Review Article
Association between netrin G1 genetic variation and schizophrenia: a meta-analysis

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Abstract: Objective: Previous researches have reported that netrin G1 gene polymorphisms was associated with schizophrenia risk, but the results are inconsistent. Consequently, we implemented a meta-analysis to reveal the connection between the single nucleotide polymorphisms (SNPs) (rs1373336, rs2218404 and rs4132604) in NTNG1 gene and schizophrenia. Methods: Eligible case-control literatures that were published up to August 2016 were collected via searching PubMed, Cochrane Library, CNKI, Medline, Embase and Science Direct web of knowledge databases. Pooled odds ratio with 95% confidence interval were applied to access the strength of association in fixed- or random-effects model. Genotype distributions in the controls were tested for agreement with the Hardy-Weinberg equilibrium (HWE) using the χ² test. Publication bias of the literature was evaluated by funnel plots and Begg’s test. Results: The meta-analysis incorporated four eligible studies. There were 2,705 cases and 2,707 controls for SNP rs1373336, 2,723 cases and 2,770 controls for SNP rs2218404 and 1,371 cases and 1,382 controls for SNP rs4132604. This meta-analysis proved a significant association between rs4132604 and schizophrenia risk under dominant, OR 0.71, 95% CI 0.61-0.84, P=0.000; heterozygous, OR 0.72, 95% CI 0.61-0.85, P=0.000; homozygous, OR 0.70, 95% CI 0.57-0.87, P=0.001; and allelic, OR 0.82, 95% CI 0.74-0.91, P=0.000. However, no combination was found in the recessive model (OR: 0.86; 95% CI: 0.71-1.03, P=0.087). In addition, there was no significant association between rs1373336, rs2218404 and schizophrenia risk. Conclusion: This meta-analysis suggested that the SNP rs4132604 in NTNG1 gene might be responsible for schizophrenia susceptibility. Keywords: NTNG1, polymorphism, schizophrenia, meta-analysis

Introduction
Schizophrenia is one of the serious mental diseases commonly seen clinically which has a strong hereditary [1]. Its primary characteristics are miscellaneous psychotic symptoms including auditory hallucinations, delusions, altered emotional reactivity, cognitive impairment, social isolation and so on [2, 3]. Several environmental factors have been observed to play a role in the etiology of schizophrenia, such as exposure to viral infections during pregnancy, vitamin D levels in infant and socioeconomic status [4]. Family studies, especially twin studies suggested that genetic factors also play an important role in schizophrenia occurrence [5-7]. Ripke et al. found that 22 genomic regions contribute to schizophrenia etiology by using multi-stage genome-wide association study (GWAS). Moreover, around 8300 independent single nucleotide polymorphisms (SNPs) were associated with the increased risk of schizophrenia [8].

A number of studies have shown that schizophrenia evolves from the early brain injury happened during neurodevelopment [9, 10]. Several cellular and signaling transduction genes for schizophrenia pathophysiology which encode the axon growth cone and nerve cell migration have been found to participate in this process. These genes include the families of ephrins, semaphorins, netrins and so on [11]. Netrin G1 (NTNG1) belonging to the family of synaptic adhesion molecules, serves as a guidance cue in axon migration during neurodevel-
opment [12, 13]. NTNG1 is located at chromosome 1p13.3 zone which is also the linkage zone of pathogenesis of schizophrenia [14, 15]. Recently, a genome wide association study found that NTNG1 genetic variants are associated with schizophrenia [14, 16]. The role of the three genotypes of tag single nucleotide polymorphisms (SNPs) (rs1373336, rs2218404 and rs4132604) of NTNG1 in the risk of schizophrenia remains controversial.

Therefore, we implemented a meta-analysis via collecting all the available studies to comprehensively evaluate the overall effect of the three SNPs on schizophrenia.

Materials and methods

Literature search

Systematic retrieval of all published literatures up to August 2016 was conducted via searching PubMed, Cochrane Library, CNKI, Medline, Embase and Science Direct web of knowledge databases using the terms “NTNG1”, “netrin G1”, “laminet-1” and “schizophrenia”, combining with both Medical Subject Headings (MeSH) and free words. Retrieval was performed by two investigators independently. In order to obtain comprehensive literatures, we evaluated possibly relevant publications by censoring their titles, abstracts and references. This meta-analysis only included published studies with full-text articles. Literature languages were limited to English and Chinese.

Inclusion and exclusion criteria

All studies met the following criteria: (1) the primary studies contained the relationship between NTNG1 gene and schizophrenia; (2) investigations were case-control or family-based studies in human subjects; (3) schizophrenia cases were diagnosed with International Classification of Diseases, Diagnostic and Statistical Manual (DSM-IV), or Chinese Classification of Mental Disorders systems (ICD-10); and (4) controls were free of schizophrenia or other major mental disorders and the genotype distribution of control group must be obedient to Hardy-Weinberg Equilibrium (HWE).

Studies with the following conditions were ruled out: (1) not providing complete data; (2) case only, case report or review; (3) not containing the three SNPs (rs1373336, rs2218404 and rs4132604); (4) genotype distributions of the control group were deflected from HWE; and (5) duplications of the published literatures.

Data extraction

Two investigators (Yajie Yu and Ming Fang) extracted data from qualified literatures independently; discussions were carried out to settled the disagreements, and the third author was consulted to assist resolving the divergences when necessary. The extracted data include the following information: the name of first author, publication year, ethnicity, mean ages and male percentage in case and control groups, definition of cases, and genotyping distributions.

Statistical analysis

HWE was assessed in control samples using a standard $\chi^2$ test ($P>0.05$), and studies not subject to HWE were removed. Odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the association between NTNG1 polymorphisms and increased risk of schizophrenia. Pooled effect was calculated for the allele model (A versus B), recessive model (AA versus AB+BB), dominant model (AA+AB versus BB) and additive model (AA versus BB or AB versus BB). Q test was applied to assess the heterogeneity among studies, and the heterogeneity was considered significant when $P<0.05$. Then heterogeneity was qualified by Higgins $I^2$ to evaluate whether the research comes were from the same overall. The fixed model was used when a significant Q test ($P>0.05$) or $P<50\%$ indicated homogeneity across studies. When $P>50\%$, the random effect model was applied. The evidence for publication bias was assessed by Funnel plot and Begg’s test. Sensitivity analysis was conducted to assess the influence of each study on overall pooled result via sequentially excluding each individual study.

Results

Characteristics of included studies

In the preliminary searching, seventy-nine possibly relevant studies were identified, among
which thirty publications were duplicate and another forty-nine were not relevant to NTNG1 polymorphism and schizophrenia. After reviewing the rest eight full texts, four studies were rejected (three didn’t focus on rs1373336, rs2218404 and rs4132604; One Chinese study had the same data with Zhu et al. 2011). Eventually, four studies [17-20] were considered eligible for this meta-analysis. The flow chart of search and selection process is illustrated in Figure 1.

All four studies were available to evaluate the association of NTNG1 polymorphisms with the risk of schizophrenia, and they all contain the three SNP genotypes (rs1373336, rs2218404 and rs4132604). A total of three races were discussed in the articles: Japanese, Chinese and North American. The characteristics included in the meta-analysis are shown in Table 1. The alleles and genotypes of these 4 studies as well as the results of HWE test are all listed in Table 2.

Figure 1. Flow diagram of the literature search and selection.
### Table 1. Characteristics of the eligible studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Published year</th>
<th>Ethnicity</th>
<th>Schizophrenia cases N</th>
<th>Mean age</th>
<th>Gender (% male)</th>
<th>Healthy controls N</th>
<th>Mean age</th>
<th>Gender (% male)</th>
<th>Definition of schizophrenia</th>
<th>Genotyping method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukasawa M</td>
<td>2004</td>
<td>Japanese</td>
<td>180</td>
<td>Male 40.3±8.6</td>
<td>50</td>
<td>180</td>
<td>Male 39.3±11.5</td>
<td>50</td>
<td>DSM-IV</td>
<td>PCR</td>
</tr>
<tr>
<td>Ohtsuki T</td>
<td>2008</td>
<td>Japanese</td>
<td>2174</td>
<td>Female 47.1±13.0</td>
<td>50</td>
<td>2056</td>
<td>Female 49.1±14.3</td>
<td>50</td>
<td>DSM-IV</td>
<td>NA</td>
</tr>
<tr>
<td>Zhu Y</td>
<td>2011</td>
<td>Chinese</td>
<td>316</td>
<td>37.75±8.83</td>
<td>53.5</td>
<td>311</td>
<td>38.5±9.81</td>
<td>51.8</td>
<td>DSM-IV</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Wilcox JA</td>
<td>2014</td>
<td>American</td>
<td>302</td>
<td>40</td>
<td>NA</td>
<td>310</td>
<td>NA</td>
<td>NA</td>
<td>DSM-IV</td>
<td>NA</td>
</tr>
</tbody>
</table>

DSM-IV, Diagnosis and statistical manual of mental health disorders, fourth edition; NA, Not available from the published study; PCR = Polymerase chain reaction, RELP = Restriction fragment length polymorphisms.

### Table 2. Distributions of alleles and genotypes in individual studies

#### (A) Studies for rs1373336 polymorphism

<table>
<thead>
<tr>
<th>First author, published year</th>
<th>Allele</th>
<th>Genotype</th>
<th>HWE P. value for controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>Control</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>T</td>
<td>C</td>
</tr>
<tr>
<td>Fukasawa M, 2004</td>
<td>238</td>
<td>118</td>
<td>205</td>
</tr>
<tr>
<td>Ohtsuki T, 2008</td>
<td>2220</td>
<td>1588</td>
<td>2200</td>
</tr>
<tr>
<td>Zhu Y, 2011</td>
<td>270</td>
<td>352</td>
<td>285</td>
</tr>
<tr>
<td>Wilcox JA, 2014</td>
<td>269</td>
<td>355</td>
<td>284</td>
</tr>
</tbody>
</table>

#### (B) Studies for rs2218404 polymorphism

<table>
<thead>
<tr>
<th>First author, published year</th>
<th>Allele</th>
<th>Genotype</th>
<th>HWE P. value for controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>Control</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>T</td>
<td>G</td>
</tr>
<tr>
<td>Fukasawa M, 2004</td>
<td>284</td>
<td>74</td>
<td>281</td>
</tr>
<tr>
<td>Ohtsuki T, 2008</td>
<td>3037</td>
<td>795</td>
<td>2971</td>
</tr>
<tr>
<td>Zhu Y, 2011</td>
<td>530</td>
<td>94</td>
<td>521</td>
</tr>
<tr>
<td>Wilcox JA, 2014</td>
<td>533</td>
<td>99</td>
<td>630</td>
</tr>
</tbody>
</table>

#### (C) Studies for rs4132604 polymorphism

<table>
<thead>
<tr>
<th>First author, published year</th>
<th>Allele</th>
<th>Genotype</th>
<th>HWE P. value for controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>Control</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>T</td>
<td>G</td>
</tr>
<tr>
<td>Fukasawa M, 2004</td>
<td>203</td>
<td>155</td>
<td>200</td>
</tr>
<tr>
<td>Ohtsuki T, 2008</td>
<td>650</td>
<td>488</td>
<td>633</td>
</tr>
<tr>
<td>Zhu Y, 2011</td>
<td>361</td>
<td>255</td>
<td>312</td>
</tr>
<tr>
<td>Wilcox JA, 2014</td>
<td>373</td>
<td>257</td>
<td>320</td>
</tr>
</tbody>
</table>

HWE, Hardy-Weinberg equilibrium.

**NTNG1 rs1373336 polymorphism was not associated with schizophrenia risk**

The ORs with corresponding 95% CIs for the possible association between rs1373336 polymorphism in NTNG1 and the risk of schizophrenia are summarized in Table 3. In the total population of 2705 cases and 2707 controls, rs1373336 polymorphism demonstrated no significant association with schizophrenia in all five genetic models: dominant, OR 0.97, 95% CI 0.86-1.09, P=0.618 ([Figure 2A](#)); recessive, OR 0.98, 95% CI 0.86-1.12, P=0.764 ([Figure 2B](#)); heterozygous, OR 0.98, 95% CI 0.87-1.11, P=0.749 ([Figure 2C](#)); homozygous, OR 0.95, 95% CI 0.82-1.11, P=0.551 ([Figure 2D](#)); allelic, OR 0.98, 95% CI 0.91-1.06, P=0.617 ([Figure 2E](#)).

**NTNG1 rs2218404 polymorphism exhibited no association with risk of schizophrenia**

For rs2218404 polymorphism, which involves 2723 schizophrenia patients and 2770 controls in four subjects, the results of analyzing the relationship between rs2218404 polymorphism and schizophrenia risk are summarized in Table 3. In different genetic models, the pooled ORs revealed no significant association between rs2218404 polymorphism and increased risk of schizophrenia. Detailed results are as follows: dominant, OR 0.94, 95% CI 0.72-1.22, P=0.625 ([Figure 2A](#)); recessive, OR 1.12, 95% CI 1.00-1.25, P=0.052 ([Figure 2B](#)); heterozygous, OR 0.86, 95% CI 0.66-1.13, P=0.277 ([Figure 2C](#)); homozygous, OR 0.98, 95%
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A total of 1371 cases and 1382 healthy controls were included in the four studies. Results of meta-analysis are shown in Table 3. The meta-analysis indicated that there was a statistically significant association between NTNG1 rs4132604 polymorphism and the risk of schizophrenia. The rs4132604 polymorphism was observed associated with elevated schizophrenia risk in four models: dominant, OR 0.71, 95% CI 0.61-0.84, \( P = 0.000 \) (Figure 2A); heterozygous, OR 0.72, 95% CI 0.61-0.85, \( P = 0.000 \) (Figure 2C); homozygous, OR 0.70, 95% CI 0.57-0.87, \( P = 0.001 \) (Figure 2D); allelic, OR 0.82, 95% CI 0.74-0.91, \( P = 0.000 \) (Figure 2E); however, no association was found in recessive model (Figure 2B). Overall, the results suggested that allele T was determined to be the protective allele and T-allele may reduce the risk of schizophrenia.

HWE and sensitivity analysis

The \( P \) value of the genotype distribution for HWE are shown in Table 1, and the control groups of the four studies were consistent with HWE. The results were stabilized because there was no significant heterogeneity in any of the genetic models. Sensitivity analysis of each individual study was not conducted due to the limitations of eligible studies.

Table 3. Main results of pooled ORs and stratification analysis of three polymorphisms on schizophrenia risk in the meta-analysis

<table>
<thead>
<tr>
<th>Gene locus</th>
<th>Genetic model</th>
<th>( \hat{I}^2 ) (%)</th>
<th>( P ) heterogeneity</th>
<th>OR</th>
<th>95% CI</th>
<th>( P_{or} )</th>
<th>( P ) for Begg's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1373336</td>
<td>C vs T</td>
<td>59.4</td>
<td>0.061</td>
<td>0.98</td>
<td>(0.91, 1.06)</td>
<td>0.617</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>TT vs CC</td>
<td>55.9</td>
<td>0.078</td>
<td>0.95</td>
<td>(0.82, 1.11)</td>
<td>0.551</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>CT vs CC</td>
<td>0</td>
<td>0.561</td>
<td>0.98</td>
<td>(0.87, 1.11)</td>
<td>0.749</td>
<td>0.308</td>
</tr>
<tr>
<td></td>
<td>TT vs CC+CT</td>
<td>51.9</td>
<td>0.101</td>
<td>0.98</td>
<td>(0.86, 1.12)</td>
<td>0.764</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>TT+TC vs CC</td>
<td>26.8</td>
<td>0.251</td>
<td>0.97</td>
<td>(0.86, 1.09)</td>
<td>0.618</td>
<td>1.000</td>
</tr>
<tr>
<td>rs2218404</td>
<td>T vs G</td>
<td>0</td>
<td>0.551</td>
<td>1.07</td>
<td>(0.98, 1.18)</td>
<td>0.142</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>GG vs TT</td>
<td>2.2</td>
<td>0.381</td>
<td>0.98</td>
<td>(0.75, 1.27)</td>
<td>0.874</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>GT vs TT</td>
<td>0</td>
<td>0.428</td>
<td>0.86</td>
<td>(0.66, 1.13)</td>
<td>0.277</td>
<td>0.308</td>
</tr>
<tr>
<td></td>
<td>GG vs TT+GT</td>
<td>0</td>
<td>0.657</td>
<td>1.12</td>
<td>(1.00, 1.25)</td>
<td>0.052</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>GG+GT vs TT</td>
<td>0</td>
<td>0.392</td>
<td>0.94</td>
<td>(0.72, 1.22)</td>
<td>0.625</td>
<td>0.734</td>
</tr>
<tr>
<td>rs4132604</td>
<td>G vs T</td>
<td>51.6</td>
<td>0.102</td>
<td>0.82</td>
<td>(0.74, 0.91)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>TT vs GG</td>
<td>55.0</td>
<td>0.083</td>
<td>0.70</td>
<td>(0.57, 0.87)</td>
<td>0.001</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>GT vs GG</td>
<td>0</td>
<td>0.905</td>
<td>0.72</td>
<td>(0.61, 0.85)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>TT vs GG+GT</td>
<td>54.4</td>
<td>0.087</td>
<td>0.86</td>
<td>(0.71, 1.03)</td>
<td>0.099</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>TT+GT vs GG</td>
<td>0</td>
<td>0.490</td>
<td>0.71</td>
<td>(0.61, 0.84)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

\( \hat{I}^2 \), Inconsistency index; OR, Odds ratio; CI, Confidence interval.

Discussion

Schizophrenia is a common and devastating mental disorder of unknown etiology [21, 22]. Multiple factors including inner genetic and outer environmental variables are thought to contribute to its overall susceptibility [17]. The developing nervous system depends on the actions of various secreted factors and membrane proteins that allow neuronal axons to find their correct targets [23]. NTNG1 is located on chromosome 1p13.3 which is also the linkage zone of pathogenesis of schizophrenia [16]. Therefore, NTNG1 has the potential relevance to neurodevelopment. Furthermore, the polymorphisms of NTNG1 gene have been reported to affect the risk of schizophrenia [11, 14, 19]. However, these studies demonstrated...
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A

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1373336</td>
<td>0.65 (0.42, 0.99)</td>
<td>8.94</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>0.98 (0.86, 1.13)</td>
<td>74.27</td>
</tr>
<tr>
<td>Ohtsuki T(2008)</td>
<td>1.08 (0.73, 1.60)</td>
<td>8.46</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>1.09 (0.74, 1.61)</td>
<td>8.33</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.97 (0.86, 1.09)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I² = 26.8%, p = 0.251)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2218404</td>
<td>0.59 (0.21, 1.65)</td>
<td>8.29</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>1.06 (0.79, 1.43)</td>
<td>72.54</td>
</tr>
<tr>
<td>Ohtsuki T(2008)</td>
<td>0.70 (0.26, 1.85)</td>
<td>8.37</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>0.57 (0.23, 1.40)</td>
<td>10.80</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.94 (0.72, 1.22)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.392)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs4132604</td>
<td>0.81 (0.52, 1.26)</td>
<td>12.45</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>0.80 (0.62, 1.02)</td>
<td>39.60</td>
</tr>
<tr>
<td>Ohtsuki T(2008)</td>
<td>0.64 (0.46, 0.91)</td>
<td>23.38</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>0.60 (0.42, 0.84)</td>
<td>24.57</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.71 (0.61, 0.84)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.490)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1373336</td>
<td>0.55 (0.29, 1.02)</td>
<td>6.21</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>0.93 (0.79, 1.10)</td>
<td>65.76</td>
</tr>
<tr>
<td>Ohtsuki T(2008)</td>
<td>1.18 (0.84, 1.65)</td>
<td>14.09</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>1.20 (0.86, 1.69)</td>
<td>13.94</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.98 (0.86, 1.12)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I² = 51.9%, p = 0.101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2218404</td>
<td>1.18 (0.77, 1.81)</td>
<td>6.54</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>1.14 (1.00, 1.29)</td>
<td>71.82</td>
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<td>1.18 (0.83, 1.67)</td>
<td>9.90</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>0.91 (0.65, 1.28)</td>
<td>11.74</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>1.12 (1.00, 1.25)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.657)</td>
<td></td>
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<tr>
<td>rs4132604</td>
<td>1.16 (0.69, 1.95)</td>
<td>10.87</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>1.05 (0.78, 1.41)</td>
<td>36.01</td>
</tr>
<tr>
<td>Ohtsuki T(2008)</td>
<td>0.68 (0.46, 1.00)</td>
<td>26.13</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>0.64 (0.44, 0.95)</td>
<td>26.98</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.86 (0.71, 1.03)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I² = 54.4%, p = 0.087)</td>
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</tbody>
</table>
Netrin G1 genetic variation and schizophrenia

**Figure C**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1373336</td>
<td>0.71 (0.45, 1.12)</td>
<td>8.67</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>1.00 (0.87, 1.16)</td>
<td>74.03</td>
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<tr>
<td>Ohtsuki T(2008)</td>
<td>1.02 (0.87, 1.54)</td>
<td>6.89</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>1.02 (0.67, 1.54)</td>
<td>8.61</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.98 (0.87, 1.11)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.561)</td>
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</tr>
<tr>
<td>rs2218404</td>
<td>0.50 (0.17, 1.46)</td>
<td>8.61</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>0.97 (0.71, 1.33)</td>
<td>72.46</td>
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<tr>
<td>Ohtsuki T(2008)</td>
<td>0.60 (0.22, 1.64)</td>
<td>8.74</td>
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<tr>
<td>Zhu Y(2011)</td>
<td>0.58 (0.23, 1.50)</td>
<td>10.19</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.86 (0.66, 1.13)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.428)</td>
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</tr>
</tbody>
</table>

**Figure D**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1373336</td>
<td>0.75 (0.47, 1.20)</td>
<td>12.99</td>
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<tr>
<td>Fukasawa M(2004)</td>
<td>0.76 (0.59, 1.00)</td>
<td>40.91</td>
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<tr>
<td>Ohtsuki T(2008)</td>
<td>0.69 (0.48, 1.00)</td>
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<tr>
<td>Zhu Y(2011)</td>
<td>0.65 (0.45, 0.94)</td>
<td>23.68</td>
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<tr>
<td>Wilcox JA(2014)</td>
<td>0.72 (0.61, 0.85)</td>
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<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.905)</td>
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<tr>
<td>rs2218404</td>
<td>0.64 (0.22, 1.82)</td>
<td>8.11</td>
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<tr>
<td>Fukasawa M(2004)</td>
<td>1.19 (0.78, 1.86)</td>
<td>10.92</td>
</tr>
<tr>
<td>Ohtsuki T(2008)</td>
<td>1.22 (0.78, 1.91)</td>
<td>10.69</td>
</tr>
<tr>
<td>Zhu Y(2011)</td>
<td>0.95 (0.82, 1.11)</td>
<td>100.00</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
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<tr>
<td>Subtotal (I-squared = 55.9%, p = 0.078)</td>
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<tr>
<td>rs4132604</td>
<td>0.64 (0.22, 1.82)</td>
<td>8.11</td>
</tr>
<tr>
<td>Fukasawa M(2004)</td>
<td>1.19 (0.78, 1.86)</td>
<td>10.92</td>
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<tr>
<td>Ohtsuki T(2008)</td>
<td>1.22 (0.78, 1.91)</td>
<td>10.69</td>
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<tr>
<td>Zhu Y(2011)</td>
<td>0.95 (0.82, 1.11)</td>
<td>100.00</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td></td>
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</tr>
<tr>
<td>Subtotal (I-squared = 2.2%, p = 0.381)</td>
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<tr>
<td>rs4132604</td>
<td>0.97 (0.54, 1.77)</td>
<td>10.91</td>
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<tr>
<td>Fukasawa M(2004)</td>
<td>0.89 (0.63, 1.24)</td>
<td>35.85</td>
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<tr>
<td>Ohtsuki T(2008)</td>
<td>0.56 (0.35, 0.85)</td>
<td>26.00</td>
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<tr>
<td>Zhu Y(2011)</td>
<td>0.49 (0.31, 0.77)</td>
<td>27.23</td>
</tr>
<tr>
<td>Wilcox JA(2014)</td>
<td>0.70 (0.57, 0.87)</td>
<td>100.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 55.0%, p = 0.083)</td>
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controversial results because of their small sample sizes and different populations. In order to get more reliable results, we conducted a comprehensive meta-analysis to access the association between NTNG1 gene and schizophrenia.

To the best of our knowledge, this is the first meta-analysis investigating the correlation between NTNG1 polymorphisms and schizophrenia. A total of 2972 cases and 2857 controls of 4 studies were included in this meta-analysis. We made a systematically analysis to explore the associations between the three potentially functional variants (rs1373336, rs2218404 and rs4132604) within NTNG1 gene and the schizophrenia risk. Overall, our results suggested that neither allele frequency nor the genetic models of rs1373336 and rs2218404 polymorphisms was associated with schizophrenia risk when all studies were pooled together. Ethnicity is usually considered as a potential influence factor of the risk of common diseases due to different genetic backgrounds and environmental exposures. This might be the main reason for the replication failure. Ohtsuki et al. found that rs2218404 of NTNG1 is associated with schizophrenia risk in Japanese whereas Wilcox et al. reported that there is no significant correlation between rs2218404 and schizophrenia in North American. The different genetic backgrounds between Japanese and North American ancestries may have led to the opposite results.

Importantly, our study demonstrated statistical evidence for a significant association between NTNG1 rs4132604 polymorphism and the risk of schizophrenia under four genetic models. In rs4132604, the frequency of allele G was significantly higher than allele T frequency, suggesting the chromosome contained allele G (OR 0.82, 95% CI 0.74-0.91, \(P=0.000\)) has markedly effects on the susceptibility to schizophrenia.

Figure 2. Forest plots for the association of rs1373336, rs2218404 and rs4132604 polymorphism and schizophrenia in five genetic models. A. (AA+AB versus BB): Dominant model; B. (AA versus AB+BB): Recessive model; C. (AA versus BB): Heterozygous; D. (AB versus BB): Homozygous; E. (A versus B): Allele model. The rs4132604 polymorphisms are significantly associated with schizophrenia. 95% CI, 95% confidence interval.
nia while allele T may reduce the risk of schizophrenia. Thus, NTNG1 may play an essential role in the etiology of schizophrenia.

Several limitations of the current meta-analysis should be noted. First of all, the sample size is small, with only 4 literatures meet our inclusion criteria; the small sample size might lead to insufficient power for the detection of slight association. Secondly, the potential effect of gene-gene or gene-environment interactions on the statistical analysis was not considered. Thirdly, we carried out a systemic literature search only in English and Chinese; some potentially relevant studies might be neglected because of the language. Finally, the majority of the samples were Asia population.

Disclosure of conflict of interest

None.

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References


