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Influence of TPH2 variants on diagnosis and response to treatment in patients with major depression, bipolar disorder and schizophrenia

Alessandro Serretti [a], Alberto Chiesa [a], Stefano Porcelli [a], Changsu Han [b], Ashwin A. Patkar [c], Soo-Jung Lee [d], Moon Ho Park [e], Chi-Un Pae [c,d,*]

[a] Institute of Psychiatry, University of Bologna, Bologna, Italy
[b] Department of Psychiatry, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea
[c] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA
[d] Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, Bucheon, Kyounggi-Do, Republic of Korea
[e] Department of Neurology, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea

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ABSTRACT

The present study is aimed at exploring whether some single nucleotide polymorphisms (SNPs) within the tryptophan hydroxylase 2 gene *(TPH2)* could be associated with major depression (MD), bipolar disorder (BD) and schizophrenia and whether they could predict clinical outcomes in Korean in-patients treated with antidepressants, mood stabilizers and antipsychotics, respectively. One hundred forty-five patients with MD, 132 patients with BD, 221 patients with schizophrenia and 170 psychiatrically healthy controls were genotyped for six *TPH2* SNPs (rs4570625, rs10748185, rs11179027, rs1386498, rs4469933, and rs17110747). Baseline and final clinical measures, including the Montgomery-Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale and Positive and Negative Syndrome Scale, for patients with MD, BD and schizophrenia, respectively were recorded. None of the SNPs under investigation were associated with MD, BD and schizophrenia. However, in patients with MD, the rs4570625-rs10748185 G-A haplotype was significantly associated with higher endpoint MADRS severity, though not with response. Our results suggest that TPH2 variants neither have a major role in MD, BD and schizophrenia nor in response to treatments.

1. Introduction

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of serotonin. It converts the amino acid tryptophan to 5-hydroxytryptophan, which is then decarboxylated into serotonin (Walther and Bader, 2003). Two isoforms, TPH1 and TPH2, are known. While TPH1 is mostly expressed in the periphery and only partially in the brain, TPH2 is exclusively expressed in neuronal cell types (Invernizzi, 2007), particularly in the raphe nuclei where the vast majority of serotonergic cell bodies are located (Walther and Bader, 2003; Patel et al., 2004; Zill et al., 2007). Following the discovery of the TPH2 in TPH1-homozygous knockout mice that continued to produce 5-HT in the brain but not in other tissues (Walther and Bader, 2003), increasing attention has been given to the role of the human homologue TPH2 located on chromosome 12q21 in mental diseases, as this is a positional candidate region for several psychiatric disorders such as major depression (MD) and bipolar disorder (BD) (Morissette et al., 1999; Abkevich et al., 2003; Curtis et al., 2003). In addition, taking into account the significant role of serotonin in mood control as well as in a wide variety of functions, including, among the others, regulation of sleep, pain perception, hormonal activity, cognition, aggression, sexual drive, appetite and energy level (Azmitia, 2007), it is not surprising that consistent efforts have been recently paid to uncover whether genetic variants within TPH2 could play a major role into the development and response to treatment of several psychiatric disorders. Indeed, serotonin is largely involved in both mood disorders and schizophrenia, as demonstrated also by the therapeutic effect of serotonin modulators.

The findings suggest a possible involvement of TPH2 in the etiology and response to drugs in MD. First of all, in drug-free depressed patients who committed suicide, the levels of TPH protein and TPH2 mRNA in the dorsal raphe nucleus have been found to be higher as compared with matched healthy controls (Boldrini et al., 2005; Bach-Mizrachi et al., 2006). Also, such patients had more TPH2 grain density per neuron in the dorsal raphe nucleus than controls (Bach-Mizrachi et al., 2006). In addition, in an animal model expressing a TPH2 variant similar to a rare human variant (R441H) previously associated with MD, the expression of such mutant TPH2 resulted in markedly decreased brain 5-HT production and led to behavioral abnormalities related to depression and anxiety (Beaulieu

* Corresponding author at: Department of Psychiatry, Bucheon St. Mary's Hospital, the Catholic University of Korea College of Medicine 2 Sosa-Dong, Wonmi-Gu, Bucheon, Kyeonggi-Do 420 717, Republic of Korea. Tel.: +82 32 340 7067; fax: +82 32 340 2255.
E-mail address: pae@catholic.ac.kr (C.-U. Pae).

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et al., 2008). Of further interest, several case-control studies have suggested that several TPH2 genetic variants could be associated with MD in both Caucasian (Zill et al., 2004; Zhang et al., 2005; Zhou et al., 2005; Van Den Bogaert et al., 2006; Haghighi et al., 2008) and Chinese (Tsai et al., 2009) patients suffering from MD, even though contrasting results have been reported as well (Garriock et al., 2005; Gizatullin et al., 2008; Mann et al., 2008; Illi et al., 2009). Additionally, several variants in TPH2 have been linked to response to antidepressants (Peters et al., 2004; Zhang et al., 2005; Tzvetkov et al., 2008; Tsai et al., 2009) as well as to electroconvulsive therapy (Anttila et al., 2009) in many independent samples including different ethnicities, even though results were not always replicated (Illi et al., 2009; Peters et al., 2009).

TPH2 variants have also been suggested to play a role in BD. First of all, higher levels of TPH2 expression have been found in the dorsolateral prefrontal cortex of patients with BD as compared with matched controls (De Luca et al., 2005a). Also, several case control studies have found significant associations between specific single nucleotide polymorphisms (SNPs) and haplotypes within TPH2 and BD in samples including mainly Caucasian subjects (Harvey et al., 2004; Van Den Bogaert et al., 2006; Harvey et al., 2007; Lin et al., 2007; Cichon et al., 2008; Roche and McKeon, 2009), even though such findings were not consistently replicated in other samples of Caucasian (Campos et al., 2010; Grigoroiu-Serbanescu et al., 2008) as well as Korean (Choi et al., 2010) subjects with BD. It is worth mentioning, however, that, even though a set of SNPs located in the 5' region of TPH2 previously associated with BD in a German sample was not replicated in a Romanian population (Grigoroiu-Serbanescu et al., 2008), the association became significant in a subgroup of patients with paternal transmission of the disease, raising the question as to whether at least some TPH2 variants could be specific for some subpopulations of patients but not for others. Additionally, recent findings (Lin et al., 2007) suggesting the existence of epistatic interactions between TPH2 and TPH1 underscore the importance of considering how complex genetic interactions could differently modulate the risk for a given disorder as compared to single genes separately analyzed.

Following such findings a number of studies began focusing on a possible role of TPH2 in schizophrenia as well. However, even though limited to a few investigations, the experimental research on this topic has not found evidence for a possible involvement of several TPH2 variants in the etiology of schizophrenia so far (De Luca et al., 2005b; Higashi et al., 2007; Shiroiwa et al., 2010; Tee et al., 2010) and for an alteration in the expression of TPH2 in the dorsolateral prefrontal cortex of schizophrenia patients as compared with patients suffering from BD and healthy controls (De Luca et al., 2005a). On the other hand, it is noteworthy that a number of studies mainly focused on the rs4570625, an SNP located in the putative promoter region of TPH2 (Kennedy et al., 2003), found an association with several further psychiatric disorders including panic disorder (Kim et al., 2009), obsessive compulsive disorder (Mossner et al., 2006) and attention deficit/hyperactive disorder (Walitza et al., 2005), even though, taking into account the lack of replications, such results should be considered with caution and deserve further investigations.

Overall, such findings suggest that several genetic variants in TPH2 could play an important role in the etiology of several psychiatric disorders as well as in the response to some of their treatments, even though there is no complete consensus yet with regard to the specific variants involved. Note, however, that significant differences across the studies in terms of psychiatric disorders, pharmacological treatments, psychometric assessments and ethnicities under investigation as well as different criteria for defining remission and response could partially explain why discrepant findings have sometimes been observed.

Accordingly, the aim of the present study was to replicate and extend such findings in a Korean population of patients suffering from different psychiatric disorders. In detail, the first aim of the present article is to investigate whether specific SNPs within TPH2 including rs4570625 located in the promoter region and further whether five SNPs which have received little or no attention so far (rs10748185, rs11179027, rs1386498, rs4469933, and rs17110747) could be associated with MD, BD and schizophrenia. The second aim of the present article is to explore whether such variants could predict clinical outcome in patients suffering from MD, BD and schizophrenia naturalistically treated with antidepressants, mood stabilizers and antipsychotics, respectively.

2. Methods

2.1. Subjects

The sample under investigation in the present study comprised 145 in-patients suffering from MD, 132 in-patients with BD and 221 in-patients with schizophrenia who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. Patients were eligible for inclusion if they had a documented clinical diagnosis of MD, BD or schizophrenia according to the DSM-IV criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998).

There was not any particular restriction with respect to treatments, concomitant comorbidities and first vs. following episodes of disease. However, patients were excluded if they had current severe or unstable medical and neurological conditions, current treatment with a long-acting antipsychotic, concomitant alcohol and substance abuse disorders and if they were not of Korean ethnicity. The choice of not using excessively tight inclusion and exclusion criteria was motivated by the decision to include a sample of subjects that could be representative of usual psychiatric in-patients in Korea. A further sample of 170 Korean psychiatrically healthy subjects, who underwent the same assessment of psychiatric patients to exclude possible psychiatric disorders, deriving from the same location of the psychiatric patients included in the present study and including both community volunteers and medical staff, was also included to compare genotype and allelic frequencies between the four populations of subjects under investigation.

All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge by means of psychometric questionnaires specific for each disorder under investigation. More in detail, MD severity was assessed by means of the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), mania severity in patients with BD with current manic or mixed state was assessed by means of the Young Mania Rating Scale (YMRS) (Young et al., 1978) and familiar history of schizophrenia severity was assessed by means of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Scorers were trained with the specific instruments with good inter-rater reliability ($\kappa > 0.8$). Additionally, the following clinical and demographic variables were recorded: gender, age, clinical subtypes, age at onset, familiar history of psychiatric disorders (based on patients' reports following direct questioning by clinicians), lifetime suicide attempts, duration of admission, drugs at discharge and concomitant anxiolytics. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All patients (18-65 years old) provided written informed consent before participating into the study.

2.2. Outcome measures

The main outcome measures of the present study were: 1) differences between genetic and allelic frequencies in patients with MD, BD and schizophrenia as well as healthy control subjects and 2) possible influence of the six SNPs within *TPH2* under investigation on clinical improvement as well as on response and remission rates in the three groups of psychiatric patients mentioned above separately analyzed. Both continuous and categorical analyses were performed. Regarding categorical ones, in accordance with previous studies, response was *a priori* defined as a $\geq$50% symptoms' reduction from baseline to discharge (e.g. (Hirschfeld et al., 2004; Leucht et al., 2007; Riedel et al., 2010)). Remission was defined as a MADRS score $\leq$7 at discharge for patients with MD (Riedel et al., 2010) and as a YMRS score $\leq$12 for patients with BD (Perlis et al., 2006). Unfortunately it was not possible to determine remission rates for patients with schizophrenia, as current consensus-based operational criteria require data from eight single items of the PANSS (Andreasen et al., 2005) (or the Brief Psychiatric Rating Scale (Flemenbaum and Zimmermann, 1973)) that was not recorded in the present study.

2.3. DNA analysis

Genomic DNA was extracted from blood by standard methods and quantified. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping six SNPs (rs4570625, rs10748185, rs11179027, rs1386498, rs4469933 and rs17110747) of TPH2 under investigation (Table 1). PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v1 (Biotage AB, Sweden) and one primer of each primer set was biotinylated.

Table 1
TPH2 SNPs considered in this study.

SNP ID	Position*	Distance	Alleles	Location
rs4570625	70618190 (-845)		G/T	Promoter
		3932		
rs10748185	70622122 (3088)		G/A	Intron
		41457		
rs11179027	70663579 (44545)		C/G	Intron
		20831		
rs1386498	70684410 (65376)		G/A	Intron
		16574		
rs4469933	70700984 (81950)		C/T	Intron
		11237		
rs17110747	70712221 (93187)		G/A	3' UTR

*Absolute chromosomal position. The relative position to the start codon is given in parenthesis. All data from www.snpper.chip.org.

2.4. Statistical analysis

Statistical analyses were performed using 'Statistica' package (StatSoft, 1995). Differences in the allelic and genetic frequencies between healthy subjects and patients with MD, BD and schizophrenia as well as effects of such variants on response and remission rates were calculated using the χ^2 statistics. Clinical improvements were calculated by means of repeated measures ANOVA. Age differences among different groups were calculated by means of ANOVA. In the case of positive findings, clinical variables associated with the outcome measure under investigation were added as covariates. Haploview 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy-Weinberg equilibrium (HWE) (Barrett et al., 2005). Tests for associations using multi-marker haplotypes were performed using the statistics environment "R" (http://www.R-project.org), package "haplo.score", to compare response and remission rates among different haplotypes. Permutations ($n=10.000$) were performed to estimate the global significance of the results for all haplotypes analyses and to validate the expectation-maximization values.

All p-values were 2-tailed, and statistical significance was conservatively set at the 0.008 level (corresponding to the Bonferroni correction for the six SNPs under investigation) in order to reduce the likelihood of false positive results. With these parameters we had a sufficient power (0.80) to detect a small-medium effect size ($\omega=0.16$) that, as an example, corresponded to an odds ratio of 1.94 between the three groups of patients and the group of controls and to detect medium to medium-large ($d=29$, 31 and 24) effect sizes for patients with MD, BD and schizophrenia respectively carrying the GG genotype of rs17110747 as compared with those carrying the GA genotype (Cohen, 1988) (analyses performed with G*power 3.0, information available at http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/). Such effects sizes corresponded to the possibility of detecting final differences on MADRS, YMRS and PANSS scores of 4, 4 and 6.5 points respectively.

3. Results

3.1. Socio-demographic features of MD patients and controls

Socio-demographic features such as gender, age and further clinical and socio-demographical variables are reported in Table 2. For control subjects only data about gender and age were collected. The groups did not differ with respect to gender ($\chi^2=6.66$, $p=0.11$), whereas they differed with respect to age ($F=3.75$, d.f. = 3,663, $p=0.01$). Patients with BD were significantly younger and patients with MD were significantly older as compared with patients with schizophrenia and healthy controls. There were no significant associations between any of the SNPs under investigation and baseline clinical variables (all p-values>0.008).

3.2. Hardy Weinberg equilibrium (HWE) and linkage disequilibrium for TPH2 rs4570625, rs10748185, rs11179027, rs1386498, rs4469933 and rs17110747

Five out of six SNPs within TPH2 were in HWE in the whole sample (rs4570625: $p=0.97$, rs10748185: $p=0.36$, rs11179027: $p=0.72$, rs4469933: $p=0.12$, rs17110747: $p=0.51$). As rs1386498 was not in linkage disequilibrium neither in the whole sample nor in single subsamples of patients and controls separately analyzed ($p<0.0001$), it was excluded from the analyses. Strong LD was observable between rs4570625, rs10748185 and rs11179027 on the one hand, and between rs4469933 and rs17110747 on the other (Fig. 1). Patients and healthy volunteers separately analyzed yielded similar results (data not shown).

3.3. Differences between genotype and allelic frequencies in MD, BD, schizophrenia patients and healthy controls

There were no significant differences between allelic and genotype frequencies in MD, BD, schizophrenia patients and healthy controls (Table 3; all p-values>0.008). Of note, genotypes and allelic frequencies in our sample did not significantly differ from those reported by international databases with respect to Asian samples (http://snpper.chip.org; Table 3).

3.4. TPH2 rs4570625, rs10748185, rs11179027, rs4469933 and rs17110747 and clinical improvement, response, remission rates and final outcomes in patients with major depression, bipolar disorder and schizophrenia

We did not observe any significant association between the five genotypes or alleles under investigation and clinical improvement, response and remission rates as well as final outcomes in any of the disorders under investigation. The haplotype analysis focused on the sliding windows haplotypes including rs4570625, rs10748185 and rs11179027 as well as rs4469933 and rs17110747. The only significant association was found in patients with MD between rs4570625-rs10748185 G-A haplotype and higher endpoint severity (global stat = 14.24, d.f. = 3, global-stat $p=0.006$, haplotype frequency = 0.47, $p=0.006$). The inclusion of covariates in the model (including age, duration of illness and a history of suicide attempts) did not significantly influence the results. No further haplotype under investigation was significantly associated with any of the clinical outcomes in patients with MD, BD or schizophrenia.

4. Discussion

The present article was aimed at exploring whether specific SNPs within TPH2 including rs4570625, rs10748185, rs11179027, rs4469933 and rs17110747 could be associated with MD, BD and schizophrenia and whether the same variants could predict clinical outcomes in such groups of patients treated with antidepressants, mood stabilizers and antipsychotics respectively. Even though five out of six SNPs under investigation were located into introns of the gene and therefore they did not alter the protein sequence, it is worth mentioning that they could have functional relevance in the regulation of gene expression (Drago et al., 2007).

Contrarily to a number of published case control studies (Harvey et al., 2004; Zill et al., 2004; Zhang et al., 2005; Zhou et al., 2005; Van Den Bogaert et al., 2006; Harvey et al., 2007; Lin et al., 2007; Cichon et al., 2008; Haghighi et al., 2008; Roche and McKeon, 2009), the results of the present study did not provide evidence for an association between any of the SNPs under investigation and MD and BD. It is noteworthy, however, that the large majority of such studies was performed in patients of Caucasian origin and that there is only a partial overlap between the SNPs selected in our study and those investigated in early studies. Note also that a number of further studies did not find any association between TPH2 variants and MD as well as BD in samples including both Caucasian (Campos et al., 2010; Garriock et al., 2005; Gizatullin et al., 2008; Grigoroiu-Serbanescu et al., 2008; Mann et al., 2008; Illi et al., 2009) as well as Korean (Choi et al., 2010) subjects. On the other hand, our results suggesting no association between schizophrenia and TPH2 variants are in line with

Table 2
Clinical and demographical characteristics of the sample.

Clinical and demographic characteristics	Major depression ($n=145$)	Bipolar disorder ($n=132$)	Schizophrenia ($n=221$)	Healthy controls ($n=170$)
Gender				
Males	75(52%)	87(66%)	126(57%)	105(62%)
Females	70(48%)	45(34%)	95(43%)	65(38%)
Age	41.37 ± 14.07	36.35 ± 11.60	38.01 ± 12.67	38.83 12.80
MADRS				
Baseline	34.35 ± 8.95			
Discharge	17.12 ± 9.88			
YMRS				
Baseline		33.27 ± 9.09		
Discharge		19.80 ± 5.25		
PANSS total				
Baseline			94.05 ± 13.75	
Discharge			76.63 ± 9.01	
PANSS positive				
Baseline			24.84 ± 4.77	
Discharge			19.86 ± 4.12	
PANSS negative				
Baseline			21.58 ± 5.09	
Discharge			20.30 ± 4.18	
PANSS general				
Baseline			47.62 ± 8.03	
Discharge			36.46 ± 6.28	
Response				
Yes	78(54%)	33(25%)	28(13%)	
No	66(45%)	99(75%)	193(87%)	
Missing	1(1%)	0(0%)	0(0%)	
Remission				
Yes	22(15%)	10(8%)	N.A.	
No	122(84%)	122(92%)		
Missing	1(1%)	0(0%)		
Clinical subtypes				
MD/BD without PF	105(72%)	73(55%)	N.Ap.	
MD/BD with PF	11(8%)	57(43%)		
Dysthymia	4(3%)	-		
MD nos	5(4%)	-		
Missing value	20(13%)	2(2%)		
Age at onset	38.08 ± 13.29	26.58 ± 10.19	28.46 ± 10.98	
Fam. hist. of psychiatric disorders				
Yes	30(21%)	42(32%)	38(17%)	
No	92(63%)	35(26%)	183(83%)	
Missing values	23(16%)	55(42%)	0 (0%)	
Suicide attempts				
Yes	36(25%)	22(17%)	43(19%)	
No	92(63%)	89(67%)	178(81%)	
Missing value	17(12%)	21(16%)	0(0%)	
Duration of admission (days)	32.31 ± 20.55	33.66 ± 21.07	37.64 ± 16.75	
Drug				
Paroxetine	40(27%)			
Venlafaxine	35(24%)			
Fluoxetine	23(16%)			
Mirtazapine	21(14%)			
Lithium		41(31%)		
Valproate		56(42%)		
Lamotrigine		5(4%)		
Risperidone			78(34%)	
Olanzapine			54(24%)	
Quetiapine			13(6%)	
Amisulpiride			32(15%)	
Other	3(3%)	-	6(4%)	
Missing value	23(16%)	30(23%)	38(17%)	

(continued on next page)

Table 2 (*continued*)

Clinical and demographic characteristics	Major depression ($n=145$)	Bipolar disorder ($n=132$)	Schizophrenia ($n=221$)	Healthy controls ($n=170$)
Concomitant anxiolytics				
Alprazolam	30(21%)	5(4%)	22(10%)	
Lorazepam	73(50%)	82(62%)	198(90%)	
Clonazepam	3(2%)	3(3%)	0(0%)	
Buspiron	4(3%)	7(5%)	0(0%)	
None	35(24%)	35(26%)	0(0%)	

MADRS = Montgomery-Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale; PANSS = Positive and Negative Syndrome Scale; MD = major depression; BD = Bipolar disorder. PF = psychotic features; Fam. His = Familial History; N.A. = not available; N.Ap. = not applicable.

other reports (De Luca et al., 2005b; Higashi et al., 2007; Shiroiwa et al., 2010; Tee et al., 2010).

It is noteworthy, however, that we observed an association between rs4570625-rs10748185 G-A haplotype and higher endpoint severity in patients with MD. Of note, such haplotype includes rs4570625 which is located in the putative promoter region of the gene (Kennedy et al., 2003) and that was found to be associated with several psychiatric disorders including panic disorder (Kim et al., 2009), obsessive compulsive disorder (Mossner et al., 2006) and attention deficit/hyperactive disorder (Walitza et al., 2005) as well as with differences in amygdala and hippocampal volumes (Inoue et al., 2010) and in personality traits and disorders related to emotional dysregulation (Gutknecht et al., 2007). Of particular interest is also the notion that rs4570625 was found to be involved in the response to drugs in MD, even though the LD to rs10879346 and Pro312Pro rather than direct functional effects of rs4570625 could be a more probable explanation for the observed association between variants in such polymorphism and response to antidepressants (Tzvetkov et al., 2008). Note, in fact, that, in an early study, no significant difference in the promoter activity was observed for the G and T alleles of rs4570625 (Scheuch et al., 2007). However, taking into account that, in the present study, neither the allelic nor the genotype analyses provided evidence for an association between rs4570625 separately analyzed and clinical outcomes and that candidate genetic studies as the present one are associated to a high likelihood of false positive findings (Sullivan, 2007), our finding should be considered with much caution and further replications are needed so as to draw more definitive conclusions. In addition, no further haplotype was found to be associated with response either to antidepressants or to other mood stabilizers and to antipsychotics, suggesting that genetic variants under investigation in the present study are not consistently associated with clinical outcomes in Korean patients suffering from MD, BD and schizophrenia.

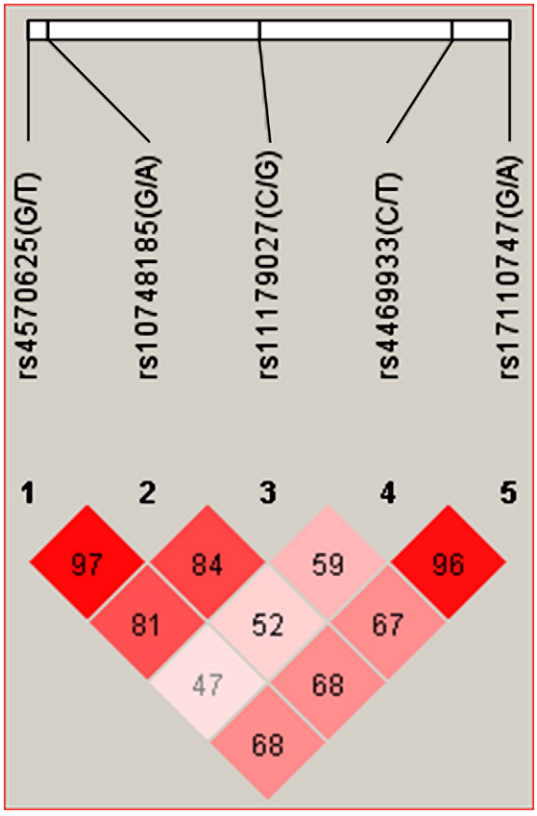

Fig. 1. Linkage disequilibrium and D' for rs4570625, rs10748185, rs11179027, rs4469933 and rs17110747 single nucleotide polymorphisms within TPH2.

Before firm conclusions are drawn, however, several limitations affecting the present study should be carefully considered. First of all, as reported above, candidate genetic studies as the present one are associated with a high likelihood of false positive findings (Sullivan, 2007) but, on the other hand, also to negative results, which could be related to the lack of statistical power that could obscure small effects exerted by single SNPs. A further concern is related to the use of several drugs with different mechanisms of action for each cohort of patients that do not allow one to draw definitive conclusions with regard to the influence of the SNPs under investigation on specific drugs or classes of drugs. However, our decision to include patients treated with different drugs could have the advantage of being closer to "real world" clinical practice. Also, the duration of hospitalization in the present study could be considered as insufficient to ascertain a lack of response and remission, though this time frame is consistent with common clinical practice (Zimmerman et al., 2002). A further limitation regards the notion that no symptom assessment instrument was applied to all three patient groups simultaneously so that symptom severity and treatment output could not be compared between the patient groups. Furthermore, we obtained only limited information about some clinical and socio-demographical variables which was particularly evident with regard to familiar history of psychiatric disorders in patients with BD, and it is therefore unclear whether additional information could have altered our results. Also, we recognize that the rationale for investigating a causal role of TPH2 in response to mood stabilizers and antipsychotics may be considered as weaker compared to antidepressants, however serotonin modulation is also important for many of the new second generation antipsychotics. Finally, in the present study we have investigated only five SNPs that further tag other 13 SNPs (data from http://hapmap.ncbi.nlm.nih.gov/), even though TPH2 include 501 validated SNPs: as a consequence we were able to cover approximately only 1% of the gene.

In conclusion our preliminary findings suggest that rs4570625-rs10748185 G-A haplotype could be associated with higher endpoint MADRS severity in Korean in-patients with MD. Further research is needed to confirm our findings in larger samples, in out-patients and in patients treated with specific drugs or classes of drugs.

Table 3
Allelic frequencies in subjects with major depression, bipolar disorder, schizophrenia, healthy controls and in the general population. Percentages of the general population from www.snpper.chip.org.

Alleles frequencies					χ^2	*p*-value
Major depression	Bipolar disorder	Schizophrenia	Healthy subjects	General population		
rs4570625						
T:144(50%)	T:143(54%)	T:237(54%)	T:191(55%)	T:52%	2.82	0.57
G:146(50%)	G:119(46%)	G:205(46%)	G:149(44%)	G:48%		
rs10748185						
G:151(52%)	G:150(57%)	G:246(56%)	G:201(59%)	G:57%	3.25	0.40
A:139(48%)	A:114(43%)	A:196(44%)	A:139(41%)	A:43%		
rs11179027						
G:173(60%)	G:141(53%)	G:251(57%)	G:191(56%)	G:59%	2.22	0.72
C:117(40%)	C:123(47%)	C:191(43%)	C:149(44%)	C:41%		
rs4469933						
C:137(48%)	C:128(48%)	C:194(44%)	C:164(48%)	C:50%	2.14	0.74
T:151(52%)	T:136(51%)	T:248(56%)	T:176(52%)	T:50%		
rs17110747						
G:219(75%)	G:209(79%)	G:329(74%)	G:254(75%)	G:74%	2.29	0.70
A:71(25%)	A:55(21%)	A:113(26%)	A:86(25%)	A:26%		
Genotypes frequencies					χ^2	*p*-value
Major depression	Bipolar disorder	Schizophrenia	Healthy subjects	General population		
rs4570625						
TT:31(21%)	TT:41(32%)	TT:62(28%)	TT:57(33%)	TT:23%	6.90	0.33
TG:82(57%)	TG:61(46%)	TG:113(51%)	TG:77(45%)	TG:57%		
GG:32(22%)	GG:29(22%)	GG:46(21%)	GG:36(21%)	GG:20%		
rs10748185						
GG:33(23%)	GG:42(32%)	GG:65(30%)	GG:63(37%)	GG:28%	8.79	0.18
GA:85(58%)	GA:66(50%)	GA:116(52%)	GA:75(44%)	GA:58%		
AA:27(19%)	AA:24(18%)	AA:40(18%)	AA:32(19%)	AA:14%		
rs11179027						
GG:48(33%)	GG:36(27%)	GG:70(32%)	GG:57(34%)	GG:33%	4.95	0.55
GC:77(53%)	GC:69(52%)	GC:111(50%)	GC:77(45%)	GC:52%		
CC:20(14%)	CC:27(21%)	CC:40(18%)	CC:36(21%)	CC:15%		
rs4469933						
CC:36(25%)	CC:32(24%)	CC:41(19%)	CC:45(27%)	CC:20%	4.69	0.58
CT:65(45%)	CT:64(49%)	CT:112(51%)	CT:74(43%)	CT:60%		
TT:43(30%)	TT:36(27%)	TT:68(30%)	TT:51(30%)	TT:20%		
rs17110747						
GG:86(59%)	GG:83(62%)	GG:120(54%)	GG:97(57%)	GG:55%	5.45	0.48
GA:47(32%)	GA:43(33%)	GA:89(40%)	GA:60(35%)	GA:39%		
AA:12(8%)	AA:6(5%)	AA:12(6%)	AA:13(8%)	AA:16%		

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