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

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Additional information is available at the end of the chapter

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## 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

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## 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].

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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].

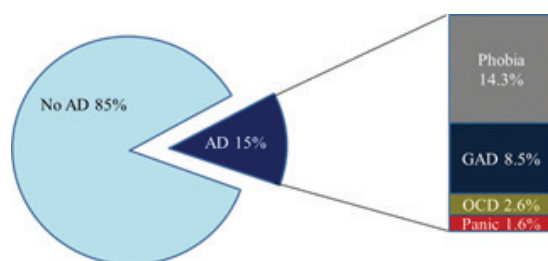
Reiger et al. [8] reported that approximately 15% of people suffered from AD, according to Diagnostic and Statistical Manual-3<sup>rd</sup> edition (DSM-III) during their lifetime. Keith et al. (1991) compared the prevalence of AD, including subtypes between community and the institute prevalence rates, 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 three-fold 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.

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 non-anxious 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<sup>-AD</sup>) [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.

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 sub-syndromal 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

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 *DRD2*s 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 BP-II 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 BP-II.

## 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 BP-II<sup>+AD</sup>, 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 BP-II. 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<sup>+AD</sup> 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<sup>-AD</sup>, and an interaction was found between *BDNF* Met/Val with *DRD3* Ser9Gly Ser/Ser genotype in BPI<sup>-AD</sup>. 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<sup>-AD</sup>, 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<sup>-AD</sup>, and an interaction was found between *BDNF* Met/Val with *DRD3* Ser9Gly Ser/Ser genotype in BPI<sup>-AD</sup>. 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<sup>-AD</sup>, 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].

### 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 *TaqI 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<sup>+AD</sup> 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<sup>+AD</sup> but not in the BPI<sup>+AD</sup>. 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<sup>+AD</sup>, 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.

## 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

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