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# Meta-analysis confirms a functional polymorphism (5-HTTLPR) in the serotonin transporter gene conferring risk of bipolar disorder in European populations

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## HIGHLIGHTS

- We investigated the 44 base pair insertion/deletion within the promoter region of 5-HTT gene.
- This polymorphism (5-HTTLPR) was associated with many psychiatric disorders.
- This is so far the largest-scale meta-analysis of 5-HTTLPR with bipolar disorder susceptibility.

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## ABSTRACT

The serotonin transporter (5-HTT) is a candidate risk gene for bipolar disorder, and a functional polymorphism of 44-bp insertion/deletion (5-HTTLPR) located in the promoter region of this gene has been investigated for the association with the illness extensively among worldwide populations, but overall results were inconsistent and its role in the disorder remains unclear. The present study attempts to find its potential association with bipolar disorder using meta-analyzes that maximize the statistical power. We applied meta-analysis techniques by combining all available case–control studies of 5-HTTLPR and bipolar disorder in samples of European ancestry (with a total of 3778 cases and 4997 controls), and we assessed the evidence for allelic associations, heterogeneity among different studies, influence of each single study, and potential publication bias. The short allele (S allele) of 5-HTTLPR showed a significant association with bipolar disorder in our meta-analysis (odds ratio = 1.10, *p*-value = 0.005), suggesting it is likely a risk polymorphism for the illness, and the observed OR is consistent with other susceptibility loci identified through recent large-scale genetic association studies on bipolar disorder, which could be regarded simply as a small but detectable effects.

## 1. Introduction

Bipolar disorder (BD) is a common and severe neuropsychiatric disorder characterized by profound mood symptoms including episodes of mania, hypomania and depression, and is often accompanied by psychotic features and cognitive changes. The etiology of BD is still unknown although the presence of a complex dysfunction at multiple levels such as neurotransmitter system has been suggested [22].

The worldwide lifetime prevalence of BD is between 1 and 2% in the general populations [1], however, family studies indicated that the rate of concordance for monozygotic twins is roughly 40–70% (compared with 5% in dizygotic twins) and the risk among the first-degree relatives of individuals with BD is 10-fold greater than among the general populations [7,15]. These lines of evidence have implied a strong genetic predisposition for BD, however, despite the relatively high heritability, only a few risk polymorphisms have been found and many cannot be successfully replicated across different samples, which is possibly caused by the small sample size in previous association studies.

Previous studies on BD have focused on genes involved in neurotransmitter systems that are influenced by medications used in the treatment of BD, mood stabilizers and antidepressants [6]. Though no definitive association results have yet emerged and the obvious inconsistency may be due to false positive studies, false negative studies or true variability in association among different samples. However, there have been some suggestive findings including

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**Table 1**
Characteristics of studies included in the meta-analysis.

| Author | Year | Country | Number of cases | Number of controls | Diagnostic system | References |
|---|---|---|---|---|---|---|
| Bellivier et al. | 1998 | France | 204 | 99 | DSM-IV | [2] |
| Collier et al. | 1996 | UK | 190 | 174 | DSM-IV | [4] |
| | | Italy | 75 | 95 | DSM-IV | |
| | | Germany | 39 | 301 | DSM-IV | |
| Cosgrove et al. | 2012 | America | 62 | 236 | DSM-IV | [5] |
| Furlong et al. | 1998 | UK | 87 | 169 | DSM-IV | [10] |
| Gutierrez et al. | 1998 | Spain | 88 | 112 | DSM-III-R | [11] |
| Hauser et al. | 2003 | Poland | 132 | 213 | DSM-IV, ICD-10 | [12] |
| Hoehe et al. | 1998 | France and Germany | 79 | 281 | DSM-IV | [13] |
| Masoliver et al. | 2006 | Spain | 103 | 101 | DSM-IV | [18] |
| Mellerup et al. | 2001 | Denmark | 66 | 108 | ICD-10 | [19] |
| Mendes de Oliveira et al. | 1998 | Brazil | 47 | 98 | DSM-IV | [20] |
| Mendlewicz et al. | 2004 | Europe | 572 | 821 | RCD, DSM III-R, DSM IV | [21] |
| Neves et al. | 2008 | Brazil | 167 | 184 | DSM-IV | [25] |
| Oliveira et al. | 2000 | Brazil | 64 | 197 | DSM-IV, ICD-10 | [26] |
| Ospina-Duque et al. | 2000 | Colombia | 103 | 112 | DSM-IV | [27] |
| Rees et al. | 1997 | UK | 168 | 118 | DSM-IV | [28] |
| Rotondo et al. | 2002 | Italy | 111 | 127 | DSM-III-R | [29] |
| Serretti et al. | 2002 | Italy | 789 | 457 | DSM-IV | [31] |
| Shcherbatykh et al. | 2000 | Russia | 40 | 274 | - | [32] |
| Van Den Bogaert et al. | 2006 | Sweden | 182 | 364 | DSM-IV | [33] |
| Vincze et al. | 2008 | France | 410 | 356 | DSM-IV | [34] |

DSM-IV, Diagnosis and Statistical Manual of Mental Health Disorders, fourth edition; ICD-10, The International Classification of Diseases 10.

those polymorphisms within the genes encoding catechol-o-methyltransferase (COMT) [29], monoamine oxidase A (MAOA) [30] and the serotonin transporter (5-HTT, also called SLC6A4) [14].

5-HTT has been implicated as a compelling candidate gene for BD as serotonin is likely to play a key role in the regulation of mood and the treatment of affective symptoms [22], and besides its important functional role, the 5-HTT gene is located in a potential locus of susceptibility (Chr. 17q11.12) to BD shown in a linkage study [24]. Polymorphisms in this gene have been studied extensively among general populations, and a 44 base pair insertion/deletion within the promoter region, named the 5-HTT gene-linked polymorphic region (5-HTTLPR), with two allelic forms, the long variant (L) and the short variant (S) [24], has attracted interest of multiple research groups. The S allele of the 5-HTTLPR has lower transcriptional activity [4,17], and several studies have reported significant associations of the S allele with BD [12,29], but negative results have also been frequently observed [31,34,35].

Given the fact on the inconsistencies of this polymorphism among individual studies, and to exclude the possibility that the results in previous analyses are false positive or negative caused by the small sample size, we aim to estimate the pooled effect size from the existing studies on the 5-HTTLPR in the European populations. Meta-analysis is an effective way to increase the statistical power by pooling all the available data together and analyzing with a large dataset, and especially interesting for genetic association studies on complex disorders, e.g., BD.

## 2. Materials and methods

### 2.1. Literature search

The PubMed, Elsevier, EMBASE, Web of Science and Wiley Online Library for all articles were searched with the following search terms: (‘SLC6A4’, ‘5-HTT’ or ‘5-HTTLPR’) and (‘bipolar disorder’). Once the articles had been collected, their bibliographies were then searched for additional references. Studies published before March 25, 2013 were considered in this analysis, and publication date and publication language were not restricted in our search.

### 2.2. Inclusion and exclusion criteria

Abstracts of all citations and retrieved studies were reviewed. Studies meeting the following criteria were included: (1) using a case–control study design; (2) detecting the relationship between variant 5-HTTLPR and BD; (3) contain at least 50 cases and 50 controls, as individual studies with quite small sample size will easily cause bias, which may influence the results of meta-analysis. According to this criteria, a study with quite small sample size (30 cases and 48 controls) was excluded [32]; (4) providing available genotype/allele data of 5-HTTLPR; and (5) control subjects are healthy without history of mental disorders.

Studies were excluded if one of the following factors existed: (1) the design is based on family or sibling pairs or case-only; (2) the genotype/allele frequency of 5-HTTLPR is not available; (3) the studies were conducted in non-European samples; or (4) the 5-HTTLPR is deviated from Hardy–Weinberg Equilibrium (HWE) in control group.

### 2.3. Data extraction

All data were extracted independently by two investigators (HYJ and FQ) according to the inclusion criteria listed above. Disagreement over eligibility of a study was resolved by discussion until a consensus was reached. The following characteristics were collected from each study: first author, year of publication, country of sample, ethnicity, number of cases and controls, definition of case status (Table 1), and data for 5-HTTLPR (Table S1).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2013.05.065.

### 2.4. Statistical analysis

Publication bias was examined with funnel plots and with Egger’s tests [9]. If there is evidence of publication bias, the funnel plot is noticeably asymmetric. For the Egger’s tests, the significance level was set at 0.05.

Power analysis was performed by the Power and Sample Size Program software [8], and the commonly observed odds ratio (OR)