorphism is linked to the density of dopamine D2 receptors [82]. A variety of studies have analyzed dopamine receptor genes for their associations with BP or AD, including polymorphisms in DRD2 [83, 84]. The *DRD3* gene is encoded as a target site for antipsychotic agents, which are efficient in the treatment of this disorder. The most frequently studied allele variation of the *DRD3* gene is the *DRD3* Ser9Gly polymorphism (rs6280) [85], causing a serine- (Ser) to-glycine (Gly) substitution and a significantly increased dopamine binding affinity [86]. The Gly9 allele is associated with significantly greater odds for treatment response to antipsychotics [87, 88]. Possible association between the *DRD2* gene, *DRD3* gene, and bipolar disorder has been reported in a family-based study [89] but not in others [83, 84, 90, 91]. Therefore, the *DRD2 and DRD3* genes are of particular interest in the study of susceptibility to bipolar disorder because both effective episodes and neurocognitive impairments are important aspects of BP [92] and AD.

In the midbrain-hindbrain regions, another important role in the development of dopaminergic neuron, brain-derived neurotrophic factor (BDNF), in which the *BDNF* gene was selectively deleted, the number of tyrosine hydroxylase-expressing dopaminergic neurons was found reduced [93]. During the developing years and in adulthood, *BDNF* gene encoded on human chromosome 11p13 was shown to regulate the expression of DRD3 in the nucleus accumbens [94]. The involvement of BDNF in the pathogenesis of mood disorders and the mechanism of mood stabilizing medication has been suggested [95]. Genetic studies explored the potential association between *BDNF* gene variants and bipolar disorders yet yield conflicting results. The most investigated *BDNF* gene is Val66Met (rs6265) with functional consequences from valine (Val) to methionine (Met) at codon 66 [95–98]. The Met allele has been pointed out to have association with impairments in intracellular trafficking and activity-dependent secretion of BDNF in neurons [95–98]. A significant association between Val66Met and bipolar disorder has also been reported in several studies conducted in North American and European populations [100–103] with overtransmission of the Val allele while other studies in the Asian populations were not [99–101]. About 80% with Val allele was reported in the European population while only 50% was reported in Asian [102], the ethnic difference could be the possibility.

2.4. The DRD2 gene associated with ALDH2 in bipolar II disorder with anxiety disorder

There is an increased risk of mental disorder among relatives of anxiety neurotics from family studies [103]. Therefore, if the *DRD2* locus is linked to a predisposition to conduct AD and BP, its relation with anxiety disorder and BP is worth further examination. Knutson et al. [104] proposed molecular explanation that a low serotonin turnover rate and aggressive behavior

http://dx.doi.org/10.5772/66117

are mediated by negative emotions such as insecurity and anxiety. Some studies also suggest that conduct disorder might lead to alcoholism because of the tendency for a person to be impulsive [105] and to exhibit behavior disinhibition [106]. Besides the association of *DRD2* gene with anxiety and mood regulation, we also set forth to determine the possible relationship with *DRD2* in AD and BP to examine any association between *DRD2* and other possible genetics.

Brain-imaging study [82] shows that healthy controls with an *A1* allele of the *DRD2 TaqIA* gene have fewer *DRD2* receptors than those without the *A1* allele. Individuals with at least one *A1* allele appear to have up to 40% fewer striatal DRD2 receptors than those carrying the A2/A2 allele [107]. The *DRD2 TaqIA A1* allele was associated with fewer DRD2s in the striatum and hence, a lower dopaminergic function.

Enzymes that function in the metabolic breakdown of acetaldehyde are considered as the *ALDH2* gene; the enzyme functioning in the metabolic process of acetaldehyde is majorly influencing drinking behavior and the development of alcoholism. The ALDH2 shows two variant alleles: *ALDH2*1* and *ALDH2*2*. The *ALDH2*1/*1*-encoded enzyme is active in the metabolism of acetaldehyde, whereas the enzymes encoded by the *ALDH2*1/*2* and *ALDH2*2/*2* are partially and totally inactive, respectively. It is believed that the *ALDH2*2* allele, with reduced enzyme activity, provides protection against the risk of developing alcoholism [108]. In previous reports, nearly half of the East Asian population has the *ALDH2*2* allele variant [109], including Han Chinese in Taiwan [108, 110], but this allele is rarely found in other ethnic populations.

Wang et al. [111] revealed the relationship among *DRD2* gene and *ALDH2* gene between BP with and without AD and found, we examined whether the DRD2 and ALDH2 genes were associated with comorbid BP-II and AD. The study results revealed the significant association of DRD2 Taq-IA A1/A2 in the BP-II with AD and the significant interaction between the ALDH2 and DRD2 genes in BP-II without AD, respectively. Our findings provide genetic evidence to support the hypothesis that BPII with or without AD might be two distinct mental illnesses [112, 113]. Such interaction also implies the complex role of dopamine system in the pathogenesis of BPII.

2.5. The DRD3 gene and BDNF gene associated with bipolar subtypes with/out anxiety disorder

Chang et al. [114] investigated the association between *DRD3* gene and *BDNF* gene in bipolar subtypes comorbid with/without AD. They found a significant main effect of the Ser/Gly of the *DRD3* Ser9Gly polymorphism in $BPII^{+AD}$, and interaction with the *BDNF* Val66Met Met/Val genotype and indicated a possible mediator by the *BDNF* Val66Met Val/Val genotype in the development to the AD comorbidity in the BPII. The involvement of the *DRD3* Ser9Gly Ser/Gly genotype disagrees with the previous studies of the risk to develop anxiety disorders, such as obsessive compulsive personality (OCD) [115, 116]. This difference may reflect the report that in Han Chinese, the most AD subtype comorbidity in BP subtypes is generalized anxiety disorder [57] instead of OCD or panic disorder mostly reported in the western population [6]. Further investigation between ethnics should be considered.

Takahashi et al. [117] has reported the effect of the *DRD3* and *BDNF* variation on brain morphology in midline and medial temporal lobe structures in healthy controls. Gourion et al. [118] earlier has reported that this interaction was associated with earlier emergence of psychosis in schizophrenia patients. The involvement of abnormal dopamine regulation in bipolar disorders have been reported in gene-gene interaction study; however, this interaction is associated with treatment response of dopamine receptor antagonists for bipolar disorders or previous psychotic symptoms may require further studies with additional characterization and phenotyping.

There have been some reports about that the Met heterozygotes compared to the Val homozygotes of the *BDNF* Val66Met polymorphism have impairment in intracellular trafficking and activity-dependent secretion of BDNF in neurons [95–98]. In addition, the Ser heterozygotes compared to the Gly homozygotes of the *DRD3* Sere9Gly polymorphism were reported to decrease the dopamine binding affinity [86]. Odds for $BPII^{+AD}$ were higher for those BDNF Met66Val Met/Met and Met/Val with the interaction of the *DRD3* Ser9Gly Ser/Gly genotype compared to those with Gly/Gly genotypes.

For the results in the BPI, a main effect of *BDNF* Met/Val genotype was found to be associated with BPI^{-AD}, and an interaction was found between *BDNF* Met/Val with *DRD3* Ser9Gly Ser/Ser genotype in BPI^{-AD}. From the results in both subtypes, it implies the different involvement of *DRD3* and *BDNF* genetic variants between two subtypes of the BP, and the variation of neuropsychological performance [119]. No case with the *DRD3* Ser9Gly Gly/Gly genotype was reported in the BPI^{-AD}, and impact of the AD comorbidity on the BPI impaired their executive function and attention, while psychomotor speed, working memory, and visual immediate memory was impaired in the BPII [119], implying the different roles of the *DRD3* Ser9Gly polymorphisms.

Chang et al. [114] have provided initial evidence of the involvement of dopaminergic pathway with *DRD3 Ser9Gly* gene in the pathogenesis of bipolar disorder. For the results in the BPI, a main effect of *BDNF* Met/Val genotype was found to be associated with BPI^{-AD}, and an interaction was found between *BDNF* Met/Val with *DRD3* Ser9Gly Ser/Ser genotype in BPI^{-AD}. From the results in both subtypes, it implies the different involvement of *DRD3* and *BDNF* genetic variants between two subtypes of the BP, and the variation of neuropsychological performance [119]. No case with the *DRD3* Ser9Gly Gly/Gly genotype was reported in the BPI^{-AD}, and impact of the AD comorbidity on the BPI impaired their executive function and attention, while psychomotor speed, working memory, and visual immediate memory was impaired in BPII [119], implying the different roles of the *DRD3* Ser9Gly polymorphisms.

The results in Chang et al.'s study [114] not only replicated Lohoff et al. [120] finding that the positive association was between the Val allele and the BPI patients, but also related to the AD comorbidity. However, a disagreement was noticed between this study and previous findings of association between the Met allele with anxiety disorders [121, 122], indicating the possible ethnic variation. Moreover, the major subtype of AD comorbidity in the Han Chinese BPI and BPII was general anxiety disorder [57] while PD or OCD was the higher comorbidity with the BP in the western population [30, 32, 34, 35]. The genotype distribution of the *BDNF* Val66Met polymorphism in current study is consistent with other Asian populations, but different from European populations [102].

http://dx.doi.org/10.5772/66117

3. Anxiety disorder as comorbidity in alcoholism of ethnics

3.1. The relationship between DRD2 gene and ALDH2 gene in anxiety-depression alcoholism

Several studies in alcohol detoxification have been reported that the *DRD2* gene may be associated with high scores of anxiety and depression in alcohol dependence. Patients with alcohol dependence comorbid with anxiety and/or depressive disorders represented the greatest risk of relapse [123–125]. In a double-blind treatment study using bromocriptine, ALC individuals with *DRD2 A1* allele showed the greatest improvement in craving and anxiety [126]. These observations are in agreement of an association between *DRD2* gene and anxiety-depressive alcohol dependence (or abuse). To elucidate the association between the *DRD2* gene and alcohol dependence in Han Chinese population with attempts to overcome the possible confounding effects and to reduce false-positive or -negative results, Huang et al. [127] compared individuals with solely anxiety-depression (ANX/DEP), individuals with both alcohol dependence and anxiety-depression (ANX/DEP ALC), and individuals with pure alcohol dependence and normal controls. Strong linkage disequilibrium between the *Taq*I A and B polymorphisms of the *DRD2* gene was reported. Huang et al. [127] found that the frequency of the *A1*/*B1* haplotype was significantly higher in the ANX/DEP ALC group than that of controls. There was no association between the *DRD2* haplotype and pure alcohol dependence or ANX/DEP when compared to controls.

Since ALDH2 is a crucial enzyme for ethanol catabolism which might also play an important role in dopamine catabolism and risk for alcoholism, the involvement of the *ALDH2* gene with the association of the *DRD2* gene and ANX/DEP ALC was further investigated. It was shown that the *DRD2* gene is associated with ANX/DEP ALC only after controlling for the *ALDH2*1/*1* genotype, supporting the contention that the *DRD2* gene may interact with the *ALDH2* genes in ANX/DEP ALC.

3.2. Interaction between personality traits and genes in anxiety-depressive alcoholism

Cloninger has hypothesized of lower novelty seeking and higher harm avoidance in type I alcoholism compared with healthy volunteers. Later, Huang et al. [127] and Huang et al. [128] have proved that anxiety-depressive alcohol dependence (ANX/DEPALC) could be a genetically well-defined subtype of alcoholism linking to *DRD2*. Similar clinical characteristics with Type I alcoholism has been found in the ANX/DEPALC with late-onset and more anxious/depressed traits, and their suffering from anxiety/depression related to heavy drinking. The higher NS and HA scores were found in the ANX/DEPALC than in the pure ALC. This result might indicate that ANX/DEP ALC belongs to a subtype of alcoholism [127]. Furthermore, an association was found between ANX/DEP ALC and NS, but only in subjects with *DRD2 TaqIA* A1+ allele (including A1/A1 or A1/A2 genotype). In addition, the difference in NS between ANX/DEP ALC and Pure ALC existed in subjects with S/S genotype of *5-HTTLPR*. The potential genes, *DRD2 TaqIA* A1+ allele and 5-HTTLPR may involve in the development of ANX/DEP ALC with novelty seeking personality trait [127].

Further analysis with stratification of the *DRD2 TaqIA* A1/A1 or A1/A2 genotype subjects, the difference in NS scores was only found in subjects with *5-HTTLPR* S/S genotype. The ANX/DEPALC was associated with HA only in subjects with *5-HTTLPR* S/L and L/L genotypes, suggesting that the personality traits of type I alcoholism in Cloninger's model might need modification. The *5-HTTLPR* polymorphism involved in both NS and HA implied that personality traits related to multiple genes could be possible in developing mental disorder. Therefore, multiple genes would be suggested to be considered in the further study .

4. Summary

Wang et al. [111] provided preliminary evidence that comorbid BP-II^{+AD} might be one of the subtypes of BPII. The *DRD2* gene could be an important candidate gene for the comorbidity of AD in other mental illness and *ALDH2* gene might moderate the impact of *DRD2* gene on BPII with or without AD. Moreover, Chang et al. [114] revealed the exact effect of this interaction on DRD3 binding affinity and neuron secretion of BDNF is not clear yet may be associated with the pathogenesis of anxiety disorders. The Gly/Gly genotypes of the *DRD3* Ser9Gly have been associated with unipolar depression [129]; this might explain the main effect was only found in the BPII^{+AD} but not in the BPI^{+AD}. A possibility could be ethnic differences or the genetic heterogeneity of AD and depressive disorder like BPII; because in the Han Chinese, GAD has been reported as the major AD comorbidity in the BPII [57] while it was reported to be associated with major depression in other ethnics [64, 130]. In addition, ADs occur most frequently during depressive and depressive manic episodes in BP patients [67] as well as during subsyndromal depressive states [68]. Since long-term follow-ups have shown that patients with BPII have a more chronic course, more mood episodes, more major and minor depressive episodes which last longer than those of patients with BPI [131–133], whether the interaction between the *BDNF* and *DRD3* genes is related to the clinical characteristics of BPII^{+AD}, for example, depression-proneness, may still require further study.

Previous studies provided initial evidence of the involvement of dopaminergic pathway as well as serotonin system in the pathogenesis of bipolar disorder [110, 113, 134, 135]. However, whether the interaction of these genes leads to dysfunctional dopaminergic signaling or serotonin regulation and to what extent these genes would affect the etiology of bipolar disorder with AD comorbidity still require further clarification. Moreover, AD playing the role of comorbidity in BP and alcoholism showed relatively lower prevalence rate in Han Chinese while compared to previous studies conducted in Western population. This finding implied an ethnic possibility which has been supported in some studies with genetic investigation. Moreover, in both BP and ALC with AD comorbidity have been reported to have relationship with dopaminergic genes as well as serotonin-related genes, the *ALDH2* gene plays the most important role in both disorders with AD comorbidity. The frequency of *ALDH2* gene has been found differently in Han Chinese compared to Caucasians, further causal-relationship investigation of this gene in AD comorbidity is needed to confirm.

http://dx.doi.org/10.5772/66117

Abbreviations

AD: anxiety disorder

ALDH2: aldehyde dehydrogenase 2

ANX/DEP ALC: anxiety/depression alcoholism

BDNF: brain-derived neurotrophic factor

BP: bipolar disorder

DOPAC: 3,4-dihydroxyphenylacetic acid

DOPAL: 3,4-dihydroxyphenylacetaldehyde

DRD2: dopamine D2 receptor

DRD3: dopamine D3 receptor

GAD: generalized anxiety disorder

PTSD: post-traumatic stress disorder

PD: panic disorder

OCD: obsession compulsive disorder

MAOA: monoamine oxidase A

Author details

Yun-Hsuan Chang[1,2,3], Sheng-Yu Lee[3,4] and Ru-Band Lu[3,5]*

*Address all correspondence to: rblu@mail.ncku.edu.tw

1 Department of Psychology, College of Medical and Health Sciences, Asia University, Taichung, Taiwan, R.O.C

2 Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan, R.O.C

3 Department of Psychiatry, National Cheng Kung University, Tainan, Taiwan, R.O.C.

4 Department of Psychiatry, Kaohsiung Veteran's General Hospital, Kaohsiung, Taiwan, R.O.C

5 Institute of Behavioural Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, R.O.C.

References

[1] Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. Journal of Chronic Diseases. 1970;23(7):455–468.

[2] Blashfield RK, Sprock J, Fuller AK. Suggested guidelines for including or excluding categories in the DSM-IV. Comprehensive psychiatry. 1990 Jan-Feb;31(1):15–19. PubMed PMID: 2297982. Epub 1990/01/01. eng.

[3] Boyd JH, Burke JD, Jr., Gruenberg E, Holzer CE, 3rd, Rae DS, George LK, et al. Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. Archives of General Psychiatry. 1984 Oct;41(10):983–989. PubMed PMID: 6477056. Epub 1984/10/01. eng.

[4] Di Nardo PA, Barlow DH. Syndrome and symptom comorbidity in the anxiety disorders. In: Maser JDC, C. R., editor. Comorbidity in anxiety and mood disorders. Washington, DC: American Psychiatric Press; 1990. pp. 205–230.

[5] Moras K, Barlow D. Definitions of secondary depression: effects on comorbidity and outcome in anxiety disorders. Psychopharmacol Bull. 1992;28(1):27–33. PubMed PMID: 1609039. Epub 1992/01/01. eng.

[6] Wittchen HU. Critical issues in the evaluation of comorbidity of psychiatric disorders. British Journal of Psychiatry Supplement. 1996;30:9–16.

[7] Angold A, Costello EJ, Erkanli A. Comorbidity. Journal of Child Psychology Psychiatry. 1999 Jan;40(1):57–87. PubMed PMID: 10102726. Epub 1999/04/02. eng.

[8] Reiger DA, Burker JD, Burke KC. Comorbidity of affective and anxiety disorders in the NIMH Epidemiological Catchment Area Program. In: Maser JD, Cloniger CR, editors. Comorbidity of mood and anxiety disorders. Washington, DC: American Psychiatric Press; 1990. pp. 113–122.

[9] Robins LN, Locke BZ, Regier DA. An overview of psychiatric disorders in America. In: Robbins LN, Regier DA, editors. Psychiatric disorders in America: the epidemiologic catchment area study. New York: Free Press; 1991. pp. 328–366.

[10] Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, et al. Prevalence and treatment of mental disorders, 1990 to 2003. New England Journal of Medicine. 2005 Jun 16;352(24):2515–2523. PubMed PMID: 15958807. Pubmed Central PMCID: 2847367. Epub 2005/06/17. eng.

[11] Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Archives of General Psychiatry. 2005 Feb;62(2):182–189. PubMed PMID: 15699295. Epub 2005/02/09. eng.

[12] Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. Offspring of depressed parents: 20 years later. The American Journal of Psychiatry. 2006 Jun;163(6):1001–1008. PubMed PMID: 16741200. Epub 2006/06/03. eng.

[13] Hoehn-Saric R, McLeod DR, Funderburk F, Kowalski P. Somatic symptoms and physiologic responses in generalized anxiety disorder and panic disorder: an ambulatory monitor study. Archives of General Psychiatry. 2004 Sep;61(9):913–921. PubMed PMID: 15351770. Epub 2004/09/08. eng.

[14] Gray JA. The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system. Oxford: Oxford University Press; 1982.

[15] Lautenbacher S, Spernal J, Krieg JC. Divided and selective attention in panic disorder. A comparative study of patients with panic disorder, major depression and healthy controls. European Archives of Psychiatry and Clinical Neuroscience. 2002 Oct;252(5):210–213. PubMed PMID: 12451461. Epub 2002/11/27. eng.

[16] Asmundson GJ, Stein MB, Larsen DK, Walker JR. Neurocognitive function in panic disorder and social phobia patients. Anxiety. 1994;1(5):201–207. PubMed PMID: 9160575. Epub 1994/01/01. eng.

[17] Lucas JA, Telch MJ, Bigler ED. Memory functioning in panic disorder: A neuropsychological perspective. Journal of Anxiety Disorders. 1991;5(1):1–20.

[18] Airaksinen E, Larsson M, Forsell Y. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. Journal of Psychiatric Research. 2005 Mar;39(2):207–214. PubMed PMID: 15589570. Epub 2004/12/14. eng.

[19] Sachs G, Anderer P, Margreiter N, Semlitsch H, Saletu B, Katschnig H. P300 event-related potentials and cognitive function in social phobia. Psychiatry Research. 2004 Sep 15;131(3):249–261. PubMed PMID: 15465294. Epub 2004/10/07. eng.

[20] Lee SY, Chen SL, Chen SH, Huang SY, Tzeng NS, Chang YH, et al. The COMT and DRD3 genes interacted in bipolar I but not bipolar II disorder. World Journal of Biological Psychiatry. 2010 Aug 10 ; 12(5):385-91. PubMed PMID: 20698735. Epub 2010/08/12. Eng.

[21] Lee SY, Chen SL, Chang YH, Chen SH, Chu CH, Huang SY, et al. The ALDH2 and DRD2/ANKK1 genes interacted in bipolar II but not bipolar I disorder. Pharmacogenet Genomics. 2010 Aug;20(8):500–506. PubMed PMID: 20577142. Epub 2010/06/26. eng.

[22] Lee SY, Chen SL, Chang YH, Chu CH, Huang SY, Tzeng NS, et al. The ALDH2 and 5-HT2A genes interacted in bipolar-I but not bipolar-II disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2012 Aug 7;38(2):247–251. PubMed PMID: 22564712. Epub 2012/05/09. eng.

[23] Angst J. Panic disorder: History and epidemiology. European Psychiatry: The Journal of the Association of European Psychiatrists. 1998;13 (Suppl 2):51s–55s. PubMed PMID: 19698673.

[24] Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. American Journal of Psychiatry. 1995;152:280–282.

[25] Endicott J, Nee J, Andreasen N, Clayton P, Keller M, Coryell W. Bipolar II Combined or keep separate? Journal of Affective Disorder. 1985;8:17–28.

[26] Rihmer Z, Szadoczky E, Furedi J, Kiss K, Papp Z. Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. Journal of Affective Disorders. 2001 Dec;67(1–3):175–179. PubMed PMID: 11869765. Epub 2002/03/01. eng.

[27] Manning JS, Haykal, RF, Connor, PD. On the nature of depressive and anxious states in family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. Comprehensive Psychiatry. 1997;38:102-108.

[28] Perugi G, Akiskal, HS, Ramaciotti, S, Nassini, S, Toni, C, Milanfranchi, A, Musetti, L. Depressive comorbidity of panic, social phobia and obsessive-compulsive disorders re-examined: is there a bipolar II connection? Journal of Psychiatric Research. 1999;33:53–61.

[29] Bauer M, Altshuler L, Evans D, Beresford T, Williford W, Hauger R, et al. Prevalence and distinct correlates of anxiety, l substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. Journal of Affective Disorder. 2005;85:301–315.

[30] Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). The American Journal of Psychiatry. 2004 Dec;161(12):2222–2229. PubMed PMID: 15569893. Epub 2004/12/01. eng.

[31] Kessler RC, DuPont RL, Berglund P, Wittchen HU. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. The American Journal of Psychiatry. 1999 Dec;156(12):1915–1923. PubMed PMID: 10588405. Epub 1999/12/10. eng.

[32] Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychological Medicine. 1997 Sep;27(5):1079–1089. PubMed PMID: 9300513. Epub 1997/09/23. eng.

[33] Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of General Psychiatry. 2007 May;64(5):543–552. PubMed PMID: 17485606. Pubmed Central PMCID: PMC1931566. Epub 2007/05/09. eng.

[34] Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. Journal of Affective Disorders. 2002 Feb;68(1):1–23. PubMed PMID: 11869778.

[35] Yerevanian BI, Koek RJ, Ramdev S. Anxiety disorders comorbidity in mood disorder subgroups: data from a mood disorders clinic. Journal of Affective Disorders. 2001 Dec;67(1-3):167–173. PubMed PMID: 11869764. Epub 2002/03/01. eng.

[36] Chen YW, Dilsaver SC. Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders. Psychiatry Research. 1995 Nov 29;59(1–2):57–64. PubMed PMID: 8771221. Epub 1995/11/29. eng.

[37] McIntyre R, Katzman M. The role of atypical antipsychotics in bipolar depression and anxiety disorders. Bipolar Disorders. 2003;5 (Suppl 2):20–35. PubMed PMID: 14700010. Epub 2004/01/01. eng.

[38] Zutshi A, Reddy YC, Thennarasu K, Chandrashekhar CR. Comorbidity of anxiety disorders in patients with remitted bipolar disorder. European Archives of Psychiatry and Clinical Neuroscience. 2006 Oct;256(7):428–436. PubMed PMID: 16783496. Epub 2006/06/20. eng.

[39] Vieta E, Colom F, Martinez-Aran A, Benabarre A, Reinares M, Gasto C. Bipolar II disorder and comorbidity. Comprehensive Psychiatry. 2000;41:339–343.

[40] Dunner DL. Correlates of suicidal behavior and lithium treatment in bipolar disorder. Journal of Clinical Psychiatry. 2004;65(Suppl 10):5–10.

[41] Krishnan KR. Psychiatric and medical comorbidities of bipolar disorder. Psychosomatic Medicine. 2005 Jan-Feb;67(1):1–8. PubMed PMID: 15673617. Epub 2005/01/28. eng.

[42] Wozniak J, Biederman J, Monuteaux M, Richards J, Faraone SV. Parsing the comorbidity between bipolar disorder and anxiety disorders: A familial risk analysis. Journal of Child and Adolescent Psychopharmacology. 2002;12:101–111.

[43] Lee JH, Dunner DL. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. Depression and Anxiety. 2008;25(2):91–97. PubMed PMID: 17311265. Epub 2007/02/22. eng.

[44] Perugi G, Akiskal HS, Ramacciotti S, Nassini S, Toni C, Milanfranchi A, et al. Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection? Journal of Psychiatric Research. 1999 Jan–Feb;33(1):53–61. PubMed PMID: 10094240. Epub 1999/03/27. eng.

[45] Bauer MS, Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. Journal of Affective Disorders. 2005 Apr;85(3):301–315. PubMed PMID: 15780700. Epub 2005/03/23. eng.

[46] Post RM. The impact of bipolar depression. Journal of Clinical Psychiatry. 2005;66 (Suppl 5):5–10. PubMed PMID: 16038596. Epub 2005/07/26. eng.

[47] McIntyre RS, Soczynska JK, Bottas A, Bordbar K, Konarski JZ, Kennedy SH. Anxiety disorders and bipolar disorder: a review. Bipolar Disorders. 2006 Dec;8(6):665–676. PubMed PMID: 17156153. Epub 2006/12/13. eng.

[48] McElroy SL, Altshuler LL, Suppes T, Keck PE, Jr., Frye MA, Denicoff KD, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. American Journal of Psychiatry. 2001 Mar;158(3):420–426. PubMed PMID: 11229983. Epub 2001/03/07. eng.

[49] Boylan KR, Bieling PJ, Marriott M, Begin H, Young LT, MacQueen GM. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. Journal of Clinical Psychiatry. 2004 Aug;65(8):1106–1113. PubMed PMID: 15323597. Epub 2004/08/25. eng.

[50] Bauer MS, Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. Journal of Affective Disorders. 2005 Apr;85(3):301–315. PubMed PMID: 15780700. Epub 2005/03/23. eng.

[51] Feske U, Frank E, Mallinger AG, Houck PR, Fagiolini A, Shear MK, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. American Journal of Psychiatry. 2000 Jun;157(6):956–962. PubMed PMID: 10831476. Epub 2000/06/01. eng.

[52] Simon GE. Social and economic burden of mood disorders. Biological Psychiatry. 2003 Aug 1;54(3):208–215. PubMed PMID: 12893097. Epub 2003/08/02. eng.

[53] Simon NM, Zalta AK, Otto MW, Ostacher MJ, Fischmann D, Chow CW, et al. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. Journal of Psychiatric Research. 2007 Apr-Jun;41(3–4):255–64. PubMed PMID: 17052730. Epub 2006/10/21. eng.

[54] Vojta C, Kinosian B, Glick H, Altshuler L, Bauer MS. Self-reported quality of life across mood states in bipolar disorder. Comprehensive Psychiatry. 2001 May–Jun;42(3):190–5. PubMed PMID: 11349236. Epub 2001/05/12. eng.

[55] Wittchen HU. Generalized anxiety disorder: prevalence, burden, and cost to society. Depression and Anxiety. 2002;16(4):162–71. PubMed PMID: 12497648. Epub 2002/12/24. eng.

[56] Kessler RC. The epidemiology of pure and comorbid generalized anxiety disorder: a review and evaluation of recent research. Acta Psychiatric Scandinavica Supplement. 2000; 406:7–13. PubMed PMID: 11131470. Epub 2000/12/29. eng.

[57] Chang YH, Chen SL, Chen SH, Chu CH, Lee SY, Yang HF, et al. Low anxiety disorder comorbidity rate in bipolar disorders in Han Chinese in Taiwan. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2012 Jan 10;36(1):194–197. PubMed PMID: 21996277. Epub 2011/10/15. eng.

[58] Kawa I, Carter J, Joyce P, Doughty C, Frampton C, Wells J, et al. Gender differences in bipolar disorder: Age of onset, course, comorbidity, and symptom presentation. Bipolar Disorders. 2005;7:119–125.

[59] Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Archives of General Psychiatry. 1994 Jan;51(1):8–19. PubMed PMID: 8279933. Epub 1994/01/01. eng.

[60] Strakowski SM, Tohen M, Stoll A, Faedda G, Goodwin D. Comorbidity in mania at first hospitalization. American Journal of Psychiatry. 1992;149:554–556.

[61] Rice J, Saccone N, Rasmussen E. Definition of the phenotype. In: Rao D, Province M, editors. Genetic discussion of complex traits. New York: Academic Press; 2001. pp. 70–74.

[62] Wittchen HU, Zhao S, Kessler RC, Eaton WW. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Archives of General Psychiatry. 1994 May;51(5):355–364. PubMed PMID: 8179459. Epub 1994/05/01. eng.

[63] Moffitt TE, Harrington H, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, et al. Depression and Generalized Anxiety Disorder: Cumulative and Sequential Comorbidity in a Birth Cohort Followed Prospectively to Age 32 Years. Archives of General Psychiatry. 2007 June 1, 2007;64(6):651–660.

[64] Silverstein B. Gender difference in the prevalence of clinical depression: the role played by depression associated with somatic symptoms. The American Journal of Psychiatry. 1999 March 1, 1999;156(3):480–482.

[65] Akiskal HS. Subaffective disorders: dysthymic, cyclothymic and bipolar II disorders in the "borderline" realm. Psychiatric Clinics of North America. 1981 Apr;4(1):25–46. PubMed PMID: 7232236. Epub 1981/04/01. eng.

[66] Cooke RG, Young LT, Levitt AJ, Pearce MM, Joffe RT. Bipolar II: Not so different when co-morbidity excluded. Depression. 1995;3(3):154–156.

[67] Dilsaver SC, Chen YW. Social phobia, panic disorder and suicidality in subjects with pure and depressive mania. Journal of Affective Disorders. 2003 Nov;77(2):173–177. PubMed PMID: 14607395. Epub 2003/11/11. eng.

[68] MacQueen GM, Marriott M, Begin H, Robb J, Joffe RT, Young LT. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. Bipolar Disorders. 2003 Oct;5(5):349–355. PubMed PMID: 14525555. Epub 2003/10/04. eng.

[69] Cassano GB, Pini S, Saettoni M, Dell'Osso L. Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. The American Journal of Psychiatry. 1999 Mar;156(3):474–476. PubMed PMID: 10080568. Epub 1999/03/18. eng.

[70] MacKinnon DF, Xu J, McMahon FJ, Simpson SG, Stine OC, McInnis MG, et al. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. The American Journal of Psychiatry. 1998 Jun;155(6):829–381. PubMed PMID: 9619158. Epub 1998/06/10. eng.

[71] Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Archives of General Psychiatry. 2003 Mar;60(3):261-269. PubMed PMID: 12622659. Epub 2003/03/08. eng.

[72] Kelsoe JR. Arguments for the genetic basis of the bipolar spectrum. Journal of Affective Disorders. 2003 Jan;73(1–2):183–97. PubMed PMID: 12507751. Epub 2003/01/01. eng.

[73] McMahon FJ, Simpson SG, McInnis MG, Badner JA, MacKinnon DF, DePaulo JR. Linkage of bipolar disorder to chromosome 18q and the validity of bipolar II disorder. Archives of General Psychiatry. 2001 Nov;58(11):1025–31. PubMed PMID: 11695948. Epub 2001/12/26. eng.

[74] Craddock N, Sklar P. Genetics of bipolar disorder: successful start to a long journey. Trends Genetics. 2009 Feb;25(2):99–105. PubMed PMID: 19144440. Epub 2009/01/16. eng.

[75] Kendler KS, Pedersen NL, Neale MC, Mathe AA. A pilot Swedish twin study of affective illness including hospital- and population-ascertained subsamples: results of model fitting. Behaviour Genetics. 1995 May;25(3):217–232. PubMed PMID: 7598665. Epub 1995/05/01. eng.

[76] McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Archives of General Psychiatry. 2003 May;60(5):497–502. PubMed PMID: 12742871. Epub 2003/05/14. eng.

[77] Coryell W, Endicott J, Reich T, Andreasen N, Keller M. A family study of bipolar II disorder. British Journal of Psychiatry. 1984 Jul;145:49–54. PubMed PMID: 6743943. Epub 1984/07/01. eng.

[78] Lee SY, Chen SL, Chen SH, Huang SY, Tzeng NS, Chang YH, et al. The COMT and DRD3 genes interacted in bipolar I but not bipolar II disorder. CORD Conference Proceedings. 2011;12(5):385–391. Eng.

[79] Sadovnick AD, Remick RA, Lam R, Zis AP, Yee IM, Huggins MJ, et al. Mood Disorder Service Genetic Database: morbidity risks for mood disorders in 3,942 first-degree relatives of 671 index cases with single depression, recurrent depression, bipolar I, or bipolar II. American Journal of Medical Genetics. 1994 Jun 15;54(2):132–140. PubMed PMID: 8074163. Epub 1994/06/15. eng.

[80] Schwartz JC, Diaz J, Pilon C, Sokoloff P. Possible implications of the dopamine D(3) receptor in schizophrenia and in antipsychotic drug actions. Brain Research. Brain Research Reviews. 2000 Mar;31(2–3):277–287. PubMed PMID: 10719154. Epub 2000/03/17. eng.

[81] Sokoloff P, Giros B, Martres M-P, Bouthenet M-L, Schwartz J-C. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature. 1990;347(6289):146–151.

[82] Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, et al. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Molecular Psychiatry. 1999 May;4(3):290–296. PubMed PMID: 10395223. Epub 1999/07/08. eng.

[83] Kirov G, Jones I, McCandless F, Craddock N, Owen MJ. Family-based association studies of bipolar disorder with candidate genes involved in dopamine neurotransmission: DBH, DAT1, COMT, DRD2, DRD3 and DRD5. Molecular Psychiatry. 1999 Nov;4(6):558–565. PubMed PMID: 10578238. Epub 1999/12/01. eng.

[84] Souery D, Lipp O, Mahieu B, Mendelbaum K, De Martelaer V, Van Broeckhoven C, et al. Association study of bipolar disorder with candidate genes involved in catecholamine neurotransmission: DRD2, DRD3, DAT1, and TH genes. American Journal of Medical Genetics. 1996 Nov 22;67(6):551–555. PubMed PMID: 8950413. Epub 1996/11/22. eng.

[85] Lannfelt L, Sokoloff P, Martres M-P, Pilon C, Giros B, Jönsson E, et al. Amino acid substitution in the dopamine D3 receptor as a useful polymorphism for investigating psychiatric disorders. Psychiatric Genetics. 1992;2(4):249–256.

[86] Lundstrom K, Turpin MP. Proposed schizophrenia-related gene polymorphism: expression of the Ser9Gly mutant human dopamine D3 receptor with the Semliki Forest virus system. Biochemical and Biophysical Research Communication. 1996 Aug 23;225(3):1068–1072. PubMed PMID: 8780735. Epub 1996/08/23. eng.

[87] Scharfetter J, Chaudhry HR, Hornik K, Fuchs K, Sieghart W, Kasper S, et al. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakastani patients. European Neuropsychopharmacology. 1999 Dec;10(1):17–20. PubMed PMID: 10647091. Epub 2000/01/26. eng.

[88] Shaikh S, Collier DA, Sham PC, Ball D, Aitchison K, Vallada H, et al. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Human Genetics. 1996 Jun;97(6):714–719. PubMed PMID: 8641685. Epub 1996/06/01. eng.

[89] Parsian A, Chakraverty S, Todd RD. Possible association between the dopamine D3 receptor gene and bipolar affective disorder. American Journal of Medicine Genetics. 1995 Jun 19;60(3):234–237. PubMed PMID: 7573178. Epub 1995/06/19. eng.

[90] Elvidge G, Jones I, McCandless F, Asherson P, Owen MJ, Craddock N. Allelic variation of a BalI polymorphism in the DRD3 gene does not influence susceptibility to bipolar disorder: results of analysis and meta-analysis. American Journal of Medicine Genetics. 2001 May 8;105(4):307–311. PubMed PMID: 11378841. Epub 2001/05/30. eng.

[91] Shaikh S, Ball D, Craddock N, Castle D, Hunt N, Mant R, et al. The dopamine D3 receptor gene: no association with bipolar affective disorder. Journal of Medical Genetics. 1993 April 1;30(4):308–309.

[92] Quraishi S, Frangou S. Neuropsychology of bipolar disorder: a review. Journal of Affective Disorders. 2002 Dec;72(3):209–226. PubMed PMID: 12450638. Epub 2002/11/27. eng.

[93] Baquet ZC, Bickford PC, Jones KR. Brain-derived neurotrophic factor is required for the establishment of the proper number of dopaminergic neurons in the substantia nigra pars compacta. Journal of Neuroscience. 2005 Jun 29;25(26):6251–6259. PubMed PMID: 15987955. Epub 2005/07/01. eng.

[94] Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature. 2001 May 3;411(6833):86–89. PubMed PMID: 11333982. Epub 2001/05/03. eng.

[95] Chen ZY, Ieraci A, Teng H, Dall H, Meng CX, Herrera DG, et al. Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. Journal of Neuroscience. 2005 Jun 29;25(26):6156–6166. PubMed PMID: 15987945. Pubmed Central PMCID: 1201519. Epub 2005/07/01. eng.

[96] Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 2006 Oct 6;314(5796):140–143. PubMed PMID: 17023662. Pubmed Central PMCID: 1880880. Epub 2006/10/07. eng.

[97] Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, et al. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. Journal of Neuroscience. 2004 May 5;24(18):4401–4411. PubMed PMID: 15128854. Epub 2004/05/07. eng.

[98] Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003 Jan 24;112(2):257–269. PubMed PMID: 12553913. Epub 2003/01/30. eng.

[99] Hong CJ, Huo SJ, Yen FC, Tung CL, Pan GM, Tsai SJ. Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. Neuropsychobiology. 2003;48(4):186–189. PubMed PMID: 14673216. Epub 2003/12/16. eng.

[100] Nakata K, Ujike H, Sakai A, Uchida N, Nomura A, Imamura T, et al. Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder. Neuroscience Letter. 2003 Jan 30;337(1):17–20. PubMed PMID: 12524161. Epub 2003/01/14. eng.

[101] Tang J, Xiao L, Shu C, Wang G, Liu Z, Wang X, et al. Association of the brain-derived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. Neuroscience Letter. 2008 Mar 12;433(2):98–102. PubMed PMID: 18242852. Epub 2008/02/05. eng.

[102] Pivac N, Kim B, Nedic G, Joo YH, Kozaric-Kovacic D, Hong JP, et al. Ethnic differences in brain-derived neurotrophic factor Val66Met polymorphism in Croatian and Korean healthy participants. Croatian Medical Journal. 2009 Feb;50(1):43-48. PubMed PMID: 19260143. Pubmed Central PMCID: 2657559. Epub 2009/03/05. eng.

[103] Harris EL, Noyes R, Jr., Crowe RR, Chaudhry DR. Family study of agoraphobia. Report of a pilot study. Archives of General Psychiatry. 1983 Oct;40(10):1061–1064. PubMed PMID: 6625854.

[104] Knutson, B., Wolkowitz, O.M., Cole, S.W., Chan, T., Moore, E.A., Johnson, R.C., Terpstra, J., Turner, R.A., Reus, V.I. (1998). Selective alteration of personality and social behavior by serotonergic intervention. The American journal of psychiatry 155, 373-379.

[105] Wiers RW, Sergeant JA, Gunning WB. Psychological mechanisms of enhanced risk of addiction in children of alcoholics: a dual pathway? Acta Paediatrica. 1994 Nov;404:9–13. PubMed PMID: 7841640.

[106] McGue M. A behavioral-genetic perspective on children of alcoholics. Alcohol Health and Research World. 1997;21(3):210–217. PubMed PMID: 15706771.

[107] Ritchie T, Noble EP. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. Neurochemical Research. 2003 Jan;28(1):73–82. PubMed PMID: 12587665. Epub 2003/02/18. eng.

[108] Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li TK, et al. Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. The American Journal of Human Genetics. 1999 Sep;65(3):795–807. PubMed PMID: 10441588. Pubmed Central PMCID: 1377988. Epub 1999/08/12. eng.

[109] Agarwal DP, Goedde HW. Medicobiological and genetic studies on alcoholism. Role of metabolic variation and ethnicity on drinking habits, alcohol abuse and alcohol-related mortality. Journal of Clinical Investigation. 1992 Jun;70(6):465–477. PubMed PMID: 1392414. Epub 1992/06/01. eng.

[110] Thomasson HR, Edenberg HJ, Crabb DW, Mai XL, Jerome RE, Li TK, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. The American Journal of Human Genetics. 1991 Apr;48(4):677–681. PubMed PMID: 2014795. Pubmed Central PMCID: 1682953. Epub 1991/04/01. eng.

[111] Wang YS, Lee SY, Chen SL, Chang YH, Wang TY, Lin SH, et al. Role of DRD2 and ALDH2 genes in bipolar II disorder with and without comorbid anxiety disorder. European Psychiatry: The Journal of the Association of European Psychiatrists. 2014 Mar;29(3):142–148. PubMed PMID: 23835015. Epub 2013/07/10. eng.

[112] Doughty CJ, Wells JE, Joyce PR, Olds RJ, Walsh AE. Bipolar-panic disorder comorbidity within bipolar disorder families: a study of siblings. Bipolar Disorders. 2004 Jun;6(3):245–252. PubMed PMID: 15117403. Epub 2004/05/01. eng.

[113] Rotondo A, Mazzanti C, Dell'Osso L, Rucci P, Sullivan P, Bouanani S, et al. Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. The American Journal of Psychiatry. 2002 Jan;159(1):23–29. PubMed PMID: 11772685. Epub 2002/01/05. eng.

[114] Chang YH, Lee SY, Chen SL, Tzeng NS, Wang TY, Lee IH, et al. Genetic variants of the BDNF and DRD3 genes in bipolar disorder comorbid with anxiety disorder. Journal of Affective Disorders. 2013 Dec;151(3):967–972. PubMed PMID: 24021960. Epub 2013/09/12. eng.

[115] Joyce PR, Rogers GR, Miller AL, Mulder RT, Luty SE, Kennedy MA. Polymorphisms of DRD4 and DRD3 and risk of avoidant and obsessive personality traits and disorders. Psychiatry Research. 2003 Jul 15;119(1–2):1–10. PubMed PMID: 12860355. Epub 2003/07/16. eng.

[116] Light KJ, Joyce PR, Luty SE, Mulder RT, Frampton CMA, Joyce LRM, et al. Preliminary evidence for an association between a dopamine D3 receptor gene variant and obsessive-

compulsive personality disorder in patients with major depression. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2006;141B(4):409–413.

[117] Takahashi T, Suzuki M, Tsunoda M, Kawamura Y, Takahashi N, Maeno N, et al. The association of genotypic combination of the DRD3 and BDNF polymorphisms on the adhesion interthalamica and medial temporal lobe structures. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2008 Jul 1;32(5):1236–1242. PubMed PMID: 18472202. Epub 2008/05/13. eng.

[118] Gourion D, Goldberger C, Leroy S, Bourdel M-C, Olié J-P, Krebs M-O. Age at onset of schizophrenia: interaction between brain-derived neurotrophic factor and dopamine D3 receptor gene variants. NeuroReport. 2005;16(12):1407–1410.

[119] Chang CT, Chang YH, Yung-Wei Wu J, Lee SY, Chen SL, Chen SH, et al. Neuropsychological functions impairment in different subtypes of bipolar disorder with or without comorbid anxiety disorders. Psychiatry Research. 2012 Jun 27 ; 200(2-3):246-51. PubMed PMID: 22748188. Epub 2012/07/04. Eng.

[120] Lohoff FW, Sander T, Ferraro TN, Dahl JP, Gallinat J, Berrettini WH. Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2005;139B(1):51–53.

[121] Frustaci A, Pozzi G, Gianfagna F, Manzoli L, Boccia S. Meta-analysis of the brain-derived neurotrophic factor gene (BDNF) Val66Met polymorphism in anxiety disorders and anxiety-related personality traits. Neuropsychobiology. 2008;58(3–4):163–170. PubMed PMID: 19088493. Epub 2008/12/18. eng.

[122] Jiang X, Xu K, Hoberman J, Tian F, Marko AJ, Waheed JF, et al. BDNF variation and mood disorders: a novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. Neuropsychopharmacology. 2005 Jul;30(7):1353–1361. PubMed PMID: 15770238. Epub 2005/03/17. eng.

[123] Driessen M, Meier S, Hill A, Wetterling T, Lange W, Junghanns K. The course of anxiety, depression and drinking behaviours after completed detoxification in alcoholics with and without comorbid anxiety and depressive disorders. Alcohol and Alcoholism (Oxford, Oxfordshire). 2001 May–Jun;36(3):249–255. PubMed PMID: 11373263. Epub 2001/05/25. eng.

[124] Finckh U, Rommelspacher H, Kuhn S, Dufeu P, Otto G, Heinz A, et al. Influence of the dopamine D2 receptor (DRD2) genotype on neuroadaptive effects of alcohol and the clinical outcome of alcoholism. Pharmacogenetics. 1997 Aug;7(4):271–281. PubMed PMID: 9295055.

[125] Lucht MJ, Kuehn KU, Schroeder W, Armbruster J, Abraham G, Schattenberg A, et al. Influence of the dopamine D2 receptor (DRD2) exon 8 genotype on efficacy of tiapride and clinical outcome of alcohol withdrawal. Pharmacogenetics. 2001 Nov;11(8):647–653. PubMed PMID: 11692072.

[126] Lawford BR, Young RM, Rowell JA, Qualichefski J, Fletcher BH, Syndulko K, et al. Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. Nature Medicine. 1995 Apr;1(4):337–341. PubMed PMID: 7585063.

[127] Huang SY, Lin WW, Ko HC, Lee JF, Wang TJ, Chou YH, et al. Possible interaction of alcohol dehydrogenase and aldehyde dehydrogenase genes with the dopamine D2 receptor gene in anxiety-depressive alcohol dependence. Alcoholism, Clinical and Experimental Research. 2004 Mar;28(3):374–384. PubMed PMID: 15084894.

[128] Huang, S.Y., Lin, W.W., Wan, F.J., Chang, A.J., Ko, H.C., Wang, T.J., Wu, P.L., Lu, R.B. (2007). Monoamine oxidase-A polymorphisms might modify the association between the dopamine D2 receptor gene and alcohol dependence. Journal of psychiatry & neuroscience : JPN 32, 185-192.

[129] Dikeos DG, Papadimitriou GN, Avramopoulos D, Karadima G, Daskalopoulou EG, Souery D, et al. Association between the dopamine D3 receptor gene locus (DRD3) and unipolar affective disorder. Psychiatr Genet. 1999;9(4):189-95.

[130] Neria Y, Besser A, Kiper D, Westphal M. A longitudinal study of posttraumatic stress disorder, depression, and generalized anxiety disorder in Israeli civilians exposed to war trauma. J Trauma Stress. 2010;23(3):322-30.

[131] Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, et al. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? Journal of affective disorders. 2003;73(1-2):19-32.

[132] Pallanti S, Quercioli L, Pazzagli A, Rossi A, Dell'Osso L, Pini S, et al. Awareness of illness and subjective experience of cognitive complaints in patients with bipolar I and bipolar II disorder. The American journal of psychiatry. 1999;156(7):1094-6.

[133] Vieta E, Gasto C, Otero A, Nieto E, Vallejo J. Differential features between bipolar I and bipolar II disorder. Comprehensive psychiatry. 1997;38(2):98-101.

[134] Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2008;33(1):73–83.

[135] Mossner R, Daniel S, Albert D, Heils A, Okladnova O, Schmitt A, et al. Serotonin transporter function is modulated by brain-derived neurotrophic factor (BDNF) but not nerve growth factor (NGF). Neurochemistry International. 2000 Mar;36(3):197–202. PubMed PMID: 10676853. Epub 2000/02/17. eng.

IntechOpen