Associations between dopamine D2 receptor gene polymorphisms and schizophrenia risk: a PRISMA compliant meta-analysis

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Objective: To determine the relationships between dopamine D2 receptor gene polymorphisms and the risk of schizophrenia using meta-analysis.

Method: The PubMed, Embase, and China National Knowledge Infrastructure databases were searched to identify relevant literature published up to February 2016. The allele contrast model was used. Stata software was used for statistical analysis, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to evaluate the associations between dopamine D2 receptor gene polymorphisms and the risk of schizophrenia. Meta-regression and publication bias, trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analyses were also performed.

Results: This meta-analysis included 81 studies. The rs1801028 and rs1799732 were associated with schizophrenia risk among Asians ($P=0.04$, OR =1.25, 95% CI =1.01–1.55; $P<0.01$, OR =0.76, 95% CI =0.63–0.92, respectively), while the rs6277 was associated with schizophrenia risk in Caucasians ($P<0.01$, OR =0.72, 95% CI =0.66–0.79). The rs1800497 was also associated with schizophrenia risk in population-based controls ($P<0.01$, OR =0.84, 95% CI =0.72–0.97). The rs6275, rs1079597, and rs1800498 were not associated with schizophrenia risk. In addition, meta-regression indicated that the controls may be sources of heterogeneity for the rs1801028 single-nucleotide polymorphism (SNP), while ethnicity may be sources of heterogeneity for the rs6277 SNP. Publication bias was significant for the rs1801028 SNP, and this result changed after the publication bias was adjusted using the trim-and-fill method.

Conclusion: This meta-analysis demonstrated that the rs1801028 may be a risk factor for susceptibility to schizophrenia among Asians, while the rs1799732 may be a protective factor for that population. Large-sample studies are necessary to verify the results of this meta-analysis.

Keywords: dopamine D2 receptor, polymorphisms, schizophrenia

Introduction

Schizophrenia is a severe mental disorder characterized by changes in its higher functions and deterioration of behavior, cognition, emotions, motivation, and perception, and is marked by socio-occupational dysfunction. Schizophrenia manifests with a wide variety of positive (auditory hallucinations and paranoid delusions), negative (affective flattening, anhedonia, and alogia), and cognitive (declined attention and memory) symptoms. It is a complex multifactorial psychiatry disorder involving genetic and environmental factors, with a global lifetime prevalence of 0.5%–1%. Family, twin, and adoption studies have shown that genetic factors play a significant role in the pathogenesis of schizophrenia, with the heritability of schizophrenia being estimated at 70%–80%. Additionally, Lee et al estimated that 23% of variation in...
liability to schizophrenia is captured by single-nucleotide polymorphisms (SNPs). For schizophrenia, some genetic factors were shared with other psychiatric disorders (bipolar disorder, major depressive disorder, autism spectrum disorders, and attention-deficit/hyperactivity disorder), and some genetic factors associated with its risk were overlapped with those associated with reproduction traits (eg, age at first birth). In short, schizophrenia is highly polygenic.

The dopamine hypothesis is one of the main ideas for explaining the etiology of schizophrenia. There are several lines of evidence implicating dopamine D2 receptor (DRD2) as the main candidate gene for the risk of schizophrenia. In humans, the DRD2 gene is located on chromosome 11 at q22–q23, extends over 270 kb, and has eight exons. Associations between schizophrenia risk and four SNPs have been widely studied: rs1799732 (–141C Ins/Del), rs1801028 (311 Ser/Cys), rs1800497 (TaqIB), and rs6277 (C957T). The rs1799732 SNP is located in the DRD2 promoter region and has been demonstrated to affect gene expression in vitro. The rs1801028 SNP is the missense variant 960C/G in exon 7 of the DRD2 gene that can alter the physiology and function of the D2 receptor. The rs1800497 SNP was previously thought to be located in the DRD2 3′-untranslated region and was recently identified as being in exon 8 of the ankyrin repeat and kinase domain containing 1 (ANKK1) gene. This SNP has been considered to alter substrate-binding specificity. The rs6277 SNP is located in exon 7 of the DRD2 gene and alters mRNA folding, leading to a decrease in mRNA stability and translation, and markedly changing dopamine-induced up-regulation of DRD2 expression. In addition, associations between schizophrenia risk and the rs6275 (C939T), rs1079957 (TaqIB), and rs1800498 (TaqID) SNPs have been widely reported.

While associations between DRD2 gene polymorphisms and the risk of schizophrenia have been studied extensively, there are still some uncertainties about these associations. The present meta-analysis was therefore performed to further identify the associations between DRD2 gene polymorphisms and schizophrenia risk. Meta-regression and publication bias, nonparametric trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analyses were also performed.

Method
Search strategy
The PubMed, Embase, and China National Knowledge Infrastructure databases were independently searched by two reviewers (He and Wu) to collect the literature related to associations between DRD2 gene polymorphisms and schizophrenia risk. The last search update was performed in February 2016, and the following keywords were used in the literature search: “schizophrenia”, “psychosis”, “schizophrenic,” “DRD2,” “dopamine receptor 2,” “dopamine receptor D2”, “dopamine D2 receptor”, “polymorphism”, “variant”, “variation”, “allele”, and “genotype”. The species was limited to human. Moreover, the literature references in all of the included documents were searched to find more studies that were consistent with the eligibility criteria.

Eligibility criteria
1. Studies that met the following inclusion criteria were included:
   a) Research study with a case–control design.
   b) Written in Chinese or English.
   c) Investigation of the associations between DRD2 gene polymorphisms and the risk of schizophrenia.
   d) Providing sufficient allele or genotype distribution data of the included cases and controls.
2. Studies that met any of the following exclusion criteria were excluded:
   a) Repetition of information in other literature.
   b) A review, comment, or conference proceedings.
   c) Results obtained in an animal model.
   d) Series of reports or case reports.

Research screening
The studies were first screened by browsing the titles and abstracts of the identified documents. Secondary screening was then performed by reading the full text of selected reports. Finally, data extraction and quality assessment were performed for the included studies.

Data extraction
In our present study, two reviewers (He and Wu) independently extracted the following information from the included literature: first author, publication year, mean age of the cases and controls, country, ethnicity, source of controls, numbers of cases and controls, DRD2 gene locus, diagnostic criteria of schizophrenia, genotyping method, and conformity with Hardy–Weinberg equilibrium (HWE) for the controls. If the allele or genotype distribution data of the cases and controls were not reported in the original articles, the corresponding author was contacted by mail to obtain this information.

Quality assessment
Two authors (HH and HW) independently performed quality assessment using quality scoring criteria based on criteria previously applied in observational studies for addressing genetic epidemiological issues, with the scores ranging from...
0 points (worst) to 9 points (best) (Table S1). A study was classified as being of low quality when it scored <6 points. Sensitivity analysis was conducted by deleting these low-quality studies.

**Statistical analysis**

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strengths of the associations between DRD2 gene polymorphisms and schizophrenia risk. Pooled effect sizes were calculated using the random-effects model. This model evaluated different underlying influences considering both within- and between-study variations, which provided the advantage of accommodating diversity between studies and yielding a more conservative estimate of the assessed effect. The present study used an allele comparison model because this maximized the number of included studies.

Cochran’s $Q$ statistic was used to estimate the degree of heterogeneity in the included studies. Heterogeneity was considered to be high when the $P$-value was <0.1. The heterogeneity was also quantified using the $I^2$ statistic and was considered high when $I^2 > 50%$. Based on clinical knowledge, the ethnicity and source of controls were considered to be responsible for heterogeneity, and so these parameters were set as covariates in the meta-regression. A subgroup analysis was also conducted.

Publication bias was analyzed using Begg’s funnel plots. An asymmetrical funnel plot indicated the presence of significant publication bias. The symmetry of Begg’s funnel plots was judged using Egger’s linear regression, and a $P$-value of <0.05 was considered to indicate that the funnel plots were significantly asymmetrical. The trim-and-fill method was used to correct for publication bias and also to assess the impact of publication bias on the results.

Sensitivity analysis was used to assess both the potential impact of single studies on the pooled effect size and the impact of removing low-quality studies on the obtained results. Cumulative analysis by publication year was used to explore temporal trends in the results. Finally, the fail-safe number of negative studies that would be required to nullify (ie, make $P > 0.05$) the effect size was calculated.

All of the statistical analyses were conducted using Stata software, version 12.0 (Stata Corporation, College Station, TX, USA).

**Results**

**Study characteristics**

A flow chart of the study selection procedure is shown in Figure 1. Briefly, 1,267 studies were identified after eliminating 304 duplications. After reviewing the abstracts or reading full texts carefully according to eligibility criteria,
a further 1,186 studies were excluded. Finally, 81 studies were identified for exploring the associations between DRD2 gene polymorphisms and susceptibility to schizophrenia in a meta-analysis.

The main features of the included studies are listed in Table 1. The 81 studies comprised 45 studies focused on Caucasians, 34 on Asians, and 2 on mixed populations. The distributions of genotypes in the control groups deviated from HWE for the rs1801028, rs1800497, and rs1800498 SNPs in seven studies.11,22–27 The quality assessment revealed that four studies were of low quality.26,28–30

Association between the rs1801028 (311 Ser/Cys) and schizophrenia risk
A meta-analysis of 42 case–control studies (9,771 cases and 11,900 controls) revealed that the variant allele G (Cys) was associated with increased schizophrenia risk in all populations (P=0.009, OR =1.23, 95% CI =1.05–1.44; Figure 2A). The fail-safe number was 104.52, and there was moderate heterogeneity (I²=35%). Meta-regression indicated that the source of controls may have been responsible for this heterogeneity (P<0.01). The subgroup analysis, whose results are presented in Table 2, revealed that the G allele was associated with increased susceptibility to schizophrenia in Asians (P=0.04, OR =1.25, 95% CI =1.01–1.55) and hospital-based controls (P<0.01, OR =1.91, 95% CI =1.39–2.61).

Sensitivity analysis indicated that no single study qualitatively changed the pooled ORs (Figure 3). Removing the low-quality studies26,29,30 did not change the results. Four of the studies deviated from HWE,22,24,26,27 but removing them from the analysis did not change the results. Cumulative analysis by publication year confirmed that pooled ORs and 95% CIs were stable and that there was a reliable temporal trend in the results from 199613 (Figure 4).

In terms of publication bias, Egger’s linear regression showed that the funnel plots were asymmetrical (P=0.023). The trim-and-fill method suggested that eight studies were missing, and the results for the association between the rs1801028 SNP and schizophrenia changed after replacing the data for these eight studies (OR =1.063, 95% CI =0.892–1.266; Figure 5). This indicates that our analyses were not stable and that future research is very likely to produce different results.

Association between the rs6277 (C957T) and schizophrenia risk
A meta-analysis of 12 case–control studies (2,919 cases and 3,600 controls) revealed that the variant allele T was associated with decreased schizophrenia risk (P=0.002, OR =0.80, 95% CI =0.69–0.92; Figure 2B). The fail-safe number was 91.00, there was high heterogeneity (I²=58.5%), and meta-regression indicated that ethnicity may have been responsible for this heterogeneity (P<0.01). A subgroup analysis based on ethnicity showed that the T allele was associated with decreased susceptibility to schizophrenia in Caucasians (P<0.01, OR =0.72, 95% CI =0.66–0.79).

Cumulative analysis by publication year did not show a reliable temporal trend. Sensitivity analysis showed that no single study qualitatively changed the pooled ORs. In terms of publication bias, Egger’s linear regression showed that the funnel plots were symmetrical (P=0.119).

Association between the rs1799732 (−141C Ins/Del) and schizophrenia risk
A meta-analysis of 27 case–control studies (6,770 cases and 7,347 controls) demonstrated that the rs1799732 SNP was not associated with schizophrenia risk (P=0.26, OR =0.91, 95% CI =0.78–1.07; Figure 2C). There was high heterogeneity (I²=76%), and meta-regression indicated that neither ethnicity (P=0.119) nor the source of controls (P=0.452) was responsible for this heterogeneity. A subgroup analysis based on ethnicity showed that the variant type (−141C Del) was associated with decreased susceptibility to schizophrenia in Asians (P=0.004, OR =0.76, 95% CI =0.63–0.92). A subgroup analysis based on the source of controls found no significant association between the rs1799732 SNP and schizophrenia risk in population-based controls or hospital-based controls. In terms of publication bias, Egger’s linear regression showed that the funnel plots were symmetrical (P=0.173).

Association between the rs1800497 (TaqIA) and schizophrenia risk
A meta-analysis of 22 case–control studies (4,017 cases and 4,209 controls) demonstrated that the rs1800497 SNP was not associated with schizophrenia risk (P=0.06, OR =0.87, 95% CI =0.75–1.01; Figure 2D). There was high heterogeneity (I²=72%), and meta-regression indicated that neither ethnicity (P=0.612) nor the source of controls (P=0.372) was responsible for this heterogeneity. A subgroup analysis based on the source of controls revealed that the variant allele A (A2) was associated with decreased schizophrenia risk in population-based controls (P<0.01, OR =0.84, 95% CI =0.72–0.97). A subgroup analysis based on ethnicity revealed that the rs1800497 SNP was also not associated with susceptibility to
Table 1 Characteristics of case–control studies on DRD2 gene polymorphisms and schizophrenia risk included in the meta-analysis

| Author                     | Year | Country     | Ethnicity | No of sample | Control sources | No of case | No of controls | Mutation analysis method | Criteria                          | SNP       | HWE (P-value) | Quality score |
|----------------------------|------|-------------|-----------|--------------|----------------|------------|----------------|-------------------------|-----------------------------------|-----------|---------------|--------------|
| Caprini et al⁸              | 2011 | Scandinavia | Caucasians | 837          | 1,471          | PB         |                |                         | ICD-10 + DSM-III-R + DSM-IV       | TaqID     | Yes           | 5            |
| Dolfus et al¹⁵              | 1996 | France      | Caucasians | 62           | 161            | PB         | PCR-RFLP       | DSM-III-R                | –                                  | TaqIA     | Yes           | 8            |
| Luo²⁴                      | 2008 | China       | Asians     | 211          | 201            | PB         | Direct sequencing | DSM-IV                  | –141C Ins/Del                    | Ser311Cys | Yes           | 7            |
| Watanabe et al²⁶            | 2012 | Japan       | Asians     | 648          | 664            | PB         | TaqMan         | DSM-IV                  | Ser311Cys                          | Yes       | 7             |
| Crawford et al¹¹            | 1996 | America     | Caucasians | 84           | 81             | HB         | Direct sequencing | DSM-III-R                | Ser311Cys                          | Yes       | 6             |
| Dubertret et al¹³           | 2010 | France      | Caucasians | 50           | 50             | PB         | PCR            | DSM-IV                  | –                                  | TaqIB     | –             | 5            |
| Hime et al³⁷                | 2002 | Japan       | Asians     | 190          | 103            | PB         | PCR-RFLP       | DSM-IV                  | –                                  | TaqIA     | –             | 8            |
| Jonsson et al³⁷             | 1996 | Sweden      | Caucasians | 118          | 78             | PB         | PCR            | DSM-III-R                | Ser311Cys                          | Yes       | 7             |
| Kunii et al²²               | 2010 | Japan       | Asians     | 12           | 12             | PB         | PCR-RFLP       | DSM-IV                  | –141C Ins/Del                    | Ser311Cys | Yes           | 8            |
| Srivastava et al⁴           | 2010 | India       | Caucasians (Indians) | 233   | 224           | PB         | PCR-RFLP       | DSM-IV                  | Ser311Cys                          | Yes       | 8             |
| Arinami et al³⁷             | 1996 | Japan       | Asians     | 136          | 279            | PB         | PCR            | ICD-10 + DSM-III-R       | –                                  | Ser311Cys | Yes           | 7            |
| Arinami et al³⁷             | 1997 | Japan       | Asians     | 260          | 312            | PB         | PCR-RFLP       | DSM-III-R                | –141C Ins/Del                    | Ser311Cys | Yes           | 7            |
| Aslan et al²³               | 2010 | Turkey      | Caucasians | 99           | 109            | PB         | PCR            | DSM-IV                  | –                                  | TaqIA     | No            | 6            |
| Behravan et al¹¹            | 2008 | Iran        | Caucasians | 38           | 63             | PB         | PCR            | DSM-IV                  | –                                  | TaqIB     | Yes           | 7            |
| Bettecheva et al¹           | 2009 | Bulgaria    | Caucasians | 255          | 556            | PB         | PCR            | DSM-IV                  | C957T                              | Yes       | 8             |
| Breen et al³³               | 1999 | England     | Caucasians | 439          | 437            | PB         | PCR            | DSM-III-R + DSM-IV       | –141C Ins/Del                    | C939T     | Yes           | 8            |
| Chen et al⁸⁰               | 1996 | China       | Asians     | 114          | 88             | PB         | PCR            | DSM-III-R                | –                                  | C957T     | Yes           | 8            |
| Cordeiro et al¹⁴            | 2009 | Brazil      | Mixed      | 229          | 733            | PB         | –              | DSM-IV                  | –141C Ins/Del                    | Ser311Cys | Yes           | 8            |
| Cordeiro and Vallada        | 2009 | Brazil      | Mixed      | 235          | 834            | PB         | PCR            | DSM-IV                  | TaqIA                              | Yes       | 8             |
| Dubertret et al¹³           | 2004 | France      | Caucasians | 103          | 83             | PB         | PCR-RFLP       | DSM-IV                  | –                                  | TaqIB     | –             | 8            |
| Dubertret et al¹³           | 2010 | France      | Caucasians | 144          | 142            | PB         | TaqMan         | DSM-IV                  | –                                  | TaqIA     | –             | 8            |
| Fan et al⁹⁰                | 2010 | China       | Asians     | 421          | 404            | PB         | PCR            | DSM-IV                  | C957T                              | –         | 7             |
| Golimbet et al⁴⁰            | 2011 | Russia      | Caucasians | 366          | 387            | PB         | PCR            | DSM-IV                  | Ser311Cys                          | Yes       | 7             |
| Gupta et al⁴¹               | 2009 | India       | Caucasians (Indians) | 254   | 225           | PB         | PCR            | DSM-IV                  | –141C Ins/Del                    | Ser311Cys | Yes           | 8            |

(Continued)
| Author                  | Year | Country | Ethnicity                  | Cases | Controls | Control Sources | Mutation Analysis Method | Criteria       | SNP            | HWE (P-value) | Quality  |
|------------------------|------|---------|----------------------------|-------|----------|----------------|--------------------------|----------------|----------------|-------------|----------|
| Haminnen et al<sup>44</sup> | 2006 | Finland | Caucasians                 | 188   | 384      | PB             | PCR                      | DSM-IV        | Ser<sup>3</sup>11Cys | Yes         | 8        |
| Haranò<sup>36</sup>    | 1997 | Japan   | Asians                     | 70    | 101      | HB             | PCR                      | DSM-III-R     | C957T        | Yes         | 8        |
| Hoenicka et al<sup>45</sup> | 2006 | Spain   | Caucasians                 | 131   | 364      | PB             | PCR                      | DSM-IV        | Ser<sup>3</sup>11Cys | Yes         | 6        |
| Hori et al<sup>33</sup> | 2001 | Japan   | Asians                     | 241   | 201      | PB             | PCR                      | DSM-IV        | C957T        | Yes         | 7        |
| Iwata et al<sup>34</sup> | 2003 | Japan   | Asians                     | 51    | 63       | PB             | PCR-RFLP                 | DSM-IV        | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Jonsson et al<sup>36</sup> | 1999 | Sweden  | Caucasians                 | 129   | 179      | HB             | PCR                      | DSM-III-R     | C957T        | Yes         | 7        |
| Jonsson et al<sup>35</sup> | 2003 | Sweden  | Caucasians                 | 173   | 236      | HB             | PCR                      | DSM-III-R     | Ser<sup>3</sup>11Cys | Yes         | 6        |
| Kaneshima et al<sup>16</sup> | 1997 | Japan   | Asians                     | 78    | 112      | PB             | PCR                      | RDC + DSM-IV  | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Kukreit et al<sup>2</sup> | 2006 | India   | Caucasians (Indians)      | 101   | 145      | PB             | PCR                      | DSM-IV        | C957T        | Yes         | 8        |
| Kurt et al<sup>47</sup> | 2011 | Turkey  | Caucasians                 | 73    | 60       | PB             | PCR-RFLP                 | DSM-IV        | −141C Ins/Del | Yes         | 7        |
| Lafuente et al<sup>48</sup> | 2008 | Spain   | Caucasians                 | 243   | 291      | HB             | PCR                      | DSM-IV        | TaqIB        | Yes         | 7        |
| Laurent et al<sup>49</sup> | 1994 | France  | Caucasians                 | 113   | 184      | PB             | −                         | DSM-III-R     | Ser<sup>3</sup>11Cys | Yes         | 6        |
| Lawford et al<sup>50</sup> | 2005 | Australia | Caucasians                | 154   | 148      | PB             | PCR                      | DSM-IV        | C957T        | Yes         | 7        |
| Li et al<sup>51</sup>   | 1998 | England | Caucasians                 | 151   | 145      | HB             | PCR                      | DSM-IV + DSM-III-R | −141C Ins/Del | Yes         | 6        |
| Monakhov et al<sup>52</sup> | 2008 | Russia  | Caucasians                 | 311   | 364      | PB             | PCR                      | DSM-IV        | C957T        | Yes         | 7        |
| Ohara et al<sup>53</sup> | 1996 | Japan   | Asians                     | 153   | 121      | PB             | PCR                      | DSM-IV        | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Ohara et al<sup>54</sup> | 1998 | Japan   | Asians                     | 170   | 121      | PB             | PCR                      | DSM-IV        | −141C Ins/Del | Yes         | 8        |
| Parsons et al<sup>55</sup> | 2007 | Spain   | Caucasians                 | 119   | 165      | PB             | PCR-RFLP                 | DSM-IV        | −141C Ins/Del | Yes         | 7        |
| Sai et al<sup>56</sup>   | 2010 | Spain   | Caucasians                 | 288   | 421      | PB             | PCR-RFLP                 | DSM-IV        | −141C Ins/Del | Yes         | 9        |
| Sanders et al<sup>57</sup> | 2008 | Europe  | Caucasians                 | 1,870 | 2,002    | PB             | TaqMan                   | DSM-IV        | Ser<sup>3</sup>11Cys | Yes         | 8        |
| Sasaki et al<sup>58</sup> | 1996 | Europe  | Caucasians                 | 273   | 255      | HB             | PCR                      | DSM-III-R     | Ser<sup>3</sup>11Cys | Yes         | 5        |
| Spurlock et al<sup>59</sup> | 1998 | Europe  | Caucasians                 | 373   | 413      | HB             | PCR                      | DSM-III-R     | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Stöber et al<sup>60</sup> | 1998 | Germany | Caucasians                 | 260   | 290      | PB             | PCR                      | ICD-10        | −141C Ins/Del | Yes         | 7        |
| Tallerico et al<sup>61</sup> | 1999 | America | Caucasians                 | 50    | 51       | PB             | PCR                      | DSM-III-R     | −141C Ins/Del | Yes         | 7        |
| Tanaka et al<sup>62</sup> | 1996 | Japan   | Asians                     | 106   | 106      | PB             | PCR                      | DSM-III-R     | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Tsutsumi et al<sup>62</sup> | 2011 | Japan   | Asians                     | 407   | 384      | PB             | PCR-RFLP                 | DSM-IV        | C957T        | Yes         | 7        |
| Verga et al<sup>63</sup>  | 1997 | Italy   | Caucasians                 | 103   | 97       | PB             | PCR                      | DSM-III-R     | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Fujimura et al<sup>64</sup> | 1997 | Japan   | Asians                     | 52    | 26       | PB             | PCR                      | DSM-IV        | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Kamman et al<sup>65</sup> | 2003 | Finland | Caucasians                 | 93    | 94       | PB             | PCR                      | DSM-IV + ICD-10 | −141C Ins/Del | Yes         | 7        |
| Morimoto et al<sup>66</sup> | 2002 | Japan   | Asians                     | 48    | 48       | PB             | PCR                      | DSM-IV + ICD-10 | Ser<sup>3</sup>11Cys | Yes         | 7        |
| Vijayan et al<sup>67</sup> | 2007 | India   | Caucasians (Indians)      | 213   | 196      | PB             | PCR                      | DSM-IV        | TaqIB        | Yes         | 8        |
| Study            | Year | Region | Ethnicity | Sample Size | PB Type | HWE | PCR Method | Assay Type | Serine | TaqIA | Publication Year |
|------------------|------|--------|-----------|-------------|---------|-----|------------|------------|--------|-------|-----------------|
|Comings et al    | 1991 | America| Caucasians| 87          | 69      | HB  | PCR        | DSM-III-R  | TaqIA  | Yes   | 7     |
| Sanders et al    | 1993 | America| Caucasians| 55          | 51      | PB  | PCR-RFLP   | DSM-III-R + RDC | TaqIA  | Yes   | 8     |
| Campion et al    | 1994 | France | Caucasians| 80          | 80      | PB  | PCR-RFLP   | DSM-III-R  | TaqIA  | Yes   | 7     |
| Itokawa et al    | 1993 | Japan  | Asians    | 50          | 110     | PB  | PCR-RFLP   | DSM-III-R  | Ser311Cys| Yes   | 7     |
| Nothen et al     | 1993 | Germany| Caucasians| 60          | 60      | PB  | PCR        | DSM-III-R  | TaqIA  | Yes   | 7     |
| Arinami et al    | 1994 | Japan  | Asians    | 156         | 300     | HB  | PCR        | DSM-III-R  | Ser311Cys| Yes   | 6     |
| Asherson et al   | 1994 | England| Caucasians| 112         | 64      | PB  | PCR        | DSM-III-R  | Ser311Cys| Yes   | 6     |
| Germain et al    | 1994 | America| Caucasians| 106         | 113     | HB  | PCR-RFLP   | DSM-III-R  | Ser311Cys| Yes   | 7     |
| Hatton et al     | 1994 | Japan  | Asian     | 100         | 100     | PB  | PCR-RFLP   | DSM-III-R  | Ser311Cys| No    | 6     |
| Nanko et al      | 1994 | Japan  | Asian     | 100         | 100     | PB  | PCR        | DSM-III-R  | Ser311Cys| Yes   | 6     |
| Nothen et al     | 1993 | Germany| Caucasians| 179         | 138     | PB  | PCR        | DSM-III-R  | Ser311Cys| Yes   | 7     |
| Shaikh et al     | 1994 | England| Caucasians| 147         | 100     | HB  | PCR        | DSM-III-R  | Ser311Cys| No    | 5     |
| Sobell et al     | 1994 | America| Caucasians| 338         | 1,914   | HB  | –          | –          | Ser311Cys| Yes   | 5     |
| Inada et al      | 1999 | Japan  | Asian     | 234         | 94      | PB  | PCR        | ICD-10      | –      | –     | –    |
| Serretti et al   | 2000 | Italy  | Caucasians| 366         | 267     | HB  | –          | –          | Ser311Cys| Yes   | –    |
| Itokawa et al    | 2010 | Japan  | Asian     | 156         | 300     | PB  | SSCP       | DSM-III-R  | Ser311Cys| Yes   | 7     |
| Li et al         | 2014 | China  | Asian     | 915         | 421     | PB  | PCR-RFLP   | ICD-10 + CCMD-II-R | TaqIA  | Yes   | 7     |
| Fan et al        | 1996 | China  | Asian     | 105         | 108     | PB  | PCR        | ICD-10      | Ser311Cys| Yes   | 7     |
| Liu et al        | 2009 | China  | Asian     | 317         | 310     | PB  | PCR        | DSM-IV      | TaqIA  | Yes   | 7     |
| Luo et al        | 2008 | China  | Asian     | 128         | 124     | PB  | PCR-RFLP   | CCMD-3      | –      | –     | –    |
| Shen et al       | 2011 | China  | Asian     | 120         | 100     | PB  | PCR        | DSM-IV      | –      | –     | –    |
| Zhang et al      | 2003 | China  | Asian     | 67          | 77      | PB  | PCR        | CCMD-II-R   | TaqIA  | Yes   | 6     |
| Zheng et al      | 2012 | China  | Asian     | 92          | 96      | PB  | PCR        | –           | C957T  | Yes   | 6     |
| Lang et al       | 2005 | China  | Asian     | 101         | 105     | PB  | PCR        | DSM-IV + CCMD-3 | –      | –     | –    |

**Abbreviations:** AFLP, amplified fragment length polymorphism; CC, complication or comorbidity; CCMD, Chinese Classification of Mental Disorders; DSM, The Diagnostic and Statistical Manual of Mental Disorder; HB, hospital-based; PB, population-based; HWE, Hardy–Weinberg equilibrium; ICD-10, International Statistical Classification of Diseases and Related Health Problems – 10th version; PCR, polymerase chain reaction; RDC, Research Diagnostic Criteria; sNP, single-nucleotide polymorphisms; RFLP, restriction fragment length polymorphism.
Figure 2 (Continued)
schizophrenia. There were four studies of the rs1800497 SNP that included controls that did not conform with HWE, but they did not influence the results.11,23–25 In terms of publication bias, Egger’s linear regression showed that the funnel plots were symmetrical (P=0.861).

Association between the other SNPs and schizophrenia risk

There was no evidence that the susceptibility to schizophrenia was associated with the rs6275 (T vs C, P=0.10, OR=0.92, 95% CI=0.83–1.02), rs1079597 (T vs C, P=0.12, OR=0.72, 95%
### Table 2: Subgroup analysis of case–control studies on DRD2 gene polymorphisms and schizophrenia risk

| SNP  | Subgroup type   | Subgroup       | N  | P-value | OR  | 95% CI     | I² (%) |
|------|-----------------|----------------|----|---------|-----|------------|--------|
| rs1801028 | Control sources | Population-based | 31 | 0.99    | 1.00 | 0.88, 1.14 | 0      |
|        |                 | Hospital-based  | 11 | <0.01   | 1.91 | 1.39, 2.61 | 31     |
|        | Ethnicity       | Caucasians     | 19 | 0.09    | 1.22 | 0.97, 1.54 | 41     |
|        |                 | Asians         | 23 | 0.04    | 1.25 | 1.01, 1.55 | 31     |
| rs6277 | Ethnicity       | Caucasians     | 8  | <0.01   | 0.72 | 0.66, 0.79 | 0      |
|        |                 | Asians         | 4  | 0.37    | 1.17 | 0.83, 1.64 | 46     |
| rs1799732 | Control sources | Population-based | 24 | 0.36    | 0.92 | 0.78, 1.10 | 77     |
|        |                 | Hospital-based  | 3  | 0.46    | 0.81 | 0.47, 1.41 | 71     |
|        | Ethnicity       | Caucasians     | 15 | 0.33    | 1.11 | 0.90, 1.36 | 71     |
|        |                 | Asians         | 11 | 0.004   | 0.76 | 0.63, 0.92 | 56     |
|        |                  | Mixed          | 1  | 0.002   | 0.61 | 0.44, 0.83 | –      |
| rs1800497 | Control sources | Population-based | 20 | 0.02    | 0.84 | 0.72, 0.97 | 71     |
|        |                 | Hospital-based  | 2  | 0.46    | 1.50 | 0.51, 4.47 | 86     |
|        | Ethnicity       | Caucasians     | 16 | 0.24    | 0.88 | 0.72, 1.08 | 71     |
|        |                 | Asians         | 5  | 0.29    | 0.85 | 0.63, 1.15 | 82     |
|        |                  | Mixed          | 1  | 0.06    | 0.82 | 0.66, 1.01 | –      |

**Abbreviations:** CI, confidence intervals; DRD2, dopamine D2 receptor; OR, odds ratios; SNP, single-nucleotide polymorphisms.

### Meta-analysis estimates, given named study is omitted

![Figure 3: Sensitivity analysis via deletion of each individual study reflecting the relative influence of each individual dataset on the pooled ORs for the rs1801028.](image)

**Abbreviations:** CI, confidence interval; OR, odds ratio.
Figure 4 Cumulative meta-analyses according to publication year for the rs1801028.
CI =0.47–1.10), or rs1800498 (T vs C, P=0.52, OR =1.03, 95% CI =0.93–1.15) SNP. Sensitivity analysis indicated that no single study of the rs1800498 SNP qualitatively changed the pooled ORs. Removing the low-quality study did not change the result.

Discussion
A comprehensive analysis about schizophrenia-associated genetic loci had been performed in a genome-wide association study. Our meta-analysis results provide evidence that the rs1801028 and rs6277 SNPs are associated with the risk of schizophrenia. A subgroup analysis indicated that the rs1801028 SNP may increase the risk of schizophrenia in Asians and hospital-based controls, the rs6277 SNP may reduce the risk of schizophrenia in Caucasians, the rs1799732 SNP may reduce the risk of schizophrenia in Asians, and the rs1800497 SNP may reduce the risk of schizophrenia in population-based controls.

Yao et al performed a similar study of the associations between DRD2 gene polymorphisms and schizophrenia risk. That study used a genetic model, while our study used an allele contrast model since this made it possible to include the largest number of documents and the maximum sample sizes. Other advantages of the present study were 1) the inclusion of more published documents (including those written in Chinese), which increased the statistical power of our results, 2) more SNPs being investigated, and 3) the application of meta-regression and publication bias, nonparametric trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analysis also being performed.

The results of the present study show that the rs1801028 SNP may increase the risk of schizophrenia in Asians and hospital-based controls. Yao et al reported the same result under the dominant model. Different results may be obtained for different races due to differences in genetic backgrounds and living conditions. Moreover, the results for the subgroup analysis based on hospital-based controls are not reliable because such controls may not be representative and samples of hospital-based controls are often too small, and so these results should be treated cautiously. The results for publication bias were significant, and these changed after being adjusted using the trim-and-fill method, which indicated that those results may not be very stable. This means that if new articles are published in the future, the results of a complete meta-analysis including all available data are very likely to change. The presence of significant publication bias was probably due to our meta-analysis including many small-sample studies. Yao et al found only slight publication bias, but this was not corrected using the trim-and-fill method.

Twelve of the included documents related to the rs6277 SNP and the meta-analysis showed that this SNP may reduce the risk of schizophrenia in Caucasians; however, Yao et al did not study this SNP. However, our included samples for this SNP were small and the cumulative analysis by publication year did not show a reliable trend. This means that the statistical power of the results may not have been high.

In our meta-analysis the rs1799732 SNP was not associated with schizophrenia risk, and Yao et al obtained the same result under the dominant model. After performing subgroup analysis, the current meta-analysis indicated that the rs1799732 SNP might reduce the risk of schizophrenia in Asians. In contrast, Yao et al did not find any correlation between the rs1799732 SNP and schizophrenia risk in different races and different populations. The possible reasons for different conclusions being drawn based on the current and previous meta-analyses of the rs1799732 SNP are 1) more documents being included in the present study, especially the Chinese literature, because this is likely to have greatly increased the sample size for Asians, and 2) the use of different genetic models.

The previous meta-analyses did not explore the correlations between the rs1800497 SNP and schizophrenia risk in all populations. After performing subgroup analysis, the present study found that the rs1800497 SNP was associated with schizophrenia risk in population-based controls. In contrast, Yao et al found that the rs1800497 SNP may increase the risk of schizophrenia in Caucasians. The possible reasons for the current and previous meta-analyses drawing different conclusions from their subgroup analyses of the rs1800497 SNP are 1) Yao et al applying the wrong allele or genotype distribution data of cases and controls regarding the study of Nothen et al; 2) the smallness of the study sample of Yao et al; 3) that study not including Chinese studies; and
4) our use of different genetic models. These factors mean that the statistical power would have been higher for the present study.

It is important to note the limitations of our meta-analysis. 1) Meaningless or negative results might not be published, which would lead to some degree of publication bias. 2) Schizophrenia is a multifactorial disease, whereas the present study only considered the impact of the DRD2 gene on schizophrenia risk, and also ignored the possible impacts of environmental factors, age, gender, lifestyle, and diagnosis standards.

In conclusion, this meta-analysis has shown that the rs1801028 SNP may be a risk factor for susceptibility to schizophrenia in Asians, the rs6277 SNP may be a protective factor for susceptibility to schizophrenia in Caucasians, and the rs1799732 SNP may be a protective factor for susceptibility to schizophrenia in Asians. However, the occurrence of schizophrenia represents the cumulative effect of multiple genes, and so only studying a single gene or single polymorphism is unlikely to be adequate. Future studies should pay more attention to the interactions within and between genes as well as within and between their polymorphisms in order to better explain the genetic mechanisms underlying mental illness.

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Author contributions
HRH and HHW performed literature research, data extraction, statistical analysis, and data interpretation. XCM contributed to the study concept and study design. LHY and FG contributed to make figures and tables. YJF and JGF were responsible for the quality control of data and algorithms. All authors contributed to the analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Scale for quality assessment

| Criteria                                           | Score |
|----------------------------------------------------|-------|
| Representativeness of cases                        |       |
| Consecutive/randomly selected form case population with clearly defined sampling frame | 2     |
| Consecutive/randomly selected form case population without clearly defined sampling frame or with extensive | 1     |
| Not described                                      | 0     |
| Definition of the DR                               |       |
| Population- or health-based                       | 2     |
| Hospital-bases                                     | 1     |
| Not described                                      | 0     |
| Hardy–Weinberg equilibrium in controls             |       |
| Hardy–Weinberg equilibrium                         | 2     |
| Hardy–Weinberg disequilibrium                      | 1     |
| Genotyping examination                             |       |
| Genotyping done under “blinded” condition          | 1     |
| Unblinded done or not mentioned                    | 0     |
| Association assessment                             |       |
| Assess association between genotypes and head and neck cancer with appropriate statistics and adjustment for confounders | 2     |
| Assess association between genotypes and head and neck cancer with appropriate statistics and without adjustment for confounders | 1     |
| Inappropriate statistics used                      | 0     |