Association between the SLC6A4 gene and schizophrenia: an updated meta-analysis

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Background: In order to explore the association between the SLC6A4 gene and the risk of schizophrenia, an updated meta-analysis was conducted using a total of 46 scientific articles.

Methods: Through a literature search, papers studied included 35 articles on serotonin-transporter-linked polymorphic region (5-HTTLPR) with 8,752 cases and 10,610 controls, 17 articles on second intron variable number of tandem repeats with 7,284 cases and 8,544 controls, four studies on rs1042173 with 1,351 cases and 2,101 controls, and four studies on rs140700 with 1,770 cases and 2,386 controls. Pooled, subgroup, and sensitivity analyses were performed, and the results were visualized by forest and funnel plots.

Results: An association between 5-HTTLPR and the risk of schizophrenia was not found, except for an Indian subgroup analysis ($P_z=0.014$, OR = 1.749, 95% CI = 1.120–2.731). A 10 repeats/12 repeats (10R/12R) genotype was a protective factor against schizophrenia ($P_z=0.020$, OR = 0.789, 95% CI = 0.646–0.963), but a 12R/12R genotype was a risk factor for schizophrenia ($P_z=0.004$, OR = 1.936, 95% CI = 1.238–3.029) in the pooled analyses. In Caucasians, a GG genotype of rs1042173 may be a risk factor for schizophrenia ($P_z=0.006$, OR = 1.299, 95% CI = 1.079–1.565). No association was found between rs140700 and the risk for schizophrenia.

Conclusion: Through meta-analysis, we were able to gain insight into previously reported associations between SLC6A4 polymorphism and schizophrenia.

Keywords: SLC6A4, gene, schizophrenia, meta-analysis, polymorphism

Introduction

Schizophrenia is a complex chronic brain dysfunction that has an elusive pathogenesis and is highly heritable. Investigations into twins and adoptees have shown that schizophrenia was caused by both genetic and environmental factors. Epidemiological genetic studies suggested that genetic factors contributed significantly to the etiology of schizophrenia. Pathological mechanisms are based on various neurotransmitter and neurodevelopmental hypotheses, and the hypothesis of a 5-hydroxytryptamine (5-HT) system defect is an important one. The serotoninergic pathway has been implicated, for several reasons, as having a major role in the pathophysiology of schizophrenia. By binding with receptors, 5-HT negatively regulates cAMP-dependent signal transduction and inhibits neuronal activity by opening G-protein–gated inwardly rectifying potassium channels. The serotonin transporter (5-HTT) has a crucial function in the regulation of 5-HT reuptake in presynaptic neurons. It has been noted that levels of 5-HTT change in schizophrenic patients. Significant differences in mRNA levels of the serotonin transporter gene (SLC6A4) and serotonin transporter protein levels were observed in schizophrenic patients compared with healthy controls. Pharmacological evidence indicated that 5-HTT was a site of action for several drugs with central nervous system effects and that 5-HTT was involved in the pathogenesis of schizophrenia.
Therefore, the SLC6A4 gene is a candidate gene for the pathogenesis of schizophrenia.

The most studied polymorphisms in the SLC6A4 gene are a 44-base pair (bp) insertion–deletion (serotonin-transporter-linked polymorphic region [5-HTTLPR]) in the promoter region, generating major L and S alleles, and a 17-bp variable number of tandem repeats (VNTR) in the second intron (STin2).14 The STin2 consists of 17-bp VNTR elements existing in 9, 10, and 12 repeats (9R, 10R, and 12R), although other rare types, such as seven-repeat units, have also been reported. The single-nucleotide polymorphisms (SNPs), rs1042173 and rs140700, are located in the three prime untranslated region and intron 5 of the SLC6A4 gene, respectively. Associations between the SLC6A4 gene and schizophrenia are controversial.15,16 Ambiguous results from different studies may possibly reflect sample sizes insufficient for obtaining adequate statistical power.

A meta-analysis is a useful method for interpreting controversial study results.17,18 Four meta-analyses of the association between the SLC6A4 gene and schizophrenia have been conducted;19–22 however, the results are still controversial. In addition, a meta-analysis of the association between schizophrenia and rs1042173 and rs140700 does not exist. Thus, we intended to perform an updated meta-analysis to better analyze the association of SLC6A4 with schizophrenia.

Materials and methods

Literature searches

To identify studies eligible for inclusion in this meta-analysis, English (PubMed and SchizophreniaGene [SzGene]) and Chinese language (China National Knowledge Infrastructure, Wanfang, and Weipu) databases were searched using the following keywords: “serotonin transporter,” “SERTPR,” “SERT-in2,” “5-HTTLPR,” “STin2 VNTR,” “SLC6A4,” and “schizophrenia.” References of the searched articles were also reviewed to uncover more data.

Inclusion and exclusion criteria

Studies included in the meta-analysis met the following criteria: 1) case–control design; 2) involved patients with schizophrenia; 3) presented relevant data for case and control groups (eg, allele/genotype frequencies, sample size, ethnicity, schizophrenia diagnostic criteria, and control group source); 4) removed duplicate sample data; and 5) published before September 2018. If the article did not contain detailed data, we e-mailed the authors for further information. Studies were excluded for the following reasons: 1) family-based studies; 2) no control group; 3) no usable genotype frequency data (attempts were made to contact authors via e-mail for such data); and 4) duplicate reported sample data.

Statistical analyses

The meta-analysis was conducted using Stata Version 10.0 (Stata Corp., College Station, TX, USA). A P-value of Hardy–Weinberg equilibrium ($P_{HWE}$) was calculated for control groups. Associations between SLC6A4 and the risk of schizophrenia were detected under the random model.23,24 A suitable genetic model was selected according to the previous articles.25 ORs and 95% CIs were calculated in the pooled and subgroup analyses.

The heterogeneity of studies was determined by using Cochran’s chi-squared $Q$-statistic test.26 The degree of heterogeneity was expressed as $I^2$, which was divided into low ($I^2<25\%$), medium ($I^2=50\%$), and high ($I^2>75\%$) heterogeneity.27,28 Publication bias was calculated by using Egger’s test and was visualized in a funnel plot, in which the SE of the log OR of each study was plotted against its log OR. Sensitivity analysis, by removing one single study in turn, was conducted to test the impact of each study on pooled results. $P$-values of association, heterogeneity, and publication bias tests were represented by $P_{a}$, $P_{h}$, and $P_{z}$, respectively. In this study, $P<0.05$ was regarded as statistically significant in all statistical tests.29 Statistical power was calculated by a PS program (Adobe Systems Incorporated, San Jose, CA, USA).25

Results

Description of studies

A total of 380 English and 16 Chinese published research articles were searched, and 46 articles were analyzed in this study after exclusion according to a PRISMA flow program (Figure 1).30 Detailed data on five articles could not be obtained after sending e-mails to the authors;31–35 therefore, they were removed in the present meta-analysis. Table 1 describes the baseline characteristics of 46 studies that were included in this meta-analysis. The studies included 35 articles about 5-HTTLPR,16,36–68 17 studies about Stin2,16,37,39–41,44,47,53,59,65,69–75 four articles about rs1042173,40,47,76,77 and four articles about rs140700.71,76,78,79

No association between 5-HTTLPR and the risk of schizophrenia

In a random model,30,81 the pooled and subgroup analyses of 8,752 cases and 10,610 controls were performed (Table 2). Table 3 summarizes the results of the pooled analyses.
and Table 4 depicts the data from the subgroup analyses. No association was found between 5-HTTLPR and the risk of schizophrenia with $P_z=0.054$ (OR = 1.085, 95% CI = 0.999–1.178) with a power of 0.935 in the dominant model.\cite{1} No associations were found in the subgroup analyses, except in an Indian group ($P_z=0.014$, OR = 1.749, 95% CI = 1.120–2.731). No significant heterogeneity was observed in the pooled analysis ($P_h=0.294$, $I^2=10.4\%$).

Genotypes 10R/12R and 12R/12R of STin2 VNTR may be associated with the risk of schizophrenia
The allele frequencies of 7,284 cases and 8,544 controls were included in the pooled and subgroup analyses, under a random model (Table 5); 10R and 12R are common alleles; therefore, alleles (10R and 12R) and genotypes (10R/10R, 10R/12R, and 12R/12R) were analyzed for an association with the risk of schizophrenia, respectively (Tables 3 and 4). A 10R/12R genotype was a protective factor against schizophrenia ($P_z=0.020$, OR = 0.789, 95% CI = 0.646–0.963), but a 12R/12R genotype was a risk factor for schizophrenia ($P_z=0.004$, OR = 1.936, 95% CI = 1.238–3.029) in the pooled analyses. The two pooled analyses had high powers of 1.00. In the subgroup analyses, 10R/12R was a protective factor against schizophrenia in East Asia ($P_z=0.040$, OR = 0.617, 95% CI = 0.389–0.978), India ($P_z=0.014$, OR = 0.635, 95% CI = 0.441–0.913) and in a population-based analysis ($P_z=0.028$, OR = 0.794, 95% CI = 0.646–0.976). A 12R/12R genotype was a risk factor for schizophrenia in East Asia ($P_z=0.000$, OR = 4.482, 95% CI = 2.312–8.689) and in population-based ($P_z=0.013$, OR = 1.755, 95% CI = 1.124–2.742) and hospital-based ($P_z=0.000$, OR = 10.689, 95% CI = 5.303–21.544) subgroup analyses. The significant heterogeneity was observed in these associated analyses.

Genotype GG of rs1042173 may be a risk factor for schizophrenia in Caucasians
In a recessive and a random model, no association was detected among 1,351 cases and 2,101 controls ($P_z=0.057$, OR = 1.199, 95% CI = 0.994–1.445; Table 6). Tables 3 and 4 shows the results. In Caucasians, a GG genotype may be a

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**Figure 1** Study selection process in this meta-analysis. **Abbreviations:** CNKI, China National Knowledge Infrastructure; 5-HTTLPR, serotonin-transporter-linked polymorphic region; STin2 VNTR, second intron variable number of tandem repeats.
Table 1 Characteristics of the qualified studies in this meta-analysis

| Authors          | Year | Country                | Ethnicity | Controls source | Mean age of the control group | Cases, n | Controls, n | Diagnostic criteria | Gender index (case) | Gender index (control) |
|------------------|------|------------------------|-----------|-----------------|-------------------------------|----------|--------------|---------------------|----------------------|------------------------|
| Li and Li³⁵      | 2013 | People's Republic of China | Han       | Population-based | 27.7±8.0                      | 526      | 528          | DSM-IV             | 1.000                | 1.000                  |
| Fröadrique et al³⁶ | 1997 | France                 | Caucasians | Population-based | –                              | 105      | 114          | DSM-IV/R           | 0.438                | 0.932                  |
| Pae et al³⁶      | 2005 | Korea                  | Korea     | Hospital-based   | –                              | 111      | 172          | DSM-IV             | 1.090                | 0.000                  |
| Saiz et al³⁷     | 2007 | Spain                  | Caucasians | Population-based | 40.6±11.3                      | 227      | 420          | DSM-IV             | 0.667                | 0.961                  |
| Naylor et al³⁸   | 1998 | Australia              | Caucasians | Population-based | –                              | 58       | 62           | DSM-III-R          | –                    | –                      |
| Liu et al³⁹      | 1999 | People's Republic of China | Han       | Population-based | 42.0±10.0                      | 260      | 362          | DSM-III-R          | 0.709                | 0.813                  |
| Ikeda et al³⁹    | 2006 | Japan                  | Japanese  | Population-based | 33.6±12.9                      | 287      | 288          | DSM-IV             | 0.939                | 0.92                   |
| Lin et al³⁹      | 2009 | People's Republic of China | Han       | Population-based | 37.0±8.16                      | 329      | 288          | DSM-IV             | 0.621                | 0.811                  |
| Vijayan et al³⁹  | 2009 | India                  | Indian    | Population-based | 31.7±6.92                      | 243      | 243          | DSM-IV             | –                    | –                      |
| Lee et al³⁹      | 2009 | Korea                  | Korea     | Population-based | –                              | 141      | 115          | DSM-IV             | –                    | –                      |
| Pae et al³⁹      | 2003 | Korea                  | Korea     | Hospital-based   | 30.3±9.4                       | 111      | 208          | DSM-IV             | 1.096                | 0.818                  |
| Gu et al³⁹       | 2013 | People's Republic of China | Han       | Population-based | 22.4±6.6                       | 404      | 385          | ICD-10             | 0.515                | 0.629                  |
| Kaiser et al³⁹   | 2001 | Germany                | Caucasians | Population-based | 30.1±7.6                       | 684      | 587          | DSM-IV             | 0.887                | 0.289                  |
| Tsai et al³⁹     | 2002 | People's Republic of China | Han       | Hospital-based   | 42.8±9.2                       | 114      | 127          | DSM-III-R          | 1.426                | 1.822                  |
| Herken et al³⁹   | 2003 | Turkey                 | Caucasians | Population-based | –                              | 143      | 68           | DSM-IV             | 1.860                | –                      |
| Serretti et al³⁹ | 2002 | Italy                  | Caucasians | Hospital-based   | 46.0±15.5                      | 261      | 457          | DSM-IV             | –                    | 1.041                  |
| Tsai et al³⁹     | 2000 | People's Republic of China | Han       | Population-based | 49.6±0.8                       | 90       | 104          | DSM-IV             | 0.525                | 2.596                  |
| Han et al³⁹      | 2004 | Korea                  | Korean    | Population-based | –                              | 168      | 158          | DSM-IV             | –                    | –                      |
| Zaboli et al³⁹   | 2008 | European               | Caucasians | Population-based | 41.0±11.2                      | 155      | 246          | DSM-III-R          | 0.667                | 0.629                  |
| Golimbet et al³⁹ | 2017 | Russian                | Russian   | Population-based | 34.3±18.1                      | 1,285    | 1,061        | ICD-10             | 1.633                | 2.333                  |
| Herken et al³⁹   | 2002 | Turkish                | Turkish   | Population-based | –                              | 128      | 135          | DSM-IV             | –                    | –                      |
| Peit et al³⁹     | 2017 | Croatia                | Croatia   | Population-based | 37.6±11.5                      | 300      | 291          | DSM-IV             | 0.376                | 0.865                  |
| Carlström et al³⁹ | 2012 | Scandinavia            | Caucasians | Population-based | –                              | 837      | 1,473        | DSM-IV             | –                    | –                      |
| Terzic et al³⁹   | 2015 | Slovenia               | Slovenian  | Population-based | –                              | 138      | 94           | DSM-IV             | –                    | –                      |
| Lu et al³⁹       | 2012 | the Netherland and Germany | Caucasians | Population-based | –                              | 2,030    | 1,288        | DSM-IV             | –                    | –                      |
| Golimbet et al³⁹ | 2010 | Russia                 | Russian   | Population-based | 55.6±20.5                      | 58       | 62           | ICD-10             | 0.277                | 0.824                  |
| Golimbet et al³⁹ | 2003 | Russia                 | Russian   | Hospital-based   | 31.6±13.5                      | 110      | 124          | ICD-10             | 0.746                | 1.696                  |
| Stoer et al³⁹    | 1998 | Germany                | Caucasians | Population-based | 29.9±10.0                      | 180      | 223          | ICD-10             | 0.622                | 0.701                  |
| Study            | Year | Region/Population | Sample Size | Gender | Age Mean ± SD | Disease Diagnostic | Odds Ratio | 95% CI |
|------------------|------|-------------------|-------------|--------|---------------|-------------------|------------|--------|
| Collier et al    | 1996 | European          | Caucasians  | Population-based | -            | 129               | 187        | DSM-III-R | -      |
| Kotler et al     | 1999 | The USA           | Caucasians  | Population-based | 28.0±15.0    | 82                | 821        | ICD-10   | 0.586  | 1.61  |
| Rao et al        | 1998 | The USA           | Caucasians  | Population-based | 30.0±10.0    | 80                | 127        | DSM-IV   | 0.667  | 1.953 |
| Rao et al        | 1998 | African            | American    | Population-based | 30.0±8.0     | 47                | 37         | DSM-IV   | 0.741  | 1.313 |
| Pakhomova et al  | 2011 | Russian            | Russian     | Population-based | 18.9±6.7     | 65                | 111        | ICD-10   | 0.444  | 0.609 |
| Mendes de        | 1998 | European          | Caucasians  | Population-based | -            | 39                | 89         | DSM-IV   | -      | -    |
| Oliveira et al   | 1997 | European          | Caucasians  | Population-based | -            | 28.0±15.0         | 821        | ICD-10   | 0.586  | 1.61  |
| Bayle et al      | 2003 | French            | Caucasians  | Population-based | 35.0±10.0    | 185               | 159        | DSM-IV   | 0.434  | 0.529 |
| Mata et al       | 2004 | Spain             | Caucasians  | Population-based | 26.9±5.5     | 187               | 278        | DSM-IV   | 0.680  | 0.887 |
| Sanjuan et al    | 2006 | Spain             | Caucasians  | Population-based | -            | 158               | 138        | DSM-IV   | 0.500  | -     |
| Pal et al        | 2009 | Croatian          | Caucasians  | Population-based | 50.3±7.5     | 104               | 131        | ICD-10   | 0.705  | -     |
| Chong et al      | 2000 | East Asia         | Population-based | -            | 338           | 103               | 103        | DSM-IV   | 0.565  | -     |
| Pae et al        | 2006 | Korean             | Koreans     | Population-based | -            | 152               | 152        | DSM-IV   | -      | -     |
| Young et al      | 2006 | The USA           | Caucasians  | Population-based | -            | 12                | 15         | DSM-IV   | -      | -     |
| Jing et al       | 2016 | People's Republic of China | Han | Population-based | 30.9±6.7 | 624 | 683 | DSM-IV | 0.830  | 0.882 |
| Li et al         | 2013 | People's Republic of China | Han | Population-based | 33.1±11.8 | 189 | 300 | DSM-IV | 2.316  | 2.297 |
| Yang et al       | 2001 | People's Republic of China | Han | Population-based | -            | 260               | 362        | DSM-III-R | -      | -     |
| Zuo et al        | 2003 | People's Republic of China | Han | Hospital-based | -            | 157               | 185        | CCMD-II-R | 0.622  | 0.312 |
| Xuan et al       | 2012 | People's Republic of China | Han | Population-based | -            | 132               | 150        | DSM-IV   | 1.000  | 1.000 |

**Abbreviations:** CCMD-II-R, Chinese Classification of Mental Disorders, Second Edition, Revised; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD-10, International Classification of Diseases-10.
risk factor for schizophrenia ($P=0.006, \text{OR}=1.299, 95\% \text{CI}=1.079–1.565$), with a power of 0.893. No significant heterogeneity was observed in the pooled or subgroup analyses.

No association between rs140700 and the risk of schizophrenia

Under a random model, the allele frequencies of 1,770 cases and 2,386 controls were included in the pooled and subgroup analyses (Table 7). In a dominant model, no association was detected between rs140700 and the risk of schizophrenia in the pooled and subgroup analyses (Tables 3 and 4). Significant heterogeneity was observed in the pooled ($P=0.000, I^2=93.2\%) and East Asia subgroup ($P=0.000, I^2=93.5\%) analyses.

Sensitivity analysis

We conducted sensitivity analyses by omitting each study individually; the pooled ORs did not change significantly. Thus, the results were considered stable and reasonable.

Publication bias

Any publication bias was made visible by funnel plots, in which the SE of the log OR of each study was plotted against its log OR. No evidence of publication bias was found in the pooled analyses (Figures 2–7).
### Table 3: Pooled association of SLC6A4 polymorphisms with schizophrenia

| Loci         | Genetic model               | Studies (n) | Statistical OR | 95% CI         | \(P_z\) | \(P_h\) | \(P_s\) |
|--------------|----------------------------|-------------|----------------|----------------|---------|---------|---------|
| 5-HTTLPR     | Allele contrast             | 35          | Random         | 0.934          | 0.868–1.004 | 0.066   | 53.6    | 0.000   | 0.587   |
|              | Homozygous codominant       | 35          | Random         | 1.142          | 0.782–0.980  | 0.021   | 15.6    | 0.026   | 0.912   |
|              | Heterozygous codominant     | 35          | Random         | 1.085          | 0.999–1.178  | 0.054   | 10.4    | 0.294   | 0.211   |
|              | Dominant                    | 35          | Random         | 1.082          | 0.961–1.218  | 0.195   | 57.8    | 0.000   | 0.846   |
| STin2 VNTR   | 10R vs others               | 17          | Random         | 0.884          | 0.725–1.077  | 0.221   | 82.8    | 0.000   | 0.951   |
|              | 12R vs others               | 17          | Random         | 1.134          | 0.931–1.381  | 0.21    | 82.8    | 0.000   | 0.936   |
|              | 10R/10R vs others           | 17          | Random         | 0.907          | 0.624–1.319  | 0.611   | 78.9    | 0.000   | 0.401   |
|              | 10R/12R vs others           | 17          | Random         | 0.789          | 0.646–0.963  | 0.020   | 71.1    | 0.000   | 0.748   |
|              | 12R/12R vs others           | 17          | Random         | 1.936          | 1.238–3.029  | 0.004   | 94.7    | 0.000   | 0.474   |
| rs1042173    | Contrast                    | 4           | Random         | 1.094          | 0.962–1.245  | 0.17    | 22.7    | 0.275   | 0.412   |
|              | Homozygous codominant       | 4           | Random         | 1.214          | 0.921–1.600  | 0.169   | 26.4    | 0.253   | 0.336   |
|              | Heterozygous codominant     | 4           | Random         | 1.011          | 0.812–1.260  | 0.920   | 18.0    | 0.301   | 0.941   |
|              | Dominant                    | 4           | Random         | 1.077          | 0.856–1.354  | 0.528   | 26.9    | 0.250   | 0.722   |
| rs140700     | Allele contrast             | 4           | Random         | 1.052          | 0.519–1.734  | 0.863   | 92.9    | 0.000   | 0.359   |
|              | Homozygous codominant       | 4           | Random         | 0.809          | 0.236–2.774  | 0.736   | 63.7    | 0.041   | 0.223   |
|              | Heterozygous codominant     | 4           | Random         | 0.971          | 0.500–1.884  | 0.931   | 91.9    | 0.000   | 0.685   |
|              | Dominant                    | 4           | Random         | 1.003          | 0.503–1.999  | 0.993   | 93.2    | 0.000   | 0.560   |

**Abbreviations:** 5-HTTLPR, serotonin-transporter-linked polymorphic region; \(P_z\), \(P_h\), and \(P_s\)=values of association, heterogeneity, and publication bias tests, respectively; R, repeats; STin2 VNTR, second intron variable number of tandem repeats.

### Table 4: Subgroup association of SLC6A4 polymorphisms with schizophrenia

| Loci         | Subgroup analysis | Studies (n) | OR   | 95% CI         | \(P_z\) | \(P_h\) | \(P_s\) |
|--------------|-------------------|-------------|------|----------------|---------|---------|---------|
| 5HTTLPR      | Caucasians        | 21          | 1.053 | 0.974–1.138   | 0.192   | 1.6     | 0.437   |
|              | East Asia         | 12          | 1.204 | 0.953–1.521   | 0.119   | 4.1     | 0.404   |
|              | African American  | 1           | 0.834 | 0.352–1.975   | 0.679   | 0.0     | 0.000   |
|              | Indians           | 1           | 1.749 | 1.120–2.731   | 0.014   | 0.0     | 0.000   |
|              | Population-based  | 26          | 1.089 | 0.982–1.209   | 0.131   | 28.3    | 0.090   |
|              | Hospital-based    | 9           | 1.094 | 0.897–1.335   | 0.273   | 0.0     | 0.939   |
| STin2 VNTR   | Caucasians        | 9           | 0.883 | 0.645–1.207   | 0.435   | 63.7    | 0.005   |
|              | East Asia         | 7           | 0.857 | 0.310–2.374   | 0.767   | 75.5    | 0.000   |
|              | Indians           | 1           | 0.639 | 0.368–1.018   | 0.111   | –       | 0.000   |
|              | Population-based  | 16          | 0.930 | 0.639–1.354   | 0.704   | 79.8    | 0.000   |
|              | Hospital-based    | 1           | 0.155 | 0.008–3.040   | 0.220   | –       | –       |
| rs1012       | 10/12R vs others  | 9           | 0.944 | 0.832–1.072   | 0.374   | 0.0     | 0.706   |
|              | East Asia         | 7           | 0.617 | 0.389–0.978   | 0.040   | 80.8    | 0.000   |
|              | Indians           | 1           | 0.635 | 0.441–0.913   | 0.014   | –       | –       |
|              | Population-based  | 16          | 0.794 | 0.646–0.976   | 0.028   | 72.8    | 0.000   |
| rs1042173    | 10/12R vs others  | 9           | 1.042 | 0.916–1.186   | 0.531   | 0.0     | 0.885   |
|              | East Asia         | 7           | 4.482 | 2.312–8.689   | 0.000   | 92.1    | 0.000   |
|              | Indians           | 1           | 1.573 | 1.086–2.280   | 0.170   | –       | –       |
| rs140700     | 10/12R vs others  | 9           | 1.299 | 1.0791.565    | 0.006   | 0.0     | 0.421   |
|              | East Asia         | 1           | 0.834 | 0.5171.346    | 0.458   | –       | –       |
|              | Indians           | 1           | 1.213 | 0.7981.843    | 0.365   | –       | –       |

**Abbreviations:** 5-HTTLPR, serotonin-transporter-linked polymorphic region; \(P_z\), \(P_h\), and \(P_s\)=values of association and heterogeneity, respectively; STin2 VNTR, second intron variable number of tandem repeats.
### Table 5 Genotype distribution and allele frequency of STin2 VNTR

| Authors      | Year | Genotype distribution | Allele frequency |
|--------------|------|-----------------------|------------------|
|              |      | Case                  | Control          |                  |
|              |      | 10 | 12 | Others | 10 | 12 | Others | 1010 | 1012 | 1212 | Others | 1010 | 1012 | 1212 | Others |
| Fridtjof    | 1997 | 80 | 120 | 6 | 79 | 143 | 6 | 24 | 36 | 39 | 6 | 18 | 41 | 50 | 5 |
| Saiz        | 2007 | 171 | 281 | 2 | 305 | 530 | 5 | 42 | 86 | 97 | 2 | 64 | 177 | 174 | 5 |
| Liu et al20 | 1999 | 22 | 498 | 0 | 58 | 665 | 1 | 2 | 18 | 240 | 0 | 5 | 48 | 308 | 1 |
| Ikeda et al19 | 2006 | 51 | 523 | 0 | 46 | 530 | 0 | 1 | 49 | 237 | 0 | 3 | 40 | 245 | 0 |
| Lin et al17 | 2009 | 55 | 425 | 0 | 107 | 457 | 0 | 6 | 43 | 191 | 0 | 9 | 89 | 184 | 0 |
| Vijayan et al16 | 2009 | 137 | 343 | 0 | 189 | 297 | 0 | 24 | 89 | 127 | 0 | 36 | 117 | 90 | 0 |
| Lee et al15 | 2009 | 36 | 246 | 0 | 23 | 207 | 0 | 4 | 28 | 109 | 0 | 3 | 17 | 95 | 0 |
| Kaiser et al14 | 2001 | 493 | 835 | 40 | 485 | 668 | 21 | 95 | 291 | 259 | 39 | 108 | 259 | 199 | 21 |
| Tsai et al12 | 2002 | 10 | 218 | 0 | 22 | 232 | 0 | 0 | 10 | 104 | 0 | 3 | 16 | 108 | 0 |
| Herken et al11 | 2003 | 82 | 204 | 0 | 31 | 59 | 0 | 12 | 58 | 73 | 0 | 8 | 15 | 22 | 0 |
| Zaboli et al10 | 2008 | 122 | 184 | 0 | 176 | 302 | 0 | 30 | 62 | 61 | 0 | 29 | 118 | 92 | 0 |
| Herken et al10 | 2002 | 72 | 184 | 0 | 71 | 198 | 1 | 9 | 54 | 65 | 0 | 7 | 57 | 70 | 1 |
| Stober       | 1998 | 141 | 217 | 2 | 204 | 254 | 8 | 29 | 83 | 66 | 2 | 54 | 96 | 75 | 8 |
| Collier et al10 | 1996 | 94 | 162 | 2 | 169 | 202 | 3 | 19 | 56 | 52 | 2 | 42 | 85 | 57 | 3 |
| Mata et al9  | 2004 | 103 | 221 | 0 | 178 | 288 | 0 | 15 | 73 | 74 | 0 | 37 | 104 | 92 | 0 |
| Li et al9    | 2013 | 333 | 45 | 0 | 418 | 182 | 0 | 149 | 35 | 5 | 0 | 142 | 134 | 24 | 0 |
| Yang         | 2001 | 22 | 498 | 0 | 58 | 665 | 1 | 2 | 18 | 240 | 0 | 5 | 48 | 308 | 1 |

**Abbreviation:** STin2 VNTR, second intron variable number of tandem repeats.

### Discussion

We found no association between 5-HTTLPR and the risk of schizophrenia, except in Indians. The scale for Indians was small and was found in only one article; therefore, the association may be a false-positive. A negative association between 5-HTTLPR and the risk of schizophrenia was consistent with the results of the previous meta-analyses,19,21 but inconsistent with the results of Allen et al.22 Differences may exist in results found because Allen et al only analyzed articles on the SzGene in their meta-analysis. An association between suicidal behavior and 5-HTTLPR was not detected in a recent meta-analysis,83 which conflicts with previous evidence suggesting an association between 5-HTTLPR and violent suicidal behavior. The L allele of the 5-HTTLPR was reported as improving transcription of the SLC6A4 gene.84 A meta-analysis noted an association between the S allele of 5-HTTLPR and the risk of bipolar disorder.85 Psychiatric disorders share genetic variants.21 A haplotype, including 5-HTTLPR and rs16965628 markers, is thought to be associated with an obsessive–compulsive disorder.86 Therefore, 5-HTTLPR may link with other SNPs to influence the serotonergic pathway.

STin2 VNTR was associated with the risk of schizophrenia, but a significant difference was not detected in the allele analysis, inconsistent with other meta-analyses.9,19,20 Gatt et al reviewed the relevant meta-analysis between STin2 VNTR and schizophrenia and found that the 12R genotype was associated with schizophrenia as a protective factor, while 9R and 10R genotypes were not associated with schizophrenia.21 Our results showed that the 10R/12R genotype was a protective factor for schizophrenia, while the 12R/12R genotype was a risk factor for schizophrenia, in the pooled and several subgroup analyses. Genotypes with 12R may significantly increase relative 5-HTT gene expression,87 leading to increasing vulnerability to schizophrenia. STin2.12R has a superior enhancer-like property in the developing rostral hindbrain, which

### Table 6 Genotype distribution and allele frequency of rs1042173

| Authors      | Year | Genotype distribution | Allele frequency |
|--------------|------|-----------------------|------------------|
|              |      | Cases, n             | Controls, n      | \( P_{HWE} \) | Allele frequency |
|              |      | GG | GT | TT |       | GG | GT | TT |       | Cases, % | G | T | Controls, % | G | T |
| Vijayan et al15 | 2009 | 63 | 119 | 50 | 55 | 112 | 67 | 0.538 | 245 | 219 | 222 | 246 |
| Zaboli et al14 | 2008 | 39 | 78 | 38 | 59 | 129 | 59 | 0.444 | 156 | 154 | 245 | 247 |
| Carlstrom     | 2012 | 207 | 402 | 223 | 291 | 770 | 410 | 0.039 | 816 | 848 | 1,352 | 1,590 |
| Xuan et al17  | 2012 | 77 | 43 | 12 | 94 | 48 | 8 | 0.568 | 197 | 67 | 236 | 64 |

**Abbreviation:** \( P_{HWE} \), \( P \)-value of Hardy–Weinberg equilibrium.
Table 7 Genotype distribution and allele frequency of rs140700

| Authors       | Year | Genotype distribution |                 | P_{HWE} | Allele frequency |     |
|---------------|------|-----------------------|------------------|---------|------------------|-----|
|               |      | Cases, n | Controls, n | Cases, % | Controls, % | G  | A  | G  | A  |
| Li et al      | 2013 | 369      | 127         | 30       | 259      | 212 | 57 | 865 | 187 | 730 | 326 |
| Lin et al     | 2009 | 277      | 30          | 2        | 244      | 18  | 1  | 584 | 34  | 506 | 20  |
| Carlstrom     | 2012 | 689      | 140         | 2        | 1,233    | 221 | 10 | 1,518| 144 | 2,687| 241 |
| Pal et al     | 2009 | 80       | 19          | 5        | 112      | 18  | 1  | 179 | 29  | 242 | 20  |

Abbreviation: P_{HWE}, P-value of Hardy-Weinberg equilibrium.

In addition, STin2 acts as a transcriptional regulator in an allele-dependent manner in the developing mouse brain. Haplotype analysis demonstrated that two STin2-containing haplotypes were associated with the risk of schizophrenia, but no association was found in the single locus. No association was detected in Caucasians and Indians, which may be the result of different genetic backgrounds. Significant heterogeneity was assessed in the pooled analysis, and heterogeneity was found in all subgroups, except Caucasians. This was the first meta-analysis of the association between the risk of schizophrenia and rs1042173 and rs140700.

Gatt et al comprehensively reviewed a meta-analysis of the association between SLC6A4 (5-HTTLPR and STin2 VNTR) and schizophrenia. To some extent, it would seem that our meta-analysis is superfluous. However, it was an updated analysis, assessing the association of the SLC6A4 gene with schizophrenia using high statistical powers. Our study also included seven studies published after 2013 and three studies in Chinese. Moreover, four variations (5-HTTLPR, STin2 VNTR, rs1042173, and rs140700) were analyzed in our meta-analysis. Genome-wide association studies (GWASs) can discover novel and unexpected candidate loci in an unbiased manner. Previous GWAS analyses found that the SLC6A4 gene was not associated with schizophrenia. A comparison of 12 single-disorder GWAS meta-analyses suggested no overlap in significant genetic variants identified from the different studies. However, structural magnetic resonance imaging scans suggested that SLC6A4 was related to deficits of brain structural networks in schizophrenia. Our results are inconsistent with those of the previous meta-analysis. Several reasons for this may exist: First, many recently published studies were included in our analysis; therefore, the scale of samples used was larger than those used before. Second, the articles from both English and Chinese language databases were included. Third, geographical environment, culture, lifestyle, and genetic background and diseases may affect genetic polymorphisms.

Significant heterogeneity was found in overall and subgroup analyses, especially for STin2 VNTR and rs140700. Although we performed subgroup analyses according to ethnicity to investigate potential sources of heterogeneity,
this did not completely account for the heterogeneity. These results suggest that other aspects may partially contribute to heterogeneity, such as distinct genetic backgrounds and the different habits and customs of the people sampled.97

Overall, however, the results described herein should be interpreted with caution. First, the small sample size for rs1042173 and rs140700 should be borne in mind. Several associations only appeared in the subgroup analyses, for which only one or two articles were used. Therefore, these samples may not be representative and comprehensive. In addition, it was hard to conduct subgroup analyses for some SNPs because of so few articles. Second, deviations in the $P_{\text{HWE}}$ and significant heterogeneity were observed in this study because of sample bias. Third, family-based studies, which were more robust than case-control designs, were not included in this analysis.98–101 Fourth, interactions between multiple genes and SNPs may affect the risk of schizophrenia,21 meaning that genetic interactional and functional studies are needed.

**Conclusion**

Our meta-analysis showed a lack of association between 5-HTTLPR and the risk of schizophrenia, except in an Indian subgroup analysis. The 10R/12R genotype was a protective factor against schizophrenia, while the 12R/12R genotype was a risk factor for schizophrenia in the pooled analyses. In Caucasians, the GG genotype of rs1042173 may be a risk factor for schizophrenia. No association was found between rs140700 and the risk of schizophrenia. Increased genetic interactional and functional studies are warranted to explore the association between polymorphisms of the *SLC6A4* gene and schizophrenia risk.
Disclosure

The authors report no conflicts of interest in this work.

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