No association between the Ser9Gly polymorphism of the dopamine receptor D3 gene and schizophrenia: a meta-analysis of family-based association studies

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Abstract

Background: Ser9Gly (rs6280) is a functional single nucleotide polymorphism (SNP) in the human dopamine receptor D3 gene (DRD3) that may be involved in the occurrence of schizophrenia. We performed a meta-analysis of family-based studies to explore the role of Ser9Gly in the etiology of schizophrenia.

Methods: The published family-based association studies were retrieved from the relevant literature databases according to the established inclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the strength of the relationship between Ser9Gly SNP and the occurrence of schizophrenia.

Results: We finally pooled up 13 family-based association studies between Ser9Gly SNP and schizophrenia. It contained 11 transmission disequilibrium test (TDT) studies with 1219 informative meiosis and 5 haplotype-based haplotype relative risk (HHRR) studies. There was no statistical significance for the heterogeneity in TDT and HHRR studies. Therefore, the fixed effect model was used to measure the pooled effect size. The results showed that neither of the associations between Ser9Gly and the risk of schizophrenia were observed in TDT (1219 samples, OR=1.005, 95% CI = 0.898-1.125, Z-value = 0.086, p = 0.932) and HHRR studies (1704 samples, OR=0.869, 95% CI = 0.713-1.059, Z-value = -1.395, p = 0.163), except for the significantly preferential transmission of DRD3 Ser9 allele in East Asian in TDT studies (204 samples, OR=0.744, 95% CI = 0.564-0.980, Z-value = -2.104, p = 0.035).

Conclusions: Our meta-analysis found no association between DRD3 gene Ser9Gly polymorphism and the risk of schizophrenia. These data provide possible avenues for future family-based studies related to schizophrenia.

1. Introduction

Schizophrenia is a complex mental disorder and affects approximately 1% of the population all over the world, which is caused by synergic effects of multiple genetic and environmental factors.[1] Heritability up to 80% has been reported for schizophrenia.[2] Despite the extensive efforts for many years, the precise etiology of this disease is still unclear.[3, 4] Presently, the dysregulated dopaminergic neurotransmission has been found to play a role in the pathogenesis of schizophrenia.[5-8] The genes related to the dopaminergic pathways are considered as the candidate susceptible genes of the disease.

As an endogenous neurotransmitter, dopamine plays a regulatory function by binding to the dopamine receptors. Its regulatory roles are mediated by two families of G protein-coupled receptors: the D1 and D2 receptor families. Presently, the known subtypes of dopamine receptors include the D1-like receptors, such as D1 and D5 receptors; and the D2-like receptors, such as D2, D3 and D4 receptors.[9] Dopamine receptor D3 (DRD3) is a candidate susceptible gene for the risk of schizophrenia. DRD3 is located on the chromosome 3q13.3 and has 52% global homology with the D2 receptor band. It is primarily expressed in limbic areas of the human brain[10] and contributes emotional, cognitive, as well as endocrine functions.[11]

Ser9Gly variant (rs6280) is a functional polymorphic site in the first exon, which corresponds to a serine to glycine amino acid substitution at position 9 in the extracellular N-terminal domain of DRD3. Ser9Gly SNP has been involved in the alternation of dopamine binding affinity.[12] The substituted glycine allele is thought to yield D3 autoreceptors owning a higher affinity for dopamine and more robust intracellular signaling.[13] Presently, Ser9Gly polymorphisms are reported to be associated with acute pain in sickle cell disease, bipolar disorder, Parkinson's disease, and suicidical behaviors.[14-17] Recently, a number of molecular epidemiologic studies have addressed the association between Ser9Gly and schizophrenia risk. However, some reporters suggested that Ser9Gly was associated with the disease,[18, 19] whereas the others found no association.[20-22] These contradictory results may be due to small sample size, inclusion of various genetic backgrounds, and other potential confounding bias.[23]

Meta-analyses are proven to be the powerful tool for ascertaining associations of gene polymorphisms with disease.[24, 25] Since 1998, the meta-analysis have been performed to assess the association between Ser9Gly SNP and schizophrenia risk.[26-32] However, all of the pooled results were based on the case-control studies, but not the family-based studies. The family-based studies are more powerful to detect risk factors of schizophrenia, considering that the ability to exploit the cosegregation of variants with schizophrenia within families helps distinguish causal from noncausal factors.[33] Therefore, we perform a meta-analysis of family-based association studies to better evaluate the relationship between DRD3 Ser9Gly SNP and the risk of schizophrenia.

2. Materials And Methods

2.1. Literature search
To identify studies eligible for this meta-analysis, the computerized search was conducted on three online electronic English databases (Medline, Embase, and Web of Science) and one online Chinese CNKI database using the following key words: “DRD3”, “dopamine receptor 3”, “dopamine D3 receptor”, “dopamine receptor D3”, “schizophrenia”, and “Ser9Gly”. We also screened the reference lists of the accessed articles and of potentially relevant review articles to identify additional studies.

2.2. Inclusion criteria

Only the studies examining Ser9Gly SNP were included in the present meta-analysis. Moreover, the studies needed to meet the following inclusion criteria: (1) family-based design (transmission disequilibrium test (TDT) or haplotype-based haplotype relative risk (HHRR)); (2) original data, or available data to calculate an effect; (3) independent from other studies (i.e., studies reported by the same authors contained the same or overlapping data, the latest literature was selected). Using this approach, a total of 13 articles were identified and included in our meta-analysis. The flow diagram of the literature search process was showed in Fig. 1.

2.3 Data extraction

According to the inclusion criteria listed above, two authors extracted information from all eligible publications independently. Any disagreement was resolved through discussion until the two authors reached a consensus. The following details of each article were recorded: the first author’s last name, publication year, location, ethnicity, diagnostic criteria, and numbers of transmissions.

2.4. Meta-analytic methods

The meta-analysis of the family-based association studies was divided into two parts: TDT and HHRR. For the TDT study, each study provided the two-by-two transmission disequilibrium table, which classifies heterozygous parental alleles (informative meioses) by transmission status (Ser9 allele transmitted to the schizophrenic offspring) and data type (the number of observed transmission vs. the number of theoretic transmission).[34] For one informative meiosis, the expected transmitted number that the allele is transmitted from heterozygous parents to the proband is 0.5 and the expected untransmitted number that the allele is not transmitted from heterozygous parents to proband is also 0.5. For the HHRR studies, each study provided the two-by-two HHRR table, which classifies parental alleles by type of allele (Ser9 or Gly9) and transmission status (transmitted to the schizophrenic offspring or not).[34]

The degree of heterogeneity between studies was determined by means of the Q statistic.[35, 36] Specifically, $P > 0.05$ by the Q test indicated the absence of heterogeneity, and $P < 0.05$ indicated heterogeneity. $I^2$ was defined as the proportion of observed variance in effect sizes attributable to true differences among studies. Conventional interpretations of $I^2$ include limits for low (<25%), moderate (approximately 50%), and high (>75%) heterogeneity.[37] A random effect model was used when heterogeneity was present ($P<0.05$ and/or $I^2 >50$); otherwise, a fixed effect model was applied[35] and the fixed effect model used the method of Mantel and Haenszel.[38]

For the pooled analysis, odds ratios (ORs) with accompanying 95% confidence intervals (CIs) were used to assess the strength of the association in the two-by-two tables. $P > 0.05$ indicated the absence of statistical significance, and $P < 0.05$ indicated statistical significance. When $P < 0.05$, OR < 1 meant the variation as a protective factor, and OR > 1 meant the variation as a risk factor. Pooled calculations of ORs were obtained and compared with the controls (observed transmission vs. expected transmission for TDT study or transmitted vs. untransmitted for HHRR study) using test statistic z and 95% CIs. Subgroup analysis was carried out by ethnicity (i.e., East Asian, Caucasian, and other populations).

Publication bias was assessed by the funnel plot (the standard normal deviate of the OR is regressed on the precision of the OR). When there is no publication bias, the regression line should pass through the origin, and the expected value of intercept will be zero.[34]

All the calculations of the meta-analysis were conducted by Comprehensive Meta Analysis V2 software (Biostat, Englewood, NJ, USA).

3. Results

A total of 13 articles were identified by database searches, which included 16 studies.[26, 39-50] Among them, 11 studies were for TDT and 5 studies were for HHRR.

Table 1 showed the pooled ORs and 95% CIs for the 11 TDT studies with 1219 samples. There was no statistical significance for the heterogeneity ($I^2=28.3%$) and the fixed effect model was selected. The pooled results indicated that there were no association between Ser9Gly SNP and schizophrenia (1219 samples, OR=1.005, 95% CI = 0.898-1.125, Z-value = 0.086, $p = 0.932$). The forest plot was showed in Fig. 2. Furthermore, we performed the subgroup analysis to further explore the association of Ser9Gly in Caucasian and East Asian populations, respectively. The results indicated the significantly preferential transmission of DRD3 Ser9 allele in East Asian (204 samples, OR=0.744, 95% CI = 0.564-0.980, Z-value = -2.104, $p = 0.035$), but not in Caucasian (885 samples, OR=1.053, 95% CI = 0.923-1.202, Z-value = 0.771, $p = 0.441$).
The studies distribution of the funnel plot was substantially symmetrical for the pooled effect size (Fig. 3). Thus, there was not enough evidence for publication bias for TDT studies.

Table 2 showed the pooled ORs and 95% CIs for the 5 HHRR studies with 1704 samples. There was no statistical significance for the heterogeneity ($I^2=30.372\%$) and the fixed effect model was selected. The pooled results indicated that there were no association between Ser9Gly SNP and schizophrenia (1704 samples, OR=0.869, 95% CI = 0.713-1.059, Z-value = -1.395, $p = 0.163$). The forest plot was showed in Fig. 4. Furthermore, we performed the subgroup analysis to further explore the association of Ser9Gly in Caucasian population. The results indicated no significantly preferential transmission of DRD3 Ser9 allele in Caucasian (OR=0.871, 95% CI = 0.604-1.254, Z-value = -0.744, $p = 0.457$) (Table 3).

The studies distribution of the funnel plot was slightly asymmetrical for the pooled effect size (Fig. 5). A small but significant effect of publication bias for HHRR studies was detected.

4. Discussion

We conducted a meta-analysis of family-based association studies (11 for TDT and 5 for HHRR) to investigate the putative association of the Ser9Gly SNP in DRD3 with the risk of schizophrenia. Our overall results suggest that no association exists, except for the significantly preferential transmission of DRD3 Ser9 allele in East Asian in TDT studies.

Several previous meta-analyses have assessed the potential association of DRD3 Ser9Gly with the risk of schizophrenia in case-control studies.[27, 28, 30-32, 51] The latest meta-analysis, which included seventy-three studies comprising 10,634 patients with schizophrenia (cases) and 11,258 controls, suggested that the Ser9Gly SNP is not associated with schizophrenia.[32] Its finding was consistent with our study. Although the subgroup analysis of TDT meta-analysis observed the significant association between Ser9Gly and schizophrenia in East Asian population, it only included two studies with the limited sample size (204 meiosis).[44, 45] Moreover, one study of HHRR in East Asian also found the significant association, but its sample size was still small (404 samples).[44] Thus, the positive results need to be interpreted cautiously and more work is required to validate the association in East Asian population. Additionally, it is reasonable that the genetic heterogeneity can lead to the differences in the subgroup analysis of Caucasian and East Asian. Actually, the genetic heterogeneity will complicate the etiology of schizophrenia because the allele distributions of DRD3 Ser9Gly vary in different ethnicity population. Gly9 allele frequencies vary almost as much in the Japanese control populations (22%–34%) as they do in northern and western Caucasian control populations (30%–44%).[28, 32] Therefore, in order to reduce the genetic heterogeneity, it is necessary to study the homogeneous populations.

Presently, numerous candidate genes are involved in the susceptibility of the complex disease, such as schizophrenia. Family-based association studies can provide an informative way to investigate the putative susceptible genes. Unlike population-based tests for association, the family-based tests for transmission disequilibrium are protected against population stratification and the results can avoid the effects of genetic background heterogeneity effectively.[52] Compared with the case-control study with the same sample size, the family-based study is less prone to confounding. Methodologically, it uses a more rigorous approach than the population-based study.[53] Thus, although our previous meta-analysis of case-control studies did not find the significant association of Ser9Gly locus with the risk of schizophrenia, it was still necessary to perform the meta-analysis of family based association.

There were two limitations in our current meta-analysis. Initially, we detected a slight but significant publication bias in the HHRR studies. This bias might be due to only English- and Chinese-language studies included. Subordinately, we just evaluated the role of Ser9Gly SNP in the risk of schizophrenia. Nevertheless, only one variation just plays a minute role in the overall genetic susceptibility of the disease. Regrettably, the gene-gene interactions and epigenetics were not assessed without the sufficient information.

5. Conclusions

In conclusion, our meta-analysis of family-based association studies found no association between DRD3 Ser9Gly SNP and the risk of schizophrenia. The large sample homogeneous population studies will be necessary to further explore the role of DRD3 in the etiology of schizophrenia.

Abbreviations

SNP: single nucleotide polymorphism; DRD3: dopamine receptor D3; TDT: transmission disequilibrium test; HHRR: haplotype-based haplotype relative risk; ORs: Odds ratios; CIs: confidence interval.

Declarations
Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Author Contributions

XNL, JLZ and XHW conceived and designed the experiments. XNL and BJW searched the literature, extracted and analyzed the data. JY wrote the paper.

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Not applicable

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Table 1. Meta-analysis of TDT studies of the association between DRD3 Ser9Gly and schizophrenia.
| Author | Year | Location | Ethnicity | Diagnostic criteria | Number of transmissions | Ser9 allele | Expected distribution | OR  | 95% CI | Z-value | P-value |
|--------|------|----------|-----------|--------------------|------------------------|------------|----------------------|-----|--------|----------|---------|
| lhotra | 1998 | USA      | Caucasian | DSM-III-R          | 108                    | 57 51      | 54 54                | 1.118 | 0.766-1.630 | 0.577   | 0.564   |
| Kalsi  | 1998 | USA      | Caucasian | DSM-III-R          | 149                    | 74 75      | 75 75                | 0.987 | 0.716-1.360 | -0.082  | 0.935   |
| Williams | 1998 | USA      | Caucasian | DSM-III-R          | 78                     | 33 45      | 39 39                | 0.733 | 0.469-1.146 | -1.361  | 0.173   |
| lliams | 1998 | Italy    | Caucasian | DSM-III-R          | 160                    | 64 76      | 80 80                | 1.105 | 0.811-1.507 | 0.633   | 0.527   |
| Kowski | 1999 | India    | Indians   | DSM-IV             | 264                    | 67 65      | 62 70                | 1.164 | 0.718-1.886 | 0.615   | 0.538   |
| Kowskii | 2000 | Palestine | Arabian  | DSM-IV             | 516                    | 173 85     | 172 86               | 1.018 | 0.705-1.468 | 0.094   | 0.925   |
| Kowskii | 2004 | Portugal | Caucasian | DSM-IV             | 360                    | 122 58     | 126 54               | 0.901 | 0.577-1.409 | -0.455  | 0.649   |
| Li       | 2005 | China    | East Asian | CCMD-III          | 404                    | 94 108     | 120 82               | 0.595 | 0.401-0.882 | -2.584  | 0.010   |
| Liwe    | 2010 | Poland   | Caucasian | DSM-IV, ICD-10     | 120                    | 57 63      | 60 60                | 0.905 | 0.632-1.294 | -0.548  | 0.584   |
|         |      |          | East Asian |                | 204                    | 87 117     | 102 102              | 0.744 | 0.564-0.980 | -2.104  | 0.441   |

Note: T, transmitted (number of times the allele is transmitted from heterozygous parents to the proband); NT, not transmitted.

Table 2. Meta-analysis of HHRR studies of the association between DRD3 Ser9Gly and schizophrenia.

| Year | Location | Ethnicity | Diagnostic criteria | Sample size | Transmitted Ser9 | Untransmitted Ser9 | OR  | 95% CI | Z-value | P-value |
|------|----------|-----------|---------------------|-------------|-----------------|-------------------|-----|--------|----------|---------|
| 17   | 1999     | India     | Indians             | DSM-IV      | 264             | 67 65 62 70       | 1.164 | 0.718-1.886 | 0.615   | 0.538   |
| 48   | 2000     | Palestinian | Arabian          | DSM-IV      | 516             | 173 85 172 86     | 1.018 | 0.705-1.468 | 0.094   | 0.925   |
| 342  | 2004     | Portugal  | Caucasian          | DSM-IV      | 360             | 122 58 126 54     | 0.901 | 0.577-1.409 | -0.455  | 0.649   |
|      | 2005     | China     | East Asian         | CCMD-III    | 404             | 94 108 120 82     | 0.595 | 0.401-0.882 | -2.584  | 0.010   |
|      | 2010     | Canada    | Caucasian          | DSM-IV      | 120             | 57 63 60 60       | 0.905 | 0.632-1.294 | -0.548  | 0.584   |
|      |          |           | East Asian         |              | 204             | 87 117 102 102    | 0.744 | 0.564-0.980 | -2.104  | 0.441   |
|      |          |           |                     |              | 1704            | 502 350 530 322   | 0.869 | 0.713-1.059 | -1.395  | 0.163   |

Table 3. Subgroup analysis of the association between DRD3 Ser9Gly and schizophrenia in HHRR studies.
| Year | Location | Ethnicity | Diagnostic criteria | Transmitted | Untransmitted | OR (95% CI) | Z-value | P-value |
|------|----------|-----------|---------------------|-------------|---------------|-------------|---------|---------|
| 2004 | Portugal | Caucasian | DSM-IV              | Ser9 122    | Gly9 58       | 126 54      | 0.901   | 0.577-1.409 | -0.455 | 0.649   |
| 2010 | Canada   | Caucasian | DSM-IV              | Ser9 46     | Gly9 34       | 50 30       | 0.812   | 0.431-1.530 | -0.645 | 0.519   |

Figures

Figure 1

The search flow diagram.
Figure 2

Forest plot for TDT studies.

Figure 3

Funnel plot of study precision by log odds ratio for TDT studies.
**Supplementary Files**

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