Gene-Temperament Interactions Might Distinguish Between Bipolar I and Bipolar II Disorders: A Cross-Sectional Survey of Han Chinese in Taiwan

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ABSTRACT

Background: Whether bipolar II disorder is a distinct disorder or simply a milder form of bipolar I disorder has been debated. Family, twin, and adoption studies provide robust evidence of genetic contributions to bipolar disorder, and heritable temperaments are also believed to contribute to the susceptibility to bipolar disorders. In this study, we sought to clarify the relationship between bipolar I and bipolar II disorder.

Method: In this cross-sectional survey, 314 participants (82 bipolar I disorder patients, 121 bipolar II disorder patients, and 111 healthy controls) completed the Hamilton Depression Rating Scale, the Young Mania Rating Scale, and the Tridimensional Personality Questionnaire, which assessed the personality dimensions of novelty seeking and harm avoidance. We also determined which participants carried the serine-to-glycine substitution at amino acid position 9 polymorphism of the dopamine D_3 receptor gene (*DRD3*) and the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) genotypes. All patients met the *DSM-IV-TR* diagnosis criteria for bipolar disorder. This study was conducted from September 2005 to July 2009 at National Cheng Kung University Hospital, Tainan, Taiwan, and Tri-Service General Hospital, Taipei, Taiwan.

Results: Binary logistic regression analysis showed significant main effects for the *5-HTTLPR* polymorphism ($P = .045$), novelty seeking ($P = .022$), and harm avoidance ($P = .017$) scores and a significant interaction effect between harm avoidance and *5-HTTLPR* genotypes ($P = .042$) in distinguishing between bipolar I and bipolar II disorder patients. Bipolar I disorder patients with the long allele at *5-HTTLPR* had lower harm avoidance scores than did bipolar II disorder patients (bipolar I disorder = 16.23, bipolar II disorder = 19.80; $P = .023$); however, the difference was not significant after multiple test correction. All these data suggest a distinction between bipolar I and bipolar II disorder.

Conclusions: We provide initial evidence that *5-HTTLPR* genotypes might moderate the association between harm avoidance and bipolar I and bipolar II disorder. There appear to be unique differences in the gene-temperament interactions of bipolar I and bipolar II disorder patients.

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Bipolar disorder is divided into several categories, including bipolar I disorder, bipolar II disorder, and cyclothymic disorder. Several studies[1–3] have suggested that bipolar I disorder and bipolar II disorder might have different etiologies, symptomatologies, pathologies, and characteristics. Bipolar II disorder has been perceived as a common disorder, with a prevalence of approximately 3%–6%.[4] Recent studies[5] have focused on the specific clinical signature and management of this disorder instead of the differences between bipolar I and bipolar II disorder. However, some have questioned whether bipolar II disorder might be a milder form of bipolar I disorder or a distinct disorder.[6] Thus, it is necessary to clarify the relationship between bipolar I and bipolar II disorder to improve our understanding of bipolar II disorder.

Family, twin, and adoption studies[2] provide robust evidence of genetic contributions to bipolar disorder. Pharmacologic evidence[7] suggests that monoaminergic pathways, such as the serotonin transporter (*5-HTT*) and dopamine D_3 receptor genes (*DRD3*), are involved in their underlying mechanisms. The most frequently studied allelic variations of these genes have been the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) and the *DRD3* serine-to-glycine substitution at amino acid position 9 *(Ser9Gly)* polymorphism.[8–10] The *5-HTTLPR* gene is −1 kb upstream of the transcription initiation site.[11] The short variant and the L_G allele of the *5-HTTLPR* polymorphism reduce the transcription efficiency of the *5-HTT* gene promoter; only L_A is associated with high levels of *5-HTT* messenger RNA (mRNA) transcription.[12–15] The *DRD3 Ser9Gly* polymorphism causes a serine (Ser)-to-glycine (Gly) substitution and a significantly higher dopamine binding affinity.[16]

Heritable temperaments are also believed to contribute to the susceptibility to bipolar disorders.[17] A number of studies[18–20] of both psychiatric and nonpsychiatric populations have proposed associations between candidate genes and personality traits. Accordingly, temperament was hypothesized as an influence on the symptomatology or course of the illness.[18–22] The association between the *5-HTTLPR* gene and depressive outcome in affective disorders might be moderated by the personality traits of neuroticism[23] and harm avoidance.[24] The *DRD3* gene is implicated in novelty seeking in bipolar disorder patients.[25]

The Tridimensional Personality Questionnaire (TPQ) has been widely used in many studies of mental illness.[17,26] In Cloninger's tridimensional theory of personality,[17] the unified neurobiological model of personality is divided into 3 independent heritable dimensions of temperament: novelty seeking, harm avoidance, and reward dependence, which are proposed in relation to dopamine, serotonin, and norepinephrine, respectively.

Clinical Points

- An initial study shows that *5-HTTLPR* genotypes might moderate the association between harm avoidance and bipolar I and bipolar II disorder.
- There appear to be unique differences in the gene-temperament interactions of bipolar I and bipolar II disorder patients.

Inconsistent findings on the TPQ measurements and the associations with temperaments and genes between psychiatric disorders have been reported, and several possible explanations for these inconsistencies have been given. First, in a series of reports, Coryell et al concluded that bipolar I disorder and bipolar II disorder were separate disorders based on a family study,[27] a 5-year course and outcome study,[28] and a study of the stability of polarity distinctions.[29] Therefore, differentiating between bipolar I disorder and bipolar II disorder is necessary in personality studies. Second, patients' scores on personality questionnaires may reflect effects of the symptoms, which implies the importance of controlling for the severity of symptoms and the mood state of bipolar disorder patients. For example, novelty-seeking scores were significantly higher for hospitalized bipolar-manic patients than for unipolar-depressive patients but not higher for a combined group of hospitalized manic and depressive bipolar patients than for unipolar-depressive patients.[30] Third, some studies[31,32] did not control for comorbidities in their patients; however, different comorbidities may have different personality profiles[33] and genetic bases. A high rate of comorbidity was found between borderline personality disorder and substance dependence in patients with bipolar II disorder; comorbidities might be confounding in the results.[5] Thus, in the present study, we excluded patients with borderline personality disorder and substance dependence. Fourth, in most association studies conducted, researchers did not subdivide the long alleles of the *5-HTTLPR* polymorphism into L_A and L_G.[12,34] We separated these 2 alleles in the present study for L_A and L_G because they are associated with different transcription efficiencies.[13–15] Fifth, ethnic origin is a frequent cause of stratification bias; thus, we controlled the potential confounding variables of age, sex, and ethnic difference.

Finally, genetic polymorphisms of dopaminergic and serotonergic neurotransmission may strongly interact at the molecular level in humans with schizophrenia[35] and in animals.[36] Therefore, we also investigated whether the *DRD3 Ser9Gly* and *5-HTTLPR* genotypes interact in both bipolar I and bipolar II disorder. In addition, temperaments may be a mediating factor between genetic susceptibility and psychotic disorder[12,34,37]; thus, we included an analysis of gene-temperament interaction.

We explored the relationship between personality dimensions and genes in bipolar I and bipolar II disorders, and examined whether the *DRD3* and *5-HTT* genes, as well as harm avoidance and novelty seeking test scores, can be used to discriminate between individuals as healthy or having bipolar I or bipolar II disorder and to categorize them that way and to classify Han Chinese patients in Taiwan as having bipolar I or bipolar II disorder.

METHOD

Participants

This study was conducted from September 2005 to July 2009 at National Cheng Kung University Hospital, Tainan, Taiwan, and Tri-Service General Hospital, Taipei, Taiwan. The protocol was approved by the National Cheng Kung University Medical Center Institutional Review Board for the Protection of Human Subjects. Before this study began, all participants provided written informed consent.

Outpatients and inpatients with bipolar I and bipolar II disorder were recruited. All participants were initially evaluated in an interview by an attending psychiatrist and subsequently in a more detailed interview to determine their *DSM-IV* diagnoses. Interviews were conducted by a research clinical psychologist using the Chinese Version of the Modified Schedule of Affective Disorders and Schizophrenia-Life Time (SADS-L),[38] which has good interrater reliability.[39] Patients with major mental illnesses other than bipolar I and bipolar II disorder or with comorbid major mental illnesses, such as borderline personality disorder, drug dependence, and cognitive disorders, were excluded.

The TPQ was administered to each patient after at least a 1-week interepisode stage, based on Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) scores lower than 10.[32]

DSM-IV-TR[40] criteria require hypomania symptoms to last for a minimum of 4 days. This is derived from averaging the 2-day (probable) and 7-day (definite) threshold in the Research Diagnostic Criteria,[41] which lack evidence-based research. Epidemiologic data[42–47] suggest that a 2-day duration of hypomania symptoms is more prevalent than a 7-day duration in community samples. Therefore, we used the 2-day cutoff when diagnosing bipolar II disorder.[42–47] In our bipolar II disorder group, some patients were "bipolar not otherwise specified" by *DSM-IV-TR* definition.

The healthy control group consisted of 111 healthy volunteers recruited from the community and screened using the Chinese version of the SADS-L. Inclusion criteria were no major or minor mental illness (such as affective disorders, schizophrenia, anxiety disorders, personality disorders, and substance use disorders), nor any family history of psychiatric disorders among their first-degree relatives. Those who met the inclusion criteria were asked to take the TPQ.

Assessments

Tridimensional Personality Questionnaire. Personality dimensions were measured using the Chinese version of the TPQ. Because the Cronbach's α of novelty seeking was 0.70 and of harm avoidance was 0.87 and the reward dependence dimension of the TPQ is not reliable for Han Chinese

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Table 1. Demographic and Clinical Characteristics and Temperament Scores of Han Chinese Patients With Bipolar Disorder and Healthy Controls

Characteristic	Bipolar I Disorder (n = 82)	Bipolar II Disorder (n = 121)	Control (n = 111)	Statistic	*P* Value	Post Hoc
Sex, male, %	46.3	54.5	82.0	$\chi^2 = 30.23$	< .001	Control > BP-I, BP-II
Age, mean ± SD, y	32.93 ± 10.39	31.31 ± 10.92	36.88 ± 8.70	$F = 9.230$	< .001	Control > BP-I, BP-II
HDRS score, mean ± SD	4.94 ± 2.71	5.33 ± 2.62	NA	$t = 1.032$	.304	
YMRS score, mean ± SD	3.82 ± 3.13	4.31 ± 2.53	NA	$t = 1.198$	.233	
Harm avoidance score, mean ± SD	17.48 ± 6.18	19.00 ± 7.16	10.20 ± 4.48	$F = 66.76$	< .001	BP-I, BP-II > Control
Novelty seeking score, mean ± SD	16.11 ± 4.40	15.14 ± 4.76	12.95 ± 4.20	$F = 13.14$	< .001	BP-I, BP-II > Control
5-HTTLPR homozygous *S* allele[a] vs *L* allele carrier,[b] n/n (%/%)	51/31 (62/38)	81/40 (67/33)	60/51 (54/46)	$\chi^2 = 4.099$	.129	
DRD3 Ser9Gly Ser/Ser vs *Ser/Gly* or *Gly/Gly*, n/n (%/%)	49/33 (60/40)	63/58 (52/48)	50/61 (45/55)	$\chi^2 = 4.104$	.128	

[a]Homozygous *S* allele: *S/S, S/*L_G, L_G/L_G.
[b]*L* allele carrier: *S/XL, S/*L_A, L_A*/XL,* L_A/L_A.
Abbreviations: BP-I = bipolar I disorder, BP-II = bipolar II disorder, *DRD3* = dopamine D3 receptor gene, *5-HTTLPR* = serotonin transporter gene-linked polymorphic region, *Gly* = glycine, HDRS = 17-item Hamilton Depression Rating Scale, *L* = long allele, NA = not applicable, *S* = short allele, *Ser* = serine, *XL* = extra-long allele, YMRS = Young Mania Rating Scale.

in Taiwan,[26] only the novelty seeking and harm avoidance dimensions were analyzed in our study.

The Hamilton Depression Rating Scale and Young Mania Rating Scale. The 17-item HDRS (for determining the severity of depression[32,48,49]) and the 11-item YMRS (for ranking the symptoms of mania[50,51]) are both widely accepted as valid for assessing the Han Chinese population in Taiwan.

Blood samples and DNA extraction. Twenty milliliters of venous blood was drawn from the antecubital vein of each participant. DNA was extracted from lymphocytes.

Genotyping of the* DRD3 Ser9Gly *polymorphism. Genotyping for the *Ser9Gly* polymorphism of the DRD_3 gene was done using a modified method described elsewhere.[52]

Genotyping of the* 5-HTTLPR *polymorphism. The *5-HTTLPR* polymorphism was amplified using a polymerase chain reaction with oligonucleotide primers flanking the 5′ regulatory region of the *SLC6A4* gene.[11,12]

Statistical Analysis

SPSS software version 17.0 (SPSS Institute, Chicago, Illinois) was used for all statistical analyses. Demographic and clinical variables involving continuous data (age and HDRS, YMRS, harm avoidance, and novelty seeking scores) were analyzed using a 1-way analysis of variance (ANOVA) or *t* test. A χ^2 test was used for categorical variables (sex and genotype frequencies).

Hardy-Weinberg equilibrium was assessed for each group. When examining the *DRD3 Ser9Gly* gene, we divided the patients into 2 groups: patients with the *Ser/Ser* genotype and patients with the *Ser/Gly* or *Gly/Gly* genotype.[53] When investigating the *5-HTTLPR* gene, we also divided the patients into 2 groups: patients with the homozygous *S* allele (*S/S, S/*L_G, *or* L_G/L_G) and those with the *L* allele (*S/XL, S/*L_A, L_A/L_A, or L_A/XL). The *S* variant and L_G allele are associated with low levels of *5-HTT* mRNA transcription.[8,13–15,54] Finally, too few of our participants had the homozygous *L* genotype (L_A/L_A or L_A/XL) to allow us to draw any valid conclusions about the association of this genotype with bipolar I and bipolar II disorder; therefore, we combined those with heterozygous and homozygous genotypes to measure the difference in *5-HTTLPR* genotypes between the groups.

Binary logistic regression (outcome variable = bipolar I disorder vs bipolar II disorder; predictors = [a] the *5-HTTLPR* genotypes, [b] *DRD3 Ser9Gly* genotypes, [c] novelty seeking, [d] harm avoidance, [e] the gene and temperament combination, and [f] gene-gene interaction, covarying for age and sex) was used to examine the association between the control group and the 2 patient groups. The associations are expressed as odds ratios with corresponding 95% CIs. Statistical significance was set at $P < .05$, and *P* values are 2-tailed.

RESULTS

Of the 314 participants, 82 were bipolar I disorder patients, 121 were bipolar II disorder patients, and 111 were healthy controls (Table 1). The mean ± SD age of all participants was 33.7 ± 10.31 years. The mean ± SD age (healthy controls = 36.88 ± 8.70 years, bipolar I disorder = 32.93 ± 10.39 years, and bipolar II disorder = 31.31 ± 10.92 years) and percentage of males (healthy controls = 82%, bipolar I disorder = 46.3%, and bipolar II disorder = 54.5%) were significantly higher in the healthy control group than in the bipolar I and bipolar II disorder groups ($P < .001$). The HDRS, YMRS, novelty seeking, and harm avoidance scores were not significantly different between the bipolar I and bipolar II disorder groups; however, the novelty seeking and harm avoidance scores of bipolar I and bipolar II disorder groups were significantly higher than those of the healthy control group in post hoc tests.

The genotype distributions of the *Ser9Gly* polymorphism at the *DRD3* gene and *5-HTTLPR* polymorphism at *5-HTT* gene in all participants were in Hardy-Weinberg equilibrium ($P > .1$; data not shown).

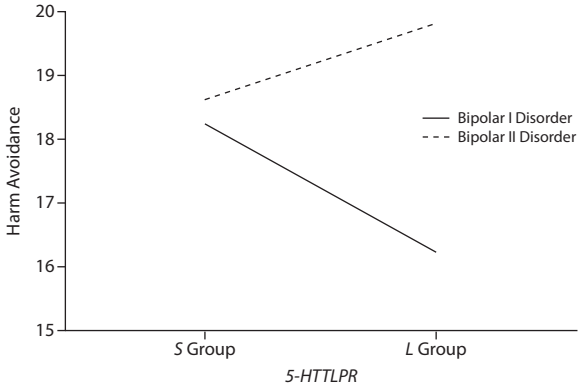
When older individuals were filtered from the healthy control group (n = 96, mean ± SD age = 34.51 ± 6.71 years), the mean ± SD harm avoidance scores (10.10 ± 4.49), mean ± SD

Table 2. Binary Logistic Regression[a]

Variable	Bipolar I Disorder vs Bipolar II Disorder[b]			
	B	Odds Ratio	95% CI	*P* Value
DRD3 Ser9Gly	−1.645	0.193	0.020–1.863	.155
5-HTTLPR	2.014	7.494	1.049–53.537	.045
Novelty seeking	−0.123	0.884	0.796–0.983	.022
Harm avoidance	0.100	1.105	1.108–1.200	.017
NS**DRD3 Ser9Gly*	0.081	1.084	0.950–1.237	.230
HA**5-HTTLPR*	−0.101	0.904	0.821–0.996	.042
*DRD3 Ser9Gly***5-HTTLPR*	0.117	1.124	0.322–3.919	.855

[a]Covarying for age and sex. Reference groups are *DRD3 Ser9Gly Gly+* group (*Ser/Gly* or *Gly/Gly*) and *5-HTTLPR L* allele carrier (*S/XL, S/L_A, L_A/XL, L_A/L_A*).
[b]Reference group.
*Interaction.
Abbreviations: *DRD3* = dopamine D_3 receptor gene, *5-HTTLPR* = serotonin transporter gene-linked polymorphic region, *Gly* = glycine, HA = harm avoidance, *L* = long allele, NS = novelty seeking, *S* = short allele, *Ser* = serine, *XL* = extra-long allele.

Figure 1. *5-HTTLPR* Genotypes Moderate the Association Between Harm Avoidance and Bipolar Disorders[a]



[a]Bipolar II disorder (BP-II) patients who carried the long allele at *5-HTTLPR* had higher harm avoidance scores than did bipolar I disorder (BP-I) patients with other genotypes at *5-HTTLPR* (BP-I = 16.23, BP-II = 19.80; *P* = .023).
Abbreviation: *5-HTTLPR* = serotonin transporter gene-linked polymorphic region.

novelty seeking scores (13.25 ± 4.21), and genotype distributions (*S/S* vs *L* carrier = 54% vs 46%; *Ser/Ser* vs *Gly+* = 45% vs 55%) of this younger healthy control group did not differ significantly from the whole healthy control group. There were no significant differences in these variables between men and women in the healthy control group (data not shown).

In the binary logistic regression analysis, the main effects for the *5-HTTLPR* genotypes (*P* = .045), novelty seeking (*P* = .022), and harm avoidance (*P* = .017) were all significant, and there was a significant interaction effect between harm avoidance and the *5-HTTLPR* genotypes (*P* = .042) in distinguishing between bipolar I and bipolar II disorder patients (Table 2).

5-HTTLPR genotypes moderated the association between harm avoidance and bipolar disorders (Figure 1). Bipolar I disorder patients who carried the L_A allele at *5-HTTLPR* had lower harm avoidance scores than did bipolar II disorder patients with the same allele (bipolar I disorder = 16.23, bipolar II disorder = 19.80; *P* = .023). However, the difference was not significant after the multiple comparison correction.

DISCUSSION

We found significant main effects for the *5-HTTLPR* genotypes, novelty seeking, and harm avoidance, and a significant interaction effect between harm avoidance and the *5-HTTLPR* genotypes that discriminated between bipolar I and bipolar II disorder patients. These findings are previously unreported evidence of a distinction between bipolar I and bipolar II disorder.

Because of the main and interaction effects that discriminated between the bipolar I and bipolar II disorder groups, we hypothesize that the distinction between bipolar I and bipolar II disorder relies on the interaction between genotypes and temperaments, especially between the *5-HTTLPR* genotypes and harm avoidance. Our direct survey indicated that harm avoidance might be sufficient for discriminating between bipolar I and bipolar II disorder patients in those who carry at least 1 long allele (*S/XL, S/L_A, L_A/XL,* and L_A/L_A genotypes) but not in those who carry the homozygous short alleles (*S/S, S/L_G,* and L_G/L_G genotypes) at *5-HTTLPR*. There was a trend that bipolar I disorder patients with the long allele at *5-HTTLPR* had lower harm avoidance scores than did bipolar II disorder patients with those genotypes at *5-HTTLPR*. It might be evidence that *5-HTTLPR* genotypes moderate the association between harm avoidance and each subtype of bipolar disorders.

We also found significant differences in temperament between euthymic bipolar patients and the healthy control group. The novelty seeking and harm avoidance scores of bipolar I disorder and bipolar II disorder groups were significantly higher than those of the healthy control group in post hoc tests, replicating the previously reported findings.[55–57]

Although the mean age and the percentage of males in the healthy control group was significantly higher than in the bipolar I and bipolar II disorder groups, all healthy control group members were included in multinomial logistic regression analysis, based on our a priori tests. When older individuals were filtered from the healthy control group, the harm avoidance and novelty seeking scores and the genotype distributions of this younger healthy control group did not differ significantly from the whole healthy control group. Further, we compared all these variables between men and women in the healthy control group and found no significant differences.

The results of the present study are different from those of our previous study,[58] in which the significant main effects for the *5-HTTLPR* genotypes, novelty seeking, and harm avoidance and the significant interaction effect between harm avoidance and the *5-HTTLPR* genotypes in discriminating bipolar I and bipolar II disorder groups did not appear. One reason for this might be the smaller sample sizes in our previous study. A second might be that, in the present study, we subdivided the long allele into the L_A and

L_G alleles, which refined the preliminary data of genotype distribution of the *5-HTTLPR* genotypes in Han Chinese in Taiwan. The distributions in our study were similar to those in Murakami et al.[34]

The harm avoidance temperament is characterized by worry, pessimism, fear of uncertainty, shyness, and fatigability.[59] Bipolar II disorder patients are preponderantly neurotic and have less ego resiliency and are less sociable than bipolar I disorder patients; they show greater interepisode mood instability,[1,57,60] which suggests that bipolar II disorder patients have a more chronic course of illness with mood episodes of longer duration than do bipolar I disorder patients. Here we found that only the bipolar II disorder patients with at least 1 *L* allele at the *5-HTTLPR* gene had higher harm avoidance scores than did the bipolar I disorder patients; therefore, we hypothesize that the *5-HTTLPR* gene moderates the expression of personality in these 2 subtypes of bipolar disorder. Having at least 1 long allele at the *5-HTTLPR* gene might be protective in bipolar I disorder but not in bipolar II disorder[34]; however, additional functional studies are needed to understand the possible relevance of the *5-HTTLPR* genotypes for temperament and BPD.

The polymorphisms of the *5-HTTLPR* genes have been examined in relation to anxiety traits in healthy populations[12,34] and in alcohol-dependent patients.[61,62] Our findings on the association of the *5-HTTLPR* genotypes and anxiety traits are generally different from those of Lesch et al[12] and more similar to those of Murakami et al,[34] which might be due to the differences between our study populations and other confounding factors. First, all of our subjects were ethnically homogeneous Han Chinese in Taiwan: ethnically homogeneous populations are crucial when analyzing genetics. However, in Lesch et al,[12] the study participants were primarily ethnically heterogeneous Caucasians and non-Hispanics. Because the genotype distributions at the *5-HTTLPR* gene might be largely different between Caucasians[12] and Asians,[34] the ethnic heterogeneity might have been confounding.

Second, we subdivided the long allele into 2 genotypes: L_A and L_G,[54] which gave us different groups from other studies. We combined individuals with the homozygous *L* allele and those with the heterozygous *L/S* genotype into the *L* group because of our very small populations with the homozygous *L* allele. The genotype distributions at the *5-HTTLPR* gene in the present study were similar to those in Murakami et al[34]; however, in our healthy control group, harm avoidance scores were not significantly different between the *S* and *L* groups, whereas in Murakami et al,[34] the *S* group had significantly higher anxiety scores. Lesch et al[12] combined participants with the heterozygous *L/S* genotype and those with the homozygous *S* allele based on their lower 5-HTT transcription activity and their lower 5-HT reuptake efficiency than those with the *L/L* genotype; they also found that *S*-group members had higher neuroticism scores. These differences might be due to our smaller study populations; larger study populations are needed to confirm our findings. The moderating effect of different measurement instruments might also explain the differences.[63]

Third, we excluded patients with comorbid alcohol abuse or dependence. The lifetime prevalence of alcohol dependence in Han Chinese is far less than in other ethnic groups.[64,65] Bipolar disorder patients often have comorbid alcohol abuse or dependence.[5] Chronic alcohol drinking may damage the brain and alter the brain functions of alcohol-dependent persons.[66–69] Such transformations may influence temperament.

A valid set of criteria for a diagnosis of bipolar disorder will provide a more differentiated research and treatment model for affective disorders and may permit us to more readily recognize bipolarity. The many aspects of bipolar disorder, such as genetics, temperament, episodes, age at onset, comorbidity, and course of illness, must be taken into account when diagnosing an affective disorder. Angst[70] suggested that using personality as a phenotype may help illuminate the unique and shared genetic liabilities for bipolar disorder, as well as help clarify how specific genes interact with other elements to cause bipolar psychopathology. The joint effects of genes, environment, and personality may be important for psychiatric genetics.[37,71–73]

This study had some limitations. First, the study population was small, which increases the risk of a type II error. A larger study population is also needed when one considers the hypothesis of polygenetic pathology and the possibility of gene × environment interaction effects on personality.[37,71,73] Second, Coryell et al[29] reported that 7.5% of bipolar II disorder patients developed manic episodes during a 10-year follow-up. Therefore, long-term follow-ups of bipolar II disorder patients are necessary. Third, the validity of self-reported temperament, particularly in psychiatric patients, remains unclear. Therefore, differences between clinical samples should be interpreted with caution. Finally, mood fluctuations in patients might, to some extent, affect the measurement of temperament.

In conclusion, we found differences between bipolar I and bipolar II disorder patients in gene and temperament variance interactions, which suggested that bipolar I disorder and bipolar II disorder are distinct subtypes of bipolar disorder. These differences merit further exploration in hopes that they will confirm the relevance of temperament and genetics to bipolar I and bipolar II disorder.

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