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ARTICLE

Gender-specific association of the *SLC6A4* and *DRD2* gene variants in bipolar disorder

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Abstract

Findings on the association between the risk for developing bipolar disorder and the functions of the *serotonin transporter-linked polymorphic region gene* (*5-HTTLPR*) and *dopamine D2 receptor gene* (*DRD2*) variants are contradictory. One explanation for this is that a gender difference may exist for genetic contributions. We compared the gender-related main effects and the gene-to-gene interaction between *serotonin transporter gene (SLC6A4)* and *DRD2* in adult male and female patients with bipolar I (BP-I) and bipolar II (BP-II) disorder. Patients with BP-I (n=400) and BP-II (n=493), and healthy controls (n=442) were recruited from Taiwan's Han Chinese population. The genotypes of the *5-HTTLPR* and *DRD2 Taq-IA* polymorphisms were determined using polymerase chain reaction–restriction fragment length polymorphism analysis. Logistic regression analysis showed a significant gender-specific association of the *DRD2 A1/A1* and the *5-HTTLPR S/S*, S/L_G, and L_G/L_G (*S+*) (p=0.01) genotypes in men with BP-I (p=0.002 and 0.01, respectively) and BP-II (p=0.001 and 0.007, respectively), but not in women. A significant interaction for the *DRD2 A1/A1* and *5-HTTLPR S+* polymorphisms was also found only in men with BP-I and BP-II (p=0.003 and 0.001, respectively). We provide preliminary evidence for a gender-specific effect of the *SLC6A4* and *DRD2* gene variants for the risk of BP-I and of BP-II. We also found gender-specific interaction between *5-HTTLPR* and *DRD2 Taq-IA* polymorphisms in patients with bipolar disorder.

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Introduction

Bipolar disorder is a severe mental illness associated with significant morbidity and mortality (Tsuang and Woolson, 1977; Coryell et al., 1993). Family, twin, and adoption studies (Wender et al., 1986; Craddock and Jones, 1999, 2001; Kelsoe, 2003) show that bipolar disorder is highly heritable and that the genetic factor contributes significantly to the development of this disorder. It is also recognized that bipolar disorder is a complex disorder with multiple genetic risk factors, and that it interacts with environmental factors as its underlying etiology (Schulze, 2010). It has been suggested (Weiss et al., 2005) that gender is a key factor, which can modify disease penetrance and expressivity, and that its effect is easier to determine than are other environmental factors. Clinical differences between genders in bipolar disorder have been described: women with bipolar disorder tend to have a higher risk than do men of developing bipolar II disorder (BP-II), rapid cycling and mixed episodes, more depressive episodes, and different comorbidities (Altshuler et al., 2010; Diflorio and Jones, 2010; Nivoli et al., 2011). Sexual dimorphism has also been reported (Cahill, 2006) to occur in a wide array of neurotransmitter systems, including serotonin and monoamine; dysregulation of these neurotransmitter systems is reported (Scott et al., 1979; Kapur and Mann, 1992) to have been involved in the pathogenesis of bipolar disorders. Therefore, gender differences may be a critical consideration for dissecting the genetic architecture of bipolar disorder.

The two most common documented subtypes of bipolar disorder are bipolar I disorder (BP-I) and BP-II. Although there is still some controversy about whether BP-II is simply a milder form of BP-I or is a distinct

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disorder, many studies (Judd et al., 2003a; Kelsoe, 2003; Akiskal et al., 2006) have reported that BP-I and BP-II have different etiologies and characteristics. Family and genetic studies have also shown the different genetic liabilities between BP-I and BP-II (Coryell et al., 1984; Sadovnick et al., 1994; Benazzi, 2007; Lee et al., 2010, 2011). In addition, although some studies (McMahon et al., 1995; Preisig et al., 2000; Dao et al., 2010; Xu et al., 2012) have suggested gender differences in the genetic risk factors for bipolar disorder, the number of studies that focus on the gender effect in the different subtypes of bipolar disorder is limited. Whether there are different gender-specific effects related to the genetic vulnerability for BP-I and BP-II requires further study.

Studies have suggested that the serotonin system is involved in the pathogenesis of bipolar disorder (Vawter et al., 2000; Muller-Oerlinghausen et al., 2002) and that genes encoding serotonin transporter (*SLC6A4*) are considered as candidate genes (Cho et al., 2005). The most studied susceptibility locus of the *SLC6A4* gene is a 44-base pair (bp) insertion/deletion within the promoter region that has two allelic forms: the long variant (*L*) and the short variant (*S*); it is termed the *5-HTT* gene-linked polymorphic region (*5-HTTLPR*) (Lesch et al., 1996). Carriers of the *S* variant show a significant reduction in serotonin transporter functional capacity *in vitro* (Heils et al., 1996; Lesch et al., 1996). In an *in vivo* imaging study (Heinz et al., 2000) and in a post-mortem brain study (Little et al., 1998), the *5-HTTLPR* polymorphisms were also associated with the binding availability of serotonin transporter. In addition to the *S* and *L* alleles, other variants of the *L* allele have been documented (Hu et al., 2005, 2006), which suggests that only the long variant with an adenosine at the single nucleotide polymorphism (SNP) rs25531 (L_A) expresses higher levels of *5-HTT* than does the long variant with a guanine at rs25531 (L_G), which, like the *S* allele, expresses lower levels. Other uncommon alleles longer than the *L* allele have also been reported (Delbruck et al., 1997; Gelernter et al., 1997; Kunugi et al., 1997; Nakamura et al., 2000; Narita et al., 2001). The extra-long alleles ('novel allelic variants') are called *XL* variants; they have 15, 18, 19, 20, or 22 repeats with unknown functions. Therefore, the past dichotomous classification of *5-HTTLPR* into *S* and *L* alleles may not be sufficient for investigating bipolar disorder. Moreover, the results of genetic association studies between the *SLC6A4* gene and bipolar disorder are controversial (Rees et al., 1997; Furlong et al., 1998b; Ospina-Duque et al., 2000; Mellerup et al., 2001; Hauser et al., 2003; Sun et al., 2004; Cho et al., 2005). Analyzing the novel tri-allelic (*S*, L_G, and L_A) *5-HTTLPR* polymorphism and considering the effect of gender difference in bipolar disorder may give us more detailed and convincing genetic association data.

Dopaminergic system dysfunction has also been implicated in the development of bipolar disorder. Dopamine agonists may induce manic episodes or manic-like symptoms (Murphy et al., 1971; Silverstone and Romans-Clarkson, 1989); dopamine-receptor antagonists are used to treat mania (Diehl and Gershon, 1992). In contrast, depressive symptoms are frequently found in diseases with dopamine deletion, such as Parkinson's disease (Taylor and Saint-Cyr, 1990), and dopaminergic drugs can augment the effect of antidepressants in patients with treatment-resistant depressive disorders (Nierenberg et al., 1998). Therefore, genes encoding dopamine receptors may be important candidates for investigating bipolar disorder. The *dopamine D2 receptor gene* (*DRD2*) encodes the D2 subtype of the dopamine receptor, which contains the *Taq-IA* (rs1800497) restriction fragment length polymorphisms *(RFLP)*. This polymorphism, recorded as *A1* and *A2*, has been linked to the density and functional effects of *DRD2* (Pohjalainen et al., 1998; Jonsson et al., 1999). *DRD2* density is lower in *A1* allele carriers than in homozygotic *A2* allele carriers (Noble et al., 1991; Ritchie and Noble, 2003). However, the exact location of the *Taq-IA* polymorphism was not identified until the ankyrin repeat and kinase domain containing-1 gene *(ANKK1)* was found (Neville et al., 2004). The *Taq-IA* polymorphism causes a missense mutation *(Glu713Lys)* in the 11th ankyrin repeat site and this polymorphism is actually located in the downstream region that extends to the *DRD2* gene (Yang et al., 2007). The changes in *ANKK1* activity may affect *DRD2* expression and provide additional explanation from previously described associations between the *DRD2 Taq-IA RFLP* and neuropsychiatric disorders (Neville et al., 2004; Bontempi et al., 2007). The *DRD2/ANKK1 Taq-IA* polymorphism has also been associated with bipolar disorder (Li et al., 1999; Massat et al., 2002; Zou et al., 2012). However, this finding is inconsistent with other studies (Souery et al., 1996; Furlong et al., 1998a; Stober et al., 1998; Bocchetta et al., 1999; Kirov et al., 1999; Leszczynska-Rodziewicz et al., 2005). To evaluate the gender effect of the *DRD2* gene for the risk of bipolar disorder may reduce the heterogeneity and controversy.

Because bipolar disorder is a complex disease, and because individual genes may have only weak effects on the development of bipolar disorder, a gene-to-gene interaction approach may be needed (Carlson et al., 2004; Craddock and Sklar, 2009). Studies (Guiard et al., 2008; Di Giovanni et al., 2010) have shown that serotonin modulates dopamine neuron activity – possibly inhibiting its expression – and that this is more marked in the mesocorticolimbic dopamine system. Different *DRD2/ANKK1 Taq-IA* genotypes may also have different levels of monoamine metabolites, including 5-hydroxyindoleacetic acid (5-HIAA) in lumbar cerebrospinal fluid, which implies that *DRD2/ANKK1-Taq IA* polymorphism affects serotonin system activity (Jonsson et al., 1996). Furthermore, genetic studies (Wu et al., 2008; Karpyak et al., 2010) have shown that the interaction between *DRD2* and *SLC6A4* variants was associated with certain types of alcoholism. Therefore, we hypothesized that the interaction

between *DRD2* and *5-HTTLPR* polymorphisms may be related to several other mental illnesses, including bipolar disorder.

In this report, we attempt to clarify the association between the *DRD2* and *SLC6A4* genes and their interaction with BP-I and BP-II by using gender as a grouping variable. We hypothesized that men and women with bipolar disorder have different genetic vulnerabilities.

Methods

Participants

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at Tri-Service General Hospital and at National Cheng Kung University Hospital, Taiwan. To minimize the effect of ethnic differences in gene frequencies, we recruited only study participants who were unrelated and came from the Han Chinese population in Taiwan. The procedures were fully explained to all participants before they were asked to sign the informed consent.

Patients with bipolar disorder were recruited both from outpatient and from inpatient settings. All participants were initially evaluated by an attending psychiatrist and then received a more detailed interview by a clinical psychologist using the Chinese version of the modified Schedule of Affective Disorder and Schizophrenia-Life Time (SADS-L) (Endicott and Spitzer, 1978), which has good inter-rater reliability (Huang et al., 2004), to determine the diagnosis. Inclusion criteria were a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edn)-based diagnosis of bipolar disorder, either first-onset or with previous episodes. Patients with major or minor mental illnesses other than bipolar disorder were excluded.

Epidemiologic data (Akiskal et al., 1977, 1979; Spitzer et al., 1979; Angst, 1998; Benazzi, 2001; Angst et al., 2003; Judd et al., 2003b) suggest that 2-d hypomanic episodes are more prevalent in community samples, and that the original 4-d minimum duration required in the DSM-IV for a diagnosis was not evidence-based. Therefore, we used a 2-d cutoff for hypomania in the diagnosis of BP-II instead of the DSM-IV 4-d criterion.

Healthy controls (n=442) were recruited from the community. Their psychiatric conditions were also screened using the Chinese Version of SADS-L. No controls had a history of major mental illness or a current mental illness, and none had a family history of psychiatric disorder among their first-degree relatives.

Blood samples and genotyping

Twenty milliliters of blood was drawn from each participant, and standard methods were used to extract genomic DNA from the lymphocytes. The *DRD2/ANKK1 Taq-IA* functional polymorphism was determined using a polymerase chain reaction–restriction fragment length polymorphism assay (PCR-RFLP) (Grandy et al., 1993). The *5-HTTLPR* functional polymorphisms were genotyped using PCR-RFLP analysis (Lesch et al., 1996). The A/G SNP of the *L* allele was determined using a modified protocol (Maron et al., 2009). All samples were re-genotyped and double checked. The genotype error rate was less than 5%.

Statistics

One-way analysis of variance (ANOVA) and Bonferroni *post-hoc* tests were used to determine the mean age differences between patients with bipolar disorder and controls. Pearson χ^2 analysis was used to examine the gender differences. Because there is no functional difference in the SNPs of S_A and S_G (Wendland et al., 2006), both the S_A and S_G alleles were recorded as the *S* allele. Because *S* and L_G carriers express lower levels of 5-HTT (Heils et al., 1996; Lesch et al., 1996; Heinz et al., 2000; Hu et al., 2005, 2006), we divided the *5-HTTLPR* polymorphisms into two groups, low-functional (*S*/*S*, *S*/L_G, L_G/L_G: hereafter *S*+) and high-functional (*S*/L_A, L_G/L_A, L_A/L_A, *S*/*XL*, L_A/*XL*, L_G/*XL*: hereafter *L*+), for data analysis. Because there were only 11 controls and 13 patients who carried the L_A/L_A genotype, we did not separate the homozygous L_A and heterozygous L_A carriers into two groups. The differences in the genotype frequencies of *5-HTTLPR* and *DRD2 Taq-IA* polymorphisms between men and women in all three groups were calculated using Pearson χ^2 analysis (two-tailed). Hardy–Weinberg equilibrium was assessed for each group.

Logistic regression was used to control the effect of the possible covariates of age when examining the main effects and the effects of gene-to-gene interaction of the *DRD2* and *SLC6A4* genes in men and women for the risk of BP-I and BP-II in compared with controls. The associations are expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). *P*-values are two-tailed, and significance was set at $p<0.05$. However, considering the possible effect of multiple comparisons in regression, we performed Bonferroni correction. We adjusted our significant *P*-value as 0.01. SPSS 17.0 for Windows was used for statistical analyses. The power analysis was done using G-Power* 3 (Faul et al., 2007, 2009).

Results

Of the 1335 participants in the study, 400 had BP-I, 493 had BP-II, and 442 were healthy controls. Significantly ($p<0.001$) more women than men were in the BP-I and BP-II groups than in the control group (Table 1). Moreover, the age difference was significant between the BP-II and control groups ($p=0.001$), but not between the BP-I and control groups ($p=0.13$) (Table 1). Other demographic data, such as education, tobacco smoking, substance or alcohol abuse history, medication history

Table 1. Demographic data for patients with bipolar disorder and healthy controls

	Age			Gender			
Group	*n*	Mean±S.D.	*P*-value	Male	Female	χ^2	*P*-value
BP-I	400	33.7±12.5	0.001*[a]	186 (46.5%)	214 (53.5%)	81.15[a]	<0.001*[a]
BP-II	493	32.6±12.0	0.13[b]	239 (48.5%)	254 (51.5%)	64.30[b]	<0.001*[b]
Healthy controls	442	35.3±9.7	0.001*[c]	325 (73.5%)	117 (26.5%)	61.10[c]	<0.001*[c]

[a] BP-I *vs.* BP-II *vs.* controls.
[b] BP-I *vs.* controls.
[c] B-II *vs.* controls.
BP-I *vs.* BP-II: Age: $p=0.40$; gender: $\chi^2=0.35$, $p=0.56$.
*$p<0.05$.

were not significantly different between BP-I and BP-II. The age onset of BP-II was significantly younger than BP-I (18.4±6.0 *vs.* 25.2±11.3, $p<0.001$). BP-I had a higher percentage to comorbid with systemic medical diseases than BP-II ($\chi^2=4.47$, $p=0.04$). In addition, bipolar patients had lower educational level, higher rate of tobacco smoking and medical comorbidities than controls ($p<0.001$).

The genotype distributions of the *DRD2/ANKK1 Taq-IA* and *5-HTTLPR* polymorphisms for each group were in Hardy–Weinberg equilibrium ($p>0.05$), except for *5-HTTLPR* in the BP-II group. Because the *5-HTTLPR XL* allele included multiple different repeats, simplifying the different repeats may have biased the Hardy–Weinberg equilibrium calculation. The distribution of the *5-HTTLPR* genotype was significantly ($p=0.01$) different between the BP-I, BP-II, and the control groups, and a higher percentage of *5-HTTLPR S+* genotypes was found in the BP-I and BP-II groups. However, there was no significant difference in the distribution of the *DRD2 Taq-IA* polymorphisms between three groups. Further analysis of the gender difference revealed that the significantly different distribution of the *5-HTTLPR* genotype was only in men (Table 2). Multiple logistic regression analysis, done to control for the possible covarying effect of age, used the healthy control, *DRD2 A2/A2*, and *5-HTTLPR L+* groups as reference groups. It showed a significant association between the *DRD2/ANKK1 Taq-IA* polymorphisms and patients with BP-I (OR=4.25, $p=0.003$) and an association between *DRD2* and *SLC6A4* and BP-II (OR=5.49 and 2.04, $p<0.001$ and 0.003, respectively). There was a significant interaction between the *DRD2/ANKK1 Taq-IA* and *5-HTTLPR* polymorphisms in BP-I and BP-II (OR=0.16 and 0.13, $p=0.001$ and <0.001, respectively) (Tables 3 and 4). A gender-specific association of the *DRD2, 5-HTTLPR* polymorphisms and the risk for BP-I and BP-II was also found in the regression model. The association between *DRD2, 5-HTTLPR*, and the gene-to-gene interaction effect for BP-I was found in male patients ($p=0.002$, 0.01 and 0.003, respectively) but not in female patients (Table 3). There were both main effects and an interaction effect of the *DRD2* and *SLC6A4* genes for the risk of BP-II in male patients ($p=0.001$, 0.007, and 0.001, respectively), although not in female patients with BP-II (Table 4).

According to Faul et al. (2007, 2009), effect size is determined as follows: small effect size=0.10, medium effect size=0.30, large effect size=0.50. In the genotype frequency analysis, the study power of the total sample, male patients, and female patients was 0.63, 0.40, and 0.27, respectively, to detect a small effect, 1.00, 0.99, and 0.99 to detect a medium effect, and 1.00 (both) to detect a large effect in the BP-I group. For the BP-II group, the study power was 0.68, 0.44, and 0.30 to detect a small effect, 1.00, 0.99, and 0.99 to detect a medium effect, and 1.00 to detect a large effect.

Discussion

Using gender as a grouping variable, we found a gender-specific association between bipolar disorder and the *SLC6A4* and *DRD2* genes. Moreover, men with BP-I and BP-II showed a gene-to-gene interaction effect of *DRD2* and *SLC6A4* for the risk of bipolar disorder; this effect was gender-specific. These intriguing findings were in line with the growing evidence about gender-specific genetic effects on behaviors and brain function (Cahill, 2006). Sexually dimorphic biological and physiological functions caused by sex-based chromosomal differences (Jazin and Cahill, 2010), gonadal hormone secretions (Ngun et al., 2011), and neuroanatomical and neurochemical mechanisms (Cahill, 2006) contribute to sex-based differences in behaviors. Studies (Nishizawa et al., 1997; Zhang et al., 1999; Weiss et al., 2005) have reported sex-based differences in the serotonin system, including the different rate of serotonin synthesis (Nishizawa et al., 1997), the levels of serotonin metabolites (Gottfries et al., 1974), and the number of cells in the human raphe nucleus (Cordero et al., 2001). Estrogen also decreases *5-HTT* gene expression (Bethea et al., 1998)

Table 2. Genotype distributions of *DRD2/ANKK1 Taq-IA* and *5-HTTLPR* polymorphisms in patients with bipolar disorder and healthy controls by gender

All (n)	BP-I 400	BP-II 493	Controls 442	χ^2	*P*-value
DRD2					
A1/A1	57 (14.3%)	70 (14.2%)	65 (14.7%)	4.11	0.39
A1/A2	183 (45.8%)	244 (49.5%)	191 (43.2%)		
A2/A2	160 (40.0%)	179 (36.3%)	186 (42.1%)		
5-HTTLPR					
S+	301 (75.3%)	370 (75.1%)	298 (67.4%)	8.86	0.01*
L+	99 (24.8%)	123 (24.9%)	144 (32.6%)		
Male (n)	186	239	325		
DRD2					
A1/A1	31 (16.7%)	36 (15.1%)	43 (13.2%)	4.13	0.39
A1/A2	80 (43.0%)	116 (48.5%)	139 (42.8%)		
A2/A2	75 (40.3%)	87 (36.4%)	143 (44.0%)		
5-HTTLPR					
S+	142 (76.3%)	185 (77.4%)	216 (66.5%)	10.18	0.01*
L+	44 (23.7%)	54 (22.6%)	109 (33.5%)		
Female (n)	214	254	117		
DRD2					
A1/A1	26 (12.1%)	34 (13.4%)	22 (18.8%)	3.51	0.48
A1/A2	103 (48.1%)	128 (50.4%)	52 (44.4%)		
A2/A2	85 (39.7%)	92 (36.2%)	43 (36.8%)		
5-HTTLPR					
S+	159 (74.3%)	185 (72.8%)	82 (70.1%)	0.68	0.71
L+	55 (25.7%)	69 (27.2%)	35 (29.9%)		

5-HTTLPR S+: S/S, S/L_G, L_G/L_G.
5-HTTLPR L+: S/L_A, L_A/L_G, L_A/L_A, S/XL, L_G/XL, L_A/XL.
* $p<0.05$.

but increases 5-HTT protein density (Bethea et al., 2002). The contradictory findings are the result of a reduction of 5-HTT degradation caused by the stabilizing effect promoted by estrogen (Bethea et al., 2002). Furthermore, women carrying *5-HTTLPR S/S* genotypes had higher CSF 5-HIAA levels than did men carrying them (Williams et al., 2003). Genetic studies (Baune et al., 2008; Brummett et al., 2008) have also reported gender-specific associations between the *SLC6A4* gene polymorphisms and several psychiatric disorders, including depressive disorder. Compared with prior reports, our study provides additional evidence of a gender-specific association between BP-I, BP-II, and *SLC6A4* gene polymorphisms. Whether the association of the *SLC6A4* gene and bipolar disorder exists only in males is unknown; however, we hypothesized that female carry *5-HTTLPR S+* genotypes may have a higher serotonergic function than do male carriers, which partially decreases the risk for the *5-HTTLPR S+* allele to lead to the development of bipolar disorder. Additional studies to investigate the underlying mechanisms are still required.

The inconsistent findings on the association between the *SLC6A4* gene and bipolar disorder have been reported (Rees et al., 1997; Ospina-Duque et al., 2000; Mellerup et al., 2001; Cho et al., 2005). We suggest that not considering the effect of gender explains these inconsistencies, because sex-based differences in the serotonin system have been well documented. There may be other reasons as well. For example, the allele frequency of *5-HTTLPR* is different in Asians and Westerners. As in our study, other studies (Kunugi et al., 1997; Ohara et al., 1998; Sun et al., 2004) reported higher percentages of the low-functional variants of *5-HTTLPR* in control groups containing Asians. Moreover, our current study analyzed the newer tri-allelic polymorphisms of *5-HTTLPR* instead of the classical *S* and *L* alleles. The L_G and L_A alleles are functionally different (Hu et al., 2005, 2006), and past dichotomous classification of *5-HTTLPR* may have improperly subgrouped some genotypes, such as S/L_G, L_G/L_A, and L_G/L_G, and caused confusing and inaccurate results. Because only a small percentage (<5%) of our participants carried the *5-HTTLPR* L_A/L_A genotype and some of our participants carried the *XL* allele, we combined participants carrying the L_A/L_A with those carrying the S/L_A, L_G/L_A and *XL* variants into the high-functional group (*L+*).

Table 3. Logistic regression analysis of *DRD2/ANKK1 Taq-IA* and *5-HTTLPR* polymorphisms and their interaction for the risk of BP-I by gender

	All			Male			Female		
	B	Odds ratio	*P*-value	B	Odds ratio	*P*-value	B	Odds ratio	*P*-value
DRD2 A1/A1	1.45	4.25	0.003*	1.99	7.33	0.002*	0.81	2.25	0.34
DRD2 A1/A2	0.02	1.02	0.93	0.35	1.42	0.38	−0.42	0.66	0.36
5-HTTLPR S+	0.53	1.71	0.03	0.89	2.43	0.01*	0.16	1.17	0.70
*5-HTTLPR S+*DRD2A1/A1*	−1.82	0.16	0.001*	−2.14	0.12	0.003*	−1.64	0.19	0.08
*5-HTTLPR S+*DRD2A1/A2*	0.13	1.14	0.70	−0.35	0.71	0.45	0.60	1.82	0.28

* $p<0.01$.
5-HTTLPR S+: S/S, S/L_G, L_G/L_G.
5-HTTLPR L+: S/L_A, L_A/L_G, L_A/L_A, S/XL, L_G/XL, L_A/XL.
Reference group: healthy controls, *5-HTTLPR L+, DRD2 A2/A2*.
Covarying for age.

Table 4. Logistic regression analysis of *DRD2/ANKK1 Taq-IA* and *5-HTTLPR* polymorphisms and their interaction for the risk of BP-II by gender

	All			Male			Female		
	B	Odds ratio	*P*-value	B	Odds ratio	*P*-value	B	Odds ratio	*P*-value
DRD2 A1/A1	1.70	5.49	<0.001*	2.15	8.56	0.001*	1.20	3.33	0.15
DRD2 A1/A2	0.45	1.56	0.10	0.53	1.70	0.16	0.10	1.11	0.82
5-HTTLPR S+	0.71	2.04	0.003*	0.93	2.53	0.007*	0.36	1.43	0.37
*5-HTTLPR S+*DRD2 A1/A1*	−2.02	0.13	<0.001*	−2.28	0.10	0.001*	−1.93	0.15	0.04
*5-HTTLPR S+*DRD2 A1/A2*	−0.19	0.83	0.55	−0.31	0.74	0.49	0.07	1.07	0.90

* $p<0.01$.
5-HTTLPR S+: S/S, S/L_G, L_G/L_G.
5-HTTLPR L+: S/L_A, L_A/L_G, L_A/L_A, S/XL, L_G/XL, L_A/XL.
Reference group: healthy controls, *5-HTTLPR L+, DRD2 A2/A2*.
Covarying for age.

This combination may also have made our study results different from those of others. It is also important that our patients had no other major and minor psychiatric comorbidities, including the highly comorbid anxiety disorder. Our previous study showed that Han Chinese in Taiwan had a lower-than-average comorbidity rate of anxiety disorder, from 26.7% in the BP-I group to 39.0% in the BP-II group (Chang et al., 2012) rather than the 90% in reports on Westerners (Kessler et al., 1997, 1999; Merikangas et al., 2007). Because the comorbidity rates in non-Asians with bipolar disorder are very high, it is possible that many members of the samples in other studies had comorbidities that our sample did not have, which might lead to conflicting results.

Past studies also found that dopamine neurotransmission was higher in females than in males, possibly due to the modulatory effects of gonadal hormones (Cyr et al., 2002). Estrogen was reported to modulate the dopamine receptors in the striatum and nucleus accumbens. Ovariectomized rats had a lower-than-normal density of D2 receptors, but the density increased in ovariectomized rats treated with β-estradiol (Le Saux et al., 2006). In a human positron emission tomography (PET) study, higher D2 receptor binding in the female cortex was also found (Kaasinen et al., 2001). The gender-specific effect of the *DRD2* gene for the risk of bipolar disorder was shown in the current study. Our data partially explain prior inconsistent findings of an association between the *DRD2* gene polymorphisms and bipolar

disorder (Souery et al., 1996; Furlong et al., 1998b; Stober et al., 1998; Bocchetta et al., 1999; Kirov et al., 1999; Leszczynska-Rodziewicz et al., 2005; Zou et al., 2012), because most of the studies did not consider the gender effect. Although the *DRD2 Taq IA A1* allele is associated with lower dopaminergic activity and may be related to the development of bipolar disorder (Noble et al., 1991; Li et al., 1999; Massat et al., 2002; Zou et al., 2012), estrogen may increase dopamine neurotransmission and *DRD2* gene expression in women with the *DRD2 A1/A1* genotype, which reduces the risk of the *DRD2 A1/A1* genotype for bipolar disorder. However, determining the exact mechanisms for this gender-specific effect of the *DRD2* gene requires additional studies to confirm.

An interaction between the *DRD2 A1/A1* and the *5-HTTLPR S+* genotypes in men with BP-I and BP-II, but not in women was also found in this study. The functionally relevant but opponent serotonin–dopamine interactions have been well demonstrated in models of some psychopathological conditions, reinforcement learning, and impulse control (Kapur and Remington, 1996; Winstanley et al., 2005; Boureau and Dayan, 2011). Although the detailed physiological mechanism of the interaction between the low-functional variants of the *5-HTTLPR* and *DRD2* genes remains unknown, substantial experimental evidence suggests that 5-HT regulates dopaminergic activity through different subtypes of 5-HT receptors (Esposito et al., 2008; Boureau and Dayan, 2011). The *5-HTTLPR S/S, S/L_G, L_G/L_G* genotype has been associated with reduced reuptake of serotonin (Greenberg et al., 1999), which may increase serotonin's tonic inhibition of dopaminergic transmission through the 5-HT2C receptor in the prefrontal cortex (Gobert et al., 2000) or stimulate the ventral tegmental area (VTA) and increase dopamine release in the nucleus accumbens through other 5-HT receptor types (5-HT1A, 5-HT2A, 5-HT3, 5-HT4) (Beart and McDonald, 1982; Guan and McBride, 1989; Van Bockstaele et al., 1994). Other studies (Pohjalainen et al., 1998; Jonsson et al., 1999) have also shown that the *DRD2 Taq-IA A1/A1* genotype-encoded D2 receptors have lower binding activity. Therefore, the combined effect of both low-functional variants of *5-HTTLPR* and *DRD2* genes may increase dopaminergic activity in the nucleus accumbens or decrease activity in the prefrontal cortex compared with the single effect of *DRD2 A1/A1* only, and it may possibly be linked to the development of bipolar disorder. In addition, the dysfunction of the amygdala, nucleus accumbens, and prefrontal cortex may be involved in the etiology of bipolar disorders (Leibenluft et al., 2003; Dickstein et al., 2005). The brain morphology is also sexually dimorphic (Cahill, 2006). The structure, volume, response to stimuli, and development process were all different between genders in the amygdala (Giedd et al., 1997; Cahill et al., 2001; Canli et al., 2002), nucleus accumbens (Lenroot et al., 2007; Geller et al., 2009), and prefrontal cortex (Goldman et al., 1974; Shansky et al., 2004). It is suspected that sexually dimorphic changes in the amygdala, nucleus accumbens, and prefrontal cortex, together with sex-based neurotransmitter regulation, may be the underlying cause for the gender-specific effect of the interaction of the *SLC6A4* and *DRD2* genes in bipolar disorder.

Although the treatment response of lithium and valproate seems not have gender difference (Viguera et al., 2000; Geddes et al., 2010), studies of olanzapine or olanzapine/fluoxetine combination therapy showed a gender different treatment response. In depressed male BP-I patients, predominantly manic polarity had significant better improvement than men with predominantly depressive polarity and this difference was not observed in the female patients (Vieta et al., 2009). Olanzapine is a serotonin–dopamine antagonist (SDA) and we supposed that its treatment effect may be partly affected by serotonin or dopamine related genes. Our study showed a significant gender-specific association between *DRD2, SLC6A4* gene and gene-to-gene interaction and bipolar disorder, which indicated that male and female bipolar patients may have different vulnerability in neurotransmitter systems and result in different treatment responses of SDAs. However, studies to compare the gender difference of SDAs treatment results in bipolar disorder were still limited. Further studies to compare the neuropsychopharmacological differences of SDAs or other serotonin–dopamine related agents between genders for bipolar disorder are necessary.

This study has several limitations. First, there were significant differences in age and gender between the patient and the control groups. It is better to recruit healthy controls who are age- and sex-matched to the patients. A control group with an older cohort may decrease the possibility that the controls will develop bipolar disorder when they get older, which will bias the findings. In addition, we used gender as a grouping variable and analyzed the specific gender effect for BP-I and BP-II. We also did a multiple logistic regression analysis to control for the confounding effects of age when examining both the main effect of each polymorphism and gene-to-gene interaction. Second, although the current sample size was fairly large in comparison with other genetic association studies, our sample of female controls was relatively small. Nevertheless, there was no significant difference in the genotype distribution between male and female controls (for *DRD2* and *5-HTTLPR* genotype distribution: $p=0.229$ and $p=0.473$; data not shown). The genotype distribution in the female control group was in Hardy–Weinberg equilibrium ($p>0.1$), which indicated that our female controls were a random and representative sample. Future studies that include more female controls may be needed for more powerful results. Third, about 7.5% of the patients diagnosed with BP-II became manic in a 10-year follow-up study (Coryell et al., 1995). Therefore, psychiatrists should be aware of

the possibility of a misdiagnosis with current subtypes, and long-term follow-ups for patients with BP-II to confirm these findings may be needed. In addition, the function of the *5-HTTLPR XL* allele remains unknown, although one study (Goldman et al., 2010) has suggested that it may function as an *L* allele. The genotype distribution of the *5-HTTLPR* in BP-II was not in Hardy-Weinberg equilibrium, which was supposed to be related to different multiple repeats of the *XL* allele and to cause inaccurate calculations. Additional studies will be required to test the function of the *XL* allele, because a significant percentage of Han Chinese carry this allele (Goldman et al., 2010). However, we should still keep in mind the possibility that our BP-II sample may not be a random sample because the distribution of the *5-HTTLPR* genotypes was not in Hardy–Weinberg equilibrium. Another limitation is the absence of replication in the current study. Because we spent more than 2 years collecting the current sample, it will be difficult for us to quickly recruit another sample. In future studies, we will recruit another population of patients with bipolar disorder and do a replication study. Other functional polymorphisms in these two genes, such as *DRD2-141C Ins/Del* and *SLC6A4 STin2 VNTR*, should be examined in future studies as well. Therefore, our current study results should be interpreted with caution.

Despite these limitations, our report provided evidence for a gender-specific role of *DRD2* and *SLC6A4* genes in both BP-I and BP-II. The present study also showed the importance of the gender-specific gene-to-gene interaction effect between the *DRD2* and *SLC6A4* genes and bipolar disorder.

Author Disclosures

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Conflicts of Interest

None.

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